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Separate determinants of dyskinesia and unpredictable OFF after fluctuation onset in incident Parkinson's disease

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Abstract

Studies timed from Parkinson's disease diagnosis report shared determinants of motor fluctuations and dyskinesia that may reflect progression. The determinants of dyskinesia and unpredictable OFF after fluctuation onset have not been compared. In 1,080 initially untreated patients with sporadic disease followed up to 12 years, we modelled motor-complication transitions and used Cox models timed from first OFF. Sustained dyskinesia was associated with younger age at diagnosis (HR 0.70 per decade, 95% CI 0.54–0.90), but not OFF burden. Unpredictable OFF was associated with OFF burden (HR 1.26 per point, 95% CI 1.09–1.46), but not consistently with dyskinesia. One-third of patients whose OFF began predictably developed unpredictable OFF within five years, but it often reverted. Device-aided therapy began almost exclusively from unpredictable-OFF states. These findings support overlapping but separable fluctuation and dyskinesia processes, and unpredictable OFF as the severe end of fluctuation. It should be measured separately in clinical trials.

Introduction

Levodopa remains the most effective pharmacological treatment for the motor symptoms of Parkinson's disease (PD), but most patients treated with it eventually develop motor complications: motor fluctuations and dyskinesia(1, 2). With motor fluctuations, the response to each dose becomes shorter and less reliable, and symptoms return between doses as OFF periods. Dyskinesia comprises involuntary movements that usually occur while the medication is working. Both impair quality of life, increase healthcare costs, and are common reasons for starting device-aided therapy(3–7).

Motor complications are not fixed once they appear. They can resolve as well as worsen, and dyskinesia can develop without preceding fluctuations(8). In a population-based incident cohort followed for five years, motor fluctuations were no longer recorded at the end of follow-up in 37% of patients who developed them, and dyskinesia in 49%(9). However, the frequency and direction of movement over time between different combinations of fluctuations and dyskinesia have not been characterised from diagnosis.

Fluctuations and dyskinesia are thought to arise through partly distinct mechanisms. Fluctuations are attributed mainly to loss of presynaptic dopamine storage as nigrostriatal terminals degenerate, whereas dyskinesia is attributed mainly to maladaptive postsynaptic plasticity under pulsatile dopaminergic stimulation(10–12). Presynaptic factors also contribute to dyskinesia: dyskinetic patients show larger levodopa-induced increases in synaptic dopamine, partly released from serotonergic terminals(13–15). Nevertheless, epidemiological studies have generally identified the same determinants for both complications. Younger age at onset, female sex, greater baseline severity and higher levodopa dose have each been associated with both(1, 16–18). In a series of 3,343 patients, younger age at diagnosis and higher levodopa dose were associated with OFF periods, dyskinesia and OFF-state dystonia(1). Each complication has also been reported to predict earlier onset of the other(8, 19).

Most previous studies have measured the onset of both complications from diagnosis or the start of treatment. As both become more likely with increasing disease duration and treatment exposure, a factor associated with one will tend to be associated with the other. It may then mark progression and not a mechanism the two share. When the two complications have been compared directly, their determinants have sometimes differed. In the CamPaIGN incident cohort, higher baseline motor severity was associated with fluctuations, whereas higher baseline Mini-Mental State Examination (MMSE) was associated with dyskinesia(20). The determinants of the two complications have not been compared from fluctuation onset.

Motor fluctuations are not uniform. Early wearing-off is usually predictable: OFF periods occur at expected times before the next dose and can often be managed by adjusting dose timing. With longer disease duration, some patients develop unpredictable, or complex, OFF. This includes sudden OFF periods unrelated to dosing, on–off oscillations, and delayed, partial or absent responses to a dose(21). Because these episodes cannot be anticipated, adjusting dose timing alone may not prevent them. They may require on-demand rescue therapy(22, 23) or continuous device-aided therapy(5). Whether unpredictable OFF represents the severe end of wearing-off or a distinct process with its own determinants has not been established.

We used the sporadic cohort of the Parkinson's Precision Medicine Initiative (PPMI)(24, 25), whose participants were untreated at enrolment and followed for up to 12 years, to address three objectives. First, we characterised how motor complications emerged from diagnosis and how often they resolved as well as worsened. Second, we tested whether fluctuations and dyskinesia represent a single severity spectrum or two separable processes. We did this by timing dyskinesia from each patient's first recorded OFF and by grouping patients according to their joint OFF and dyskinesia trajectories. Third, also measuring from first OFF, we tested whether unpredictable OFF represents a distinct process or the severe end of fluctuation.

Results

Each objective had one primary analysis. For the first, each visit was assigned to one of six motor-complication states, and a continuous-time multistate model estimated the rates of movement between them, accounting for possible intermediate transitions between visits. For the second and third objectives, Cox proportional-hazards models timed from each patient's first recorded OFF tested factors associated with conversion to sustained dyskinesia and unpredictable OFF. A group-based trajectory model provided a second analysis of the relationship between OFF and dyskinesia burden over time. Supplementary Table S1 lists every analysis, its class, its method and where its result appears.

OFF usually preceded dyskinesia, and unpredictable OFF developed in a minority of patients with OFF

The sporadic cohort comprised 1,080 patients who contributed 5,762 study visits, of which 5,639 yielded a classifiable motor-complication state. During follow-up, 63 patients (5.8%) proceeded to device-aided therapy, 115 (10.6%) died and 182 (16.9%) withdrew. The remaining 720 (66.7%) had completed the

study or were continuing at the data cut. The multistate analysis included 5,363 classified assessments from 1,017 patients, while the trajectory analysis included 852 patients contributing 4,618 patient-year observations (Supplementary Fig. S1; Supplementary Table S2). Baseline characteristics are shown in Table 1.

Table 1
Baseline characteristics, observation, and motor-complication profile of the trajectory groups.

Characteristic	Full sporadic cohort (n = 1,080)	Trajectory set (n = 852)[a]	Low-burden (n = 366)	OFF-predominant (n = 250)	Combined (n = 236)	*P*
n	1,080	852	366	250	236	
Age at diagnosis, yr, median (IQR)	63.3 (56.3–69.4)	63.2 (56.2–69.3)	63.9 (57.7–69.8)	63.9 (56.2–69.8)	62.1 (53.6–66.7)	< 0.001
Female, n (%)	371 (34%)	296 (35%)	132 (36%)	75 (30%)	89 (38%)	0.159
Disease duration at enrolment, yr, median (IQR)	0.51 (0.29–0.95)	0.48 (0.27–0.89)	0.54 (0.31-1.00)	0.50 (0.29–0.93)	0.35 (0.21–0.72)[e]	< 0.001
Baseline MDS-UPDRS Part III, median (IQR)	21 (15–28)	21 (15–28)	20 (14–27)	22 (15–32)	22 (17–29)	0.003
Baseline MoCA, median (IQR)	27 (26–29)	27 (26–29)	27 (26–29)	27 (25–29)	27 (26–29)	0.455
Education, yr, median (IQR)	16 (14–18)	16 (14–18)	16 (14–18)	16 (14–18)	16 (14–18)	0.196
PIGD or indeterminate motor phenotype at baseline, n (%)	304 (28%)	228 (27%)	105 (29%)	52 (21%)	71 (30%)	0.039
Follow-up, yr, median[d]	3.9[f]	4.5	3.6	4.5	10.4	< 0.001
Classified assessments, n, median	4[f]	4	4	4	9	< 0.001
Ever OFF, n (%)[b]	-	474 (56%)	0 (0%)	248 (99%)	226 (96%)	-
Ever dyskinesia, n (%)[b]	-	258 (30%)[c]	22 (6%)	0 (0%)	236 (100%)	-
Ever unpredictable OFF, n (%)[b]	-	146 (17%)	0 (0%)	60 (24%)	86 (36%)	-
Peak OFF burden (0–12), median[b]	-	2	0	3	4	-
Peak dyskinesia burden (0–8),	-	0	0	0	2	-

Characteristic	Full sporadic cohort (n = 1,080)	Trajectory set (n = 852)[a]	Low-burden (n = 366)	OFF-predominant (n = 250)	Combined (n = 236)	*P*
median[b]						
Mean LEDD over follow-up, mg, median	-	289	159	300	475	< 0.001

The full sporadic cohort column describes all patients contributing to the analyses reported here; the trajectory set column describes the subset entering the group-based multitrajectory model, which required classified assessments in at least three separate years within 12 years of diagnosis. The low-burden, OFF-predominant and combined groups are those identified by that model. Continuous variables are median (interquartile range), compared by Kruskal–Wallis test; binary variables are n (%), compared by χ^2 test. Disease duration at enrolment is the interval from diagnosis to the earliest analysed visit. Baseline MDS-UPDRS Part III was recorded before any dopaminergic treatment, as all participants were untreated at enrolment. Follow-up is the interval from diagnosis to the last recorded visit, and classified assessments are visits assigned a motor-complication state.

 The trajectory set did not differ materially from the full cohort on any baseline characteristic; it differed only in observed follow-up (median 4.5 versus 3.9 years), as the three-year entry requirement implies.

 Ever OFF, ever dyskinesia and the two peak-burden rows are the inputs on which the trajectory model was estimated, so between-group differences on these measures are definitional and are not tested. Item 4.5 contributes to the OFF-burden input, so the distribution of unpredictable OFF is likewise partly definitional and is reported without a test.

 Ever OFF, ever dyskinesia and ever unpredictable OFF are counted on the trajectory set within 12 years of diagnosis. They are not interchangeable with counts on other sets; for example, Results reports 154 patients reaching unpredictable OFF among 502.

 Median observed follow-up differed almost threefold across groups (3.6, 4.5 and 10.4 years). Group membership therefore partly reflects observation length, and group proportions describe the 12-year window, not fixed subtype frequencies. This is examined in the fixed-window completers analysis (Supplementary Fig. S2) and in the Discussion.

 Patients in the combined group enrolled sooner after diagnosis than those in the other groups (medians 0.35 versus 0.50 and 0.54 years; $P < 0.001$), a difference of 8–10 weeks within a 12-year window.

 Follow-up rows are based on 1,079 patients in the full cohort; one patient has no visit with a usable interval from diagnosis.

IQR, interquartile range; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; OFF, the period of reduced or absent response to dopaminergic medication; PIGD, postural instability and gait difficulty.

With device-aided therapy and death treated as competing events, the cumulative incidence of any OFF reached 50% at 5.3 years and that of dyskinesia at 9.3 years (Fig. 1). Neither OFF-dystonia nor unpredictable OFF reached 50% during follow-up. At 10 years, cumulative incidence was 78.9% for any OFF, 54.8% for dyskinesia, 36.1% for OFF-dystonia, 29.2% for unpredictable OFF (item 4.5 ≥ 2) and 14.0% for the full-fluctuator state (complex OFF with dyskinesia). Counting device-aided therapy and death as competing events only within two years of the last assessment changed incidence little to five years (any OFF 46.3% versus 45.5%). At 10 years, incidence rose to 83.3% for any OFF and 61.4% for dyskinesia, and dyskinesia reached 50% at 8.4 years instead of 9.3.

Of the 154 patients who reached unpredictable OFF within the 12-year window, 67 (43.5%) were already unpredictable at their first recorded OFF. In the remaining 87, unpredictable OFF followed the first predictable OFF by a median of 2.1 years (IQR 1.1–4.0). Among all 340 patients whose first recorded OFF was predictable, 13.5% (95% CI 10.0–18.2) had developed unpredictable OFF two years later and 32.9% (26.8–40.4) five years later, with device-aided therapy and death as competing events. Among patients who reached each, median time from diagnosis was 3.6 years (IQR 2.5–5.3) to first predictable OFF and 5.9 years (3.0–8.7) to first unpredictable OFF. Of the 542 patients who developed any motor complication, OFF was first recorded, alone or with another complication, in 473 (87.3%). Among the 251 patients who developed both OFF and dyskinesia, OFF was recorded first in 137 (54.6%), dyskinesia first in 39 (15.5%), and both at the same visit in 75 (29.9%). Of the 280 patients who developed dyskinesia, 29 (10.4%) never recorded OFF.

Complication states were dynamic, with faster escalation and slower resolution later in disease

Each visit was assigned to one of six motor-complication states from MDS-UPDRS Part IV (Fig. 2a). The states were defined by the presence of OFF (item 4.3 > 0) and dyskinesia (item 4.1 > 0). OFF was classified as complex, or unpredictable, when complexity (item 4.5) was scored 2 or more. Sustained dyskinesia was defined as a dyskinetic state at two or more visits. OFF burden was the sum of time spent OFF and the functional impact of fluctuations (items 4.3 + 4.4; range 0–8). The multistate model included 5,363 classified assessments from 1,017 patients and estimated movement between the six states, with device-aided therapy and death as absorbing states. Three transitions observed five or fewer times were fixed at zero, leaving 38 of the 41 transitions permitted. This reduced model had a lower Akaike information criterion (AIC), which balances fit against model complexity. A likelihood-ratio test gave no evidence that including the three sparse transitions improved model fit (P = 0.77).

Across successive two-year bands of disease duration, the proportion of observed patients who were complication-free declined. The proportion in fluctuation states increased earlier, followed later by an increase in states including dyskinesia (Fig. 2b,c). The number observed fell from 1,020 in the first band to 155 in the last, so the proportions are conditional on observation within each disease-duration band

rather than estimates for the whole cohort. Among visit-pairs in which the recorded state changed, 916 were escalations to a higher-burden state and 365 were de-escalations to a lower-burden state (Fig. 3a,b; Supplementary Table S3). A further 56 were lateral transitions between states of equal burden, and 177 were transitions to device-aided therapy or death. Most observed time was spent in the lower-burden states.

Mean sojourn time, the expected time before leaving a state in any direction, was 3.72 years for the complication-free state and 0.54–1.21 years for the complication states. Complex OFF had the shortest mean sojourn time, at 0.54 years. From the complication-free state, transition to predictable OFF was about four times faster than transition to dyskinesia only (0.206 versus 0.048 per year). Sojourn times include exits to device-aided therapy and death, which accounted for almost one-third of the exit rate from the full-fluctuator state (Supplementary Table S5). Device-aided therapy was initiated at a rate of 0.235 per year from the full-fluctuator state and 0.053 per year from complex OFF, but at effectively zero from the other four states. Two years after occupying the full-fluctuator state, 19.5% of patients remained in it and 21.4% had proceeded to device-aided therapy (Fig. 3c).

De-escalation to a lower-burden state was common. From complex OFF, transition to predictable OFF occurred at a rate of 1.36 per year (95% CI 0.88–2.65), compared with 0.21 per year (0.01–0.40) for progression to the full-fluctuator state. From predictable OFF, return to the complication-free state occurred at 0.33 per year (0.25–0.41; Supplementary Table S5). Two years after occupying the predictable-OFF state, 26.9% of patients were complication-free. Among those who had occupied the complex-OFF state, 49.0% were in predictable OFF or the complication-free state two years later (Fig. 3c). These transitions may reflect medication adjustment or variation in how complications presented between visits and should not be interpreted as evidence of durable improvement.

Baseline factors were at most weakly associated with escalation rate among the 1,003 patients with complete covariate data (Supplementary Table S6). The largest estimate was for female sex (hazard ratio 1.15, 95% CI 0.99–1.33). Each five-year increase in age at diagnosis was not associated with escalation (1.02, 0.98–1.06) but was associated with faster de-escalation (1.16, 1.06–1.25) and faster exit to device-aided therapy or death combined (1.24, 1.15–1.32). Deaths outnumbered starts of device-aided therapy in the multistate set (115 versus 62), so this combined estimate largely reflects mortality and does not indicate earlier device-aided therapy in older patients. Baseline putamen striatal binding ratio was associated with none of the three transition types (escalation 0.99, 0.93–1.08). Higher time-varying levodopa equivalent daily dose (LEDD), per standard deviation of 429 mg, was associated with faster escalation (1.47, 1.34–1.63) and de-escalation (1.16, 1.03–1.33), but not with exit to device-aided therapy or death (1.03, 0.94–1.11).

Transition rates changed with disease duration. Allowing rates to differ before four years, between four and eight years, and beyond eight years improved model fit compared with holding them constant (likelihood-ratio $\chi^2(6) = 160.2$, $P < 0.001$; Supplementary Table S7). Compared with the first four years, escalation was 1.84 times faster between four and eight years and 2.55 times faster beyond eight years,

while de-escalation was slower in both periods (rate ratios 0.67 and 0.77, respectively). Absorption into device-aided therapy or death changed little (1.12 and 1.07). The rates and probabilities reported above therefore summarise the full 12-year window rather than any one disease period.

Sustained dyskinesia was associated with younger age at diagnosis, not OFF burden or LEDD

From each patient's first recorded OFF, younger age at diagnosis was associated with faster conversion to sustained dyskinesia (302 patients, 82 events; Fig. 4a). The hazard fell by 30% for each decade older at diagnosis (HR 0.70, 95% CI 0.54–0.90; P = 0.005). Neither concurrent OFF burden (HR 1.00 per point, 0.86–1.16; P = 0.96) nor LEDD (HR 0.84 per 1,000 mg, 0.47–1.52; P = 0.58) was associated with conversion. There was also no independent association with sex (0.98, 0.61–1.57), baseline motor severity (1.15 per 10 points, 0.89–1.47), baseline putamen striatal binding ratio (1.96, 0.78–4.94) or motor phenotype (0.72, 0.43–1.20). The proportional-hazards assumption was not rejected globally (P = 0.30), although there was evidence of non-proportionality for motor phenotype alone (P = 0.049).

The association with younger age at diagnosis persisted in two sensitivity analyses. First, sustained dyskinesia was dated at the second dyskinetic visit, when it was confirmed and not at the first. This allowed patients whose first dyskinesia was recorded at the same visit as their first OFF to enter the risk set, giving 352 patients and 132 events. The hazard again fell with older age at diagnosis (HR 0.69 per decade, 95% CI 0.57–0.85), while OFF burden (0.97 per point, 0.86–1.10) and LEDD (1.14 per 1,000 mg, 0.78–1.66) remained unassociated with conversion. Baseline motor severity was associated with conversion under this definition (1.32 per 10 points, 1.08–1.60). Second, replacing concurrent OFF burden and LEDD with their totals summed across assessments gave a similar age association (0.67 per decade older, 0.52–0.87), while cumulative OFF burden remained unassociated (0.95, 0.89–1.02). Cumulative LEDD was inversely associated with conversion (HR 0.70 per 1,000 mg summed, 95% CI 0.54–0.91). However, a running total grows with every year a patient remains free of sustained dyskinesia, so this inverse association would arise without any effect of dose.

The available follow-up could not establish whether some patients with OFF were resistant to dyskinesia. This analysis included 399 patients with a recorded OFF state whose dyskinesia had not been recorded at or before their first OFF. From first OFF, the cumulative incidence of sustained dyskinesia was 15.5% at two years, 39.0% at six years and 47.4% at ten years, with device-aided therapy and death treated as competing events. Restricting these competing events to those occurring within two years of the last assessment increased the ten-year estimate to 61.2%. A mixture-cure model estimated that 27.6% of patients would not convert to sustained dyskinesia (95% CI 16.1–43.0) and fitted better than a model in which all patients eventually converted (AIC 515.0 versus 520.8). However, the landmark analysis did not show the decline in conversion expected if a resistant subgroup increasingly predominated among those remaining free of sustained dyskinesia. The probability of conversion over the subsequent two years was 23.5%, 22.0%, 30.0% and 26.7% among patients free of sustained dyskinesia at two, four, six and eight years, respectively. Only 12 patients remained at risk at eight years, limiting the ability to distinguish resistance from delayed conversion. High LEDD exposure did not fully explain who developed sustained

dyskinesia. Of the 196 patients in the trajectory set who reached at least 916 mg, the combined group's median peak LEDD, 44.9% did not develop sustained dyskinesia during follow-up.

The observed association between OFF and dyskinesia severity appeared to reflect whether patients had developed OFF periods, and not their severity. Across all visits, including those without OFF, greater OFF burden, including complexity (items 4.3 + 4.4 + 4.5), was associated with greater dyskinesia severity (OR 1.25 per point, 95% CI 1.17–1.33; P < 0.001). However, visits without OFF occurred earlier in the disease course, when dyskinesia was also less common. Among visits at which OFF was present, fluctuation severity was not associated with dyskinesia severity (OR 1.00, 95% CI 0.90–1.11; P = 0.96; Supplementary Table S8). A separate analysis followed 205 patients from their first recorded dyskinesia, with device-aided therapy and death as competing events. Progression to sustained dyskinesia was associated with age at diagnosis (Gray's P = 0.015) but not with OFF burden at that first dyskinetic visit (P = 0.30).

Dyskinesia distinguished the trajectory groups, while disease stage confounded apparent mutual acceleration

A group-based model fitted jointly to OFF and dyskinesia burden in 852 patients identified three trajectory groups (Fig. 5). Classification within the fitted model was strong (entropy 0.972; lowest group-specific average posterior probability 0.947). In the low-burden group (43%), no patients had recorded OFF and 6% had recorded dyskinesia. The OFF-predominant group (29%) was characterised by OFF without dyskinesia. In the combined group (28%), all patients had recorded dyskinesia and 96% had also recorded OFF.

The trajectory groups should not be interpreted as fixed patient types, because dyskinesia emerges late and their proportions therefore depended on observation length (Table 1, footnote). To quantify this dependence, we examined observed complication status in patients followed throughout fixed windows of 8, 10 and 12 years (n = 203, 162 and 128, respectively; Supplementary Fig. S2). As the window length increased, the proportion remaining complication-free fell from 27% to 8%, while the proportion developing both OFF and sustained dyskinesia rose from 18% to 44%. The share with OFF but no sustained dyskinesia changed little (48%, 48% and 41%).

The full three-group solution was only moderately reproducible across 100 random 80% subsamples (median adjusted Rand index 0.426, range 0.403–1.000). However, the separation of the combined group from the other two groups was reproduced in every refit (adjusted Rand index ≥ 0.96). The instability arose from the division of the remaining patients into the low-burden and OFF-predominant groups. In the 82 refits that differed from the original solution, this division showed almost no agreement with the original classification (adjusted Rand index 0.01). The separation of the combined group was also stable when the trajectory window was changed from 12 years to 10 or 14 years, with 96.2% and 98.0% of patients, respectively, retaining the same classification.

We next examined whether the trajectory groups corresponded to baseline clinical subtypes defined by the Fereshtehnejad criteria(26). The diffuse-malignant subtype, characterised by severe motor and non-motor features and faster progression, was distributed across all three trajectory groups and was not concentrated in the combined group ($\chi^2(4) = 4.6$, $P = 0.33$; Supplementary Table S9).

In the multistate model, each complication was acquired faster when the other was already present. OFF was acquired 3.3 times faster from the dyskinesia-only state than from the complication-free state (0.683 versus 0.206 per year), while dyskinesia was acquired 7.2 times faster from predictable OFF than from the complication-free state (0.345 versus 0.048 per year). However, patients occupying these states were at different stages of disease. Compared with patients in the complication-free state, those in the dyskinesia-only state had a median disease duration 4.8 years longer, and those in predictable OFF a median duration 2.9 years longer (Supplementary Table S10). Because the model estimated a single rate for each transition across the disease course, the rate ratios combine the presence of the other complication with the effect of later disease stage. They therefore do not establish that either complication accelerates the onset of the other.

Together, these findings support overlapping but separable fluctuation and dyskinesia processes, and not fixed patient phenotypes or a single severity spectrum. OFF became increasingly common with disease duration, whereas sustained dyskinesia was associated with younger age at diagnosis but not with OFF burden.

Unpredictable OFF was prospectively associated with greater OFF burden and longer disease duration

For the third objective, we examined whether unpredictable OFF represents a distinct process or the severe end of the fluctuation process. Within the 12-year window, 502 patients developed OFF and had complexity of motor fluctuations assessed using MDS-UPDRS item 4.5 (Supplementary Table S2). Of these, 154 (30.7%) scored 2 or more at least once, 83 (16.5%) scored 3 or more and 37 (7.4%) scored 4. Unpredictable OFF was often not sustained. Of the 103 patients assessed again after first scoring 2 or more, 76 (73.8%) were subsequently recorded in a predictable-OFF state, with or without dyskinesia, or in the complication-free state. This pattern was consistent with the de-escalation observed in the multistate model. The cumulative incidence of an item 4.5 score of 2 or more was 10.0% at five years, 20.3% at eight years and 29.2% at ten years (Fig. 1); for a score of 3 or more, the corresponding estimates were 5.3%, 9.0% and 12.8%.

From each patient's first recorded OFF, greater concurrent OFF burden was associated with faster conversion to unpredictable OFF (326 patients, 87 events; Fig. 4b). Each additional point of OFF burden (items 4.3 + 4.4) increased the hazard by 26% (HR 1.26, 95% CI 1.09–1.46; $P = 0.002$). Concurrent dyskinesia was not associated with conversion (HR 1.21, 95% CI 0.77–1.91; $P = 0.41$). There was also no association with age at diagnosis (0.91 per decade, 0.72–1.16), sex (1.17, 0.74–1.87), baseline motor severity (1.01 per 10 points, 0.79–1.28), baseline putamen striatal binding ratio (0.82, 0.31–2.17), motor phenotype (1.13, 0.69–1.84) or LEDD (0.60 per 1,000 mg, 0.33–1.10; $P = 0.10$). The proportional-hazards assumption was not rejected globally ($P = 0.64$). Graded dyskinesia burden, in place of the binary

indicator, was also not associated with conversion (HR 1.13 per point, 95% CI 0.95–1.35). At the higher unpredictability threshold of item 4.5 ≥ 3, greater OFF burden remained associated with conversion (HR 1.24 per point, 95% CI 1.02–1.51; 46 events among 345 patients).

We next modelled the full range of item 4.5 scores across visits at which OFF was present using a cumulative-link mixed model (Supplementary Table S8, panel a). Because items 4.3, 4.4 and 4.5 are rated at the same visit and describe the same OFF periods, their same-visit association may partly reflect the structure of the scale. At the same visit, each additional point of OFF burden was associated with greater unpredictability (OR 1.98, 95% CI 1.72–2.27). OFF burden at the preceding visit was also associated with greater unpredictability, although the association was smaller (OR 1.20 per point, 95% CI 1.07–1.34; P = 0.0025). In this lagged model, longer disease duration was also associated with greater unpredictability (OR 1.12 per year, 95% CI 1.04–1.20; P = 0.0027). Age at diagnosis, sex, baseline motor severity, striatal binding ratio, motor phenotype and LEDD were not associated with unpredictability (Supplementary Table S8, panel a).

Dyskinesia showed no consistent association with unpredictable OFF. It was not associated with conversion to unpredictable OFF in the Cox model. In the ordinal model, greater dyskinesia burden at the same visit was weakly associated with greater unpredictability (OR 1.17 per point, 95% CI 1.03–1.34; P = 0.02), and the estimate from the preceding visit was similar, although its confidence interval included one (OR 1.14, 95% CI 0.96–1.34; P = 0.14). Similarly, in the multistate model, the rate of developing complex OFF did not differ according to whether dyskinesia was already present (rate ratio 1.10, 95% CI 0.59–2.25; P = 0.81; Supplementary Table S10).

As a positive control, to test whether the ordinal model could detect established clinical associations, we refitted it with dyskinesia severity (item 4.1) as the outcome at the same visits. The dyskinesia burden term was removed, OFF burden also included complexity (items 4.3 + 4.4 + 4.5), and the other fixed effects were unchanged. The model identified the established correlates of greater dyskinesia severity: younger age at diagnosis (OR 0.60 per SD), female sex (1.86), greater baseline motor severity (1.56 per SD), higher LEDD (1.70 per SD) and longer disease duration (1.29 per year), all P ≤ 0.03 (Supplementary Table S8, panel b).

Together, these findings support unpredictable OFF as the severe end of the fluctuation process and not a third process alongside fluctuations and dyskinesia. Greater OFF burden was associated with subsequent unpredictability, which also increased with disease duration. In contrast, the demographic, baseline clinical, imaging and treatment factors associated with dyskinesia were not associated with unpredictable OFF, and dyskinesia itself showed no consistent association.

Discussion

We modelled transitions between motor-complication states in an incident cohort that was untreated at enrolment and followed for up to 12 years. We then examined conversion to sustained dyskinesia and unpredictable OFF from each patient's first recorded OFF rather than from diagnosis. Sustained

dyskinesia was associated with younger age at diagnosis, but not with OFF burden or LEDD. Unpredictable OFF was associated with greater preceding OFF burden and longer disease duration, but showed no consistent association with dyskinesia. Together, these findings support fluctuations and dyskinesia as overlapping but separable processes rather than a single severity spectrum, and unpredictable OFF as the severe end of the fluctuation process rather than a third process(21).

OFF was the first complication, either alone or with another, in 87.3% of patients. Among those who developed both OFF and dyskinesia, dyskinesia was recorded first in only 15.5%. This differs from an earlier cohort treated with levodopa monotherapy before adjuvant therapies were routinely used, in which dyskinesia preceded in 49 of the 54 who developed both(8), suggesting that this earlier ordering may not apply to patients treated today. Patients moved to lower- as well as higher-burden states. De-escalation was fastest from states involving unpredictable OFF and usually reflected a subsequent recording of predictable OFF. The population-based ParkWest cohort also reported reversal of motor complications during the first five years(9). In our cohort, de-escalation continued throughout follow-up but became slower after four years, while escalation became faster.

From each patient's first recorded OFF, younger age at diagnosis was associated with earlier conversion to sustained dyskinesia, with the hazard falling by 30% per decade older. Neither OFF burden nor LEDD was associated with conversion, whether sustained dyskinesia was dated at the first dyskinetic visit or at the second visit, when it was confirmed. Previous cohorts have associated motor complications with daily levodopa dose but not with earlier initiation of levodopa(9, 27). Our analysis tested a narrower association, between LEDD and the timing of sustained dyskinesia once OFF had developed, and found none, although the estimate was imprecise. LEDD was associated with dyskinesia severity at the same visit, as were female sex and greater baseline motor severity (Supplementary Table S8), but only younger age at diagnosis was consistently associated with the timing of sustained dyskinesia.

Many patients remained free of sustained dyskinesia despite high LEDD. Among 196 patients in the trajectory set whose peak LEDD reached at least 916 mg, 44.9% did not develop sustained dyskinesia during follow-up. Whether these patients were resistant to dyskinesia or simply converted more slowly remains uncertain. A mixture-cure model estimated that approximately one-quarter of patients with OFF would not convert. However, the rate of conversion among those remaining free of sustained dyskinesia did not decline over time, as would be expected if a resistant subgroup increasingly predominated. Too few patients had sufficiently long follow-up to distinguish resistance from late conversion.

Each complication has been reported to predict earlier onset of the other(8, 19). In our multistate model, acquisition of the second complication was also faster among patients who already had the first. However, these patients were further into their disease than those without either complication. Because the model estimated a single rate for each transition across the disease course, the higher rates could not be separated from the effect of disease stage. They therefore do not establish that either complication accelerates the onset of the other.

Pulsatile dopaminergic stimulation is thought to contribute to both complications: to wearing-off as presynaptic dopamine storage fails, and to dyskinesia through maladaptive postsynaptic plasticity(10–12). Their presynaptic mechanisms may nevertheless differ. Dyskinesia has been associated with larger levodopa-induced increases in synaptic dopamine, partly released from serotonergic terminals(13–15), whereas fluctuations have been linked to impaired dopamine reuptake(14). If the two complications reflected a single process, greater OFF burden might be expected to predict earlier dyskinesia. Among patients who had already developed OFF, it was not associated with conversion to sustained dyskinesia (HR 1.00 per point, 95% CI 0.86–1.16). At visits with OFF, OFF burden including its complexity was also not associated with dyskinesia severity (OR 1.00, 95% CI 0.90–1.11). As all patients in the conversion model had already developed OFF, the null association applies to OFF severity rather than its presence. Dyskinesia could also occur without previously recorded OFF: 29 of the 280 patients who developed dyskinesia (10.4%) had no recorded OFF during follow-up, although annual assessments may have missed brief or unreported episodes. Items 4.3 and 4.4 capture time spent OFF and its functional impact rather than the dosing interval, absorption and levodopa half-life that determine variation in response between doses.

Previous data-driven classifications have grouped patients by overall severity and rate of progression(26, 28–30). We instead grouped patients by their joint OFF and dyskinesia trajectories. The reproducible division separated the combined group from the low-burden and OFF-predominant groups, with an adjusted Rand index of at least 0.96 in every subsample refit. By contrast, the further division between the low-burden and OFF-predominant groups was unstable. Dyskinesia therefore provided the consistent separation, whereas OFF burden did not define stable groups. This distinction was not simply a consequence of observation time: although the combined group had the longest follow-up, 41% of patients observed throughout 12 years developed OFF without sustained dyskinesia. Nor did the trajectory groups correspond to the subtype with the fastest overall progression, as the diffuse-malignant subtype was distributed across all three groups (P = 0.33)(26).

Unpredictable OFF developed gradually in a minority of patients. Among those whose OFF began predictably, approximately one in seven developed unpredictable OFF within two years and one in three within five years. It was often not sustained: nearly three-quarters of patients assessed again were later recorded with predictable OFF, with or without dyskinesia, or without motor complications. This may reflect treatment adjustment or variation between assessments; medication adjustment was also proposed to explain reversal of early motor complications in the ParkWest cohort(9). Unpredictability is strongly associated with the functional impact of OFF periods, independently of motor severity(31). In this cohort, device-aided therapy was initiated almost exclusively from the two states involving unpredictable OFF.

Unpredictable OFF is generally attributed to a combination of peripheral and central mechanisms. Peripherally, delayed gastric emptying, variable intestinal absorption and competition with dietary amino acids at the intestinal epithelium and blood–brain barrier can alter levodopa pharmacokinetics(21, 32). Centrally, a probabilistic model of vesicular dopamine release reproduced stable responses, wearing-off

and unpredictable on–off fluctuations by varying two presynaptic parameters: dopamine release and reuptake capacity(33). In the model, the response to each dose was shortest in the unpredictable pattern. As nigrostriatal terminals are lost, dopamine release increases and reuptake capacity declines(14). This model provides a mechanistic basis for unpredictable OFF as the severe end of wearing-off rather than a separate process.

Greater OFF burden at the preceding visit and longer disease duration were associated with unpredictable OFF. By contrast, the demographic, baseline clinical, imaging and treatment factors examined showed no association, while the relationship with dyskinesia was weak and confined to measurements made at the same visit. When the same modelling approach was applied to dyskinesia severity, it recovered the expected associations with age at diagnosis, sex, baseline motor severity and LEDD (Supplementary Table S8). The contrast was clearest for LEDD, which was associated with dyskinesia severity (OR 1.70 per standard deviation, 95% CI 1.38–2.08) but not with unpredictability (OR 0.94, 95% CI 0.79–1.13).

PPMI enrolled untreated patients within two years of diagnosis. Participants were younger than patients seen in routine practice, predominantly White, and had good access to specialist care, which may limit generalisability. Enrolment was staggered, so only the earliest participants could be observed as they reached the later complication states. The trajectory-group proportions therefore depend on observation length and should not be interpreted as population estimates. Treatment was summarised using total LEDD rather than individual drug classes. Moreover, LEDD is adjusted in response to motor complications, limiting causal interpretation of its associations with subsequent outcomes.

Both conversion models began at first OFF and therefore could not test whether dyskinesia predicted the subsequent onset of OFF. Only 39 of the 251 patients who developed both complications had dyskinesia recorded first, which was insufficient to model conversion to OFF from first dyskinesia. That direction may require a cohort enriched for young-onset disease, in whom dyskinesia is more likely to occur early. MDS-UPDRS Part IV was assessed by a clinician at approximately annual visits, and unpredictability was measured using a single item. Brief changes between visits may therefore have been missed, and modest associations with unpredictability may not have been detected. Patient diaries or wearable sensors could provide more frequent and direct measurement.

Gastrointestinal autonomic symptoms worsen during the first five years in PPMI(34), but their contribution to unpredictable OFF relative to central dopaminergic loss remains uncertain. Delayed gastric emptying affects when levodopa reaches the circulation(21), whereas presynaptic dopamine release and reuptake determine whether an arriving dose produces a stable response(14, 33). Distinguishing these mechanisms could identify whether treating delayed gastric emptying remains beneficial after unpredictable OFF has developed. OFF-dystonia was not examined in detail, and its relationships with OFF burden, dyskinesia and unpredictability remain to be established.

Motor complications followed a consistent order in most patients. OFF was usually the first motor complication, and dyskinesia came first in only a minority of those who developed both. Patients moved

to lower- as well as higher-burden states, particularly through transitions from unpredictable to predictable OFF. From each patient's first recorded OFF, sustained dyskinesia was associated with younger age at diagnosis but not with OFF burden or LEDD. These findings support fluctuations and dyskinesia as overlapping but separable processes, with unpredictable OFF representing the severe end of the fluctuation process. Fluctuation severity should therefore not be assumed to predict impending dyskinesia. Total OFF time, a common primary endpoint in trials of treatments for motor fluctuations(35, 36), does not distinguish predictable wearing-off from the unpredictable OFF that develops in a minority of patients. This distinction is clinically important because unpredictable OFF was closely related to the functional impact of OFF(31) and to progression to device-aided therapy. It should be reported separately in clinical trials, and its frequent reversion should be considered when interpreting treatment effects in uncontrolled studies.

Methods

Study population and design

We analysed the sporadic cohort of PPMI, an international, multicentre, prospective observational study of early Parkinson's disease(24, 25). Eligibility required a clinical diagnosis within two years before screening, Hoehn and Yahr stage I or II, and no current treatment for Parkinson's disease. Participants had no known pathogenic variant in *LRRK2*, *GBA1*, *SNCA*, *PRKN* or *PINK1*. We excluded the Normosmic PD cohort because it permits a disease duration of up to seven years.

The multistate model required at least two observed states per patient; device-aided therapy and death each counted as an observed absorbing state. The trajectory model required classifiable MDS-UPDRS Part IV assessments in at least three separate years within 12 years of diagnosis (Supplementary Fig. S1; Supplementary Table S2).

Clinical assessments and motor-complication states

MDS-UPDRS Part IV (motor complications) was recorded at each in-person visit(37). Baseline motor severity was measured using the Part III score recorded before treatment began. Levodopa equivalent daily dose (LEDD) was calculated using standard conversion factors(38). Disease duration was measured in years from the date of diagnosis.

Each visit was assigned to one of six mutually exclusive motor-complication states (Fig. 2a). OFF was present when time spent OFF (item 4.3) was scored above zero, and dyskinesia when time with dyskinesia (item 4.1) was scored above zero. OFF was classified as complex, or unpredictable, when the complexity score (item 4.5) was 2 or more. A score of 2 indicates that OFF periods are predictable no more than 75% of the time, whereas a score of 1 indicates that they are predictable all or almost all of the time. Classification as complication-free also required the absence of OFF-dystonia (item 4.6). OFF-dystonia did not otherwise define a state, and visits with OFF-dystonia but neither OFF nor dyskinesia were left unclassified.

MDS-UPDRS Part IV was not completed before dopaminergic treatment began. Visits at which the absence of treatment was confirmed were therefore assigned to the complication-free state. Treated visits with a blank Part IV form, and visits at which treatment status was unknown, were left unclassified.

OFF burden was the sum of time spent OFF and the functional impact of fluctuations (items 4.3 + 4.4; range 0–8). Dyskinesia burden was the sum of time with dyskinesia and its functional impact (items 4.1 + 4.2; range 0–8). These definitions were used unless stated otherwise. Device-aided therapy and death were treated as absorbing states, meaning that no subsequent transitions were modelled. Device-aided therapy comprised deep brain stimulation, continuous infusion therapy or a lesional procedure. Visits on or after the start of device-aided therapy were excluded from analyses of the six living states.

Multistate transition model

We fitted a continuous-time multistate Markov model using msm, with disease duration as the time scale(39). States recorded at study visits were treated as interval-censored, whereas device-aided therapy and death were treated as exactly timed. The initial model permitted 41 transitions: every transition between the six living states and every transition from a living to an absorbing state, except dyskinesia only to device-aided therapy, which was never observed. We fixed the three living-state transitions observed five or fewer times at zero (Supplementary Table S5), leaving 38 transitions in the reduced model. The initial and reduced models were compared using the Akaike information criterion and a likelihood-ratio test. Transition intensities are reported with 95% confidence intervals from a patient-level bootstrap (B = 200), because sparse transitions made the observed information matrix nearly singular.

States were ordered by burden. The fluctuation dimension contributed 0 points for no OFF, 1 for predictable OFF and 2 for complex OFF; dyskinesia added one point. Total burden therefore ranged from 0 for the complication-free state to 3 for the full-fluctuator state (Fig. 2a). Movement to a higher-burden state was defined as escalation, movement to a lower-burden state as de-escalation or resolution, and movement between states of equal burden as lateral.

Mean sojourn time was calculated as the reciprocal of the total exit intensity and included exits to device-aided therapy and death. Using the matrix exponential, we converted transition intensities to the probabilities of occupying each state two and five years later. These probabilities allow for movement through intermediate states (Fig. 3c,d).

We also calculated observed transition rates from consecutive assessments as transitions per person-year in the origin state. In the primary calculation, time in the origin state extended to the midpoint of an interval containing a transition; a sensitivity calculation assigned the full interval to the origin state (Supplementary Table S3).

We examined three time-fixed covariates (age at diagnosis, sex and baseline putamen striatal binding ratio) and one time-varying covariate (LEDD). Age at diagnosis was centred at 60 years and scaled per

five years, and striatal binding ratio was scaled per standard deviation. LEDD was carried forward between assessments, with a value of zero before the first recorded dose. It was winsorised at the 99th percentile and standardised, with effects expressed per standard deviation (429 mg), because raw milligram values caused numerical overflow during intensity calculation.

The data did not support estimation of a separate covariate effect for every transition. We therefore grouped these effects into three transition families: escalation, de-escalation and absorption, with absorption comprising device-aided therapy and death. Lateral transitions were included in the escalation family, producing 12 hazard ratios. They accounted for 54 of the 962 transitions in this family. The joint model was weakly identified using the default optimiser. We therefore estimated covariate effects using bobyqa, with baseline intensities fixed at their maximum-likelihood estimates. Confidence intervals are percentile intervals from a patient-level bootstrap (B = 200).

The baseline model assumed that transition intensities remained constant across the disease course. To test this assumption, we divided disease duration into three epochs (before four years, four to eight years and beyond eight years) and estimated a multiplicative epoch effect for each transition family. Epoch was entered as a time-varying covariate. Because msm holds covariates constant between observations, each patient entered a new epoch at the first visit after the corresponding cut point. The piecewise model was compared with the time-homogeneous model using a likelihood-ratio test with six degrees of freedom. Its observed information matrix was not invertible, so epoch hazard ratios are reported as point estimates without confidence intervals (Supplementary Table S7).

Cumulative incidence and onset timing

We estimated cumulative incidence from diagnosis to first OFF, dyskinesia, OFF-dystonia and unpredictable OFF, using item 4.5 thresholds of ≥ 2 and ≥ 3. We used the Aalen–Johansen estimator in survival, with device-aided therapy and death treated as competing events, and we report the time at which each curve reached 50%. Device-aided therapy and death could be recorded after the last clinical assessment. A sensitivity analysis therefore counted them as competing events only within two years of that assessment, and otherwise censored follow-up there.

The order of complication onset and the interval from first predictable to first unpredictable OFF were derived from the same onset times. Complications first recorded at the same visit were classified as coincident. Within the 12-year window, we recorded each patient's highest item 4.5 score across assessments at which OFF was present. Among patients assessed again after first reaching item 4.5 ≥ 2, reversion was defined as any later assessment showing predictable OFF, with or without dyskinesia, or no motor complications. Among patients whose first recorded OFF was predictable, we also estimated cumulative incidence of unpredictable OFF from first OFF, using the same competing events.

Conversion models from each patient's first OFF

We fitted two Cox proportional-hazards models with time measured from each patient's first recorded OFF. The models shared the same time-fixed covariates and rules for updating time-varying covariates. Time-fixed covariates were age at diagnosis, per decade; sex; baseline motor severity, per 10 points; baseline putamen striatal binding ratio, per unit; and motor phenotype (tremor-dominant versus postural instability and gait difficulty or indeterminate). For each interval, time-varying covariates were taken from the most recent assessment at or before its start and before device-aided therapy. LEDD was expressed per 1,000 mg and burden measures per point. Patients were censored at device-aided therapy, death or their last assessment. The proportional-hazards assumption was assessed using scaled Schoenfeld residuals. The two models had the same time origin but different risk sets (Supplementary Table S2).

Conversion to sustained dyskinesia. The event was sustained dyskinesia, defined as a dyskinetic state at two or more visits and dated at the first of these visits. Time-varying covariates were OFF burden and LEDD. We excluded patients whose dyskinesia was recorded before their first OFF, those who had no observed dyskinesia-free time after first OFF, and those with incomplete covariate data. Dating the event at the first dyskinetic visit requires a later visit to confirm that dyskinesia was sustained. We therefore refitted the model with the event dated at the second dyskinetic visit. A further sensitivity analysis replaced current OFF burden and LEDD with cumulative values summed across assessments from first OFF.

Conversion to unpredictable OFF. The event was the first OFF-positive visit at which item 4.5 was scored 2 or more. Because item 4.5 is rated only when OFF is present, unpredictable OFF could not precede first OFF. Time-varying covariates were dyskinesia status, OFF burden and LEDD. We excluded patients who already had unpredictable OFF at their first recorded OFF because they had no observed predictable-OFF period. Patients whose dyskinesia preceded first OFF were retained, with dyskinesia status entered as a time-varying covariate from the model origin. Sensitivity analyses replaced the binary dyskinesia indicator with dyskinesia burden and raised the unpredictable-OFF threshold to an item 4.5 score of 3 or more.

Ordinal models of unpredictability and the dyskinesia positive control

We modelled the full range of item 4.5 scores (0–4) across OFF-positive visits using a cumulative-link mixed model in ordinal, with a random intercept for each patient. Fixed effects were same-visit OFF burden and dyskinesia burden, the five baseline covariates used in the conversion models, LEDD and disease duration. Age at diagnosis, baseline motor severity and striatal binding ratio were standardised. Missing LEDD was carried forward from the previous assessment or, when no earlier value was available, carried backward from the next assessment. LEDD was then winsorised at the 99th percentile and standardised, with effects expressed per standard deviation (395 mg). Disease duration was expressed per year and both burden measures per point. The contribution of dyskinesia burden was tested using a likelihood-ratio test against the model without it.

Items 4.3–4.5 are rated by the same clinician at the same visit and describe the same OFF periods. Their same-visit association may therefore partly reflect the structure of the scale. To examine temporal

associations, we refitted the model with OFF and dyskinesia burden taken from the preceding visit.

As a positive control, we refitted the ordinal model with dyskinesia severity (item 4.1) as the outcome at the same visits. The random intercept and other fixed effects were unchanged, the dyskinesia-burden term was omitted, and OFF burden included complexity (items 4.3 + 4.4 + 4.5). We fitted this control model both across all visits and after restriction to OFF-positive visits. The all-visit model captured differences associated with the presence of OFF, whereas the OFF-positive model examined differences associated with its severity.

Group-based multitrajectory model

We fitted a group-based multitrajectory model using gbmt(40) to OFF burden including complexity (items 4.3 + 4.4 + 4.5; range 0–12) and dyskinesia burden, independently of the six motor-complication states. Complexity was included in the OFF composite because item 4.5 is defined only when OFF is present. Visits before device-aided therapy and within 12 years of diagnosis were assigned to the nearest whole year of disease duration. Values from multiple visits assigned to the same year were averaged. Trajectories were modelled as quadratic functions of disease duration, and both burden measures were retained on their original scales without within-patient normalisation. No covariates were included in the model; baseline characteristics and clinical subtype were compared across the resulting groups.

We fitted models with one to five groups. Eligible solutions required every group to contain at least 5% of patients and to have an average posterior probability of at least 0.70. Among these, we selected the solution with the lowest Bayesian information criterion and refitted it using 25 random starting values. Groups were labelled according to their complication profiles as low-burden, OFF-predominant and combined. The 12-year window was pre-specified because motor complications have no natural endpoint and stable quadratic trajectories across groups require a common time horizon.

Sensitivity and falsification analyses

Supplementary Table S1 classifies each analysis and identifies the alternative explanation addressed by each falsification analysis.

Mixture-cure and landmark analyses.

Among patients with OFF who had no recorded dyskinesia at or before their first recorded OFF, we estimated cumulative incidence of sustained dyskinesia from first OFF using both competing-event conventions described above. A mixture-cure model with Weibull latency estimated the proportion who would not convert to sustained dyskinesia. We compared this model, using the Akaike information criterion, with a Weibull model in which all patients were assumed eventually to convert. At landmarks two, four, six and eight years after first OFF, we estimated the probability of conversion over the subsequent two years among patients who remained free of sustained dyskinesia. Both analyses censored patients without sustained dyskinesia at their last assessment.

Peak-dose comparison.

Among patients in the trajectory set whose peak LEDD reached or exceeded the median peak LEDD of the combined group, we calculated the proportion who did not develop sustained dyskinesia during follow-up.

Fixed-window completers.

For each fixed window of 8, 10 or 12 years, eligible patients had a classified assessment at or after the end of the window and classified assessments in at least three separate years within it. Within each window, we tabulated observed complication status, defined by any OFF and by sustained dyskinesia (dyskinesia recorded in at least two separate years), without fitting a trajectory model. We also refitted the trajectory model using 8- and 10-year windows and compared group assignments with those from the 12-year full-cohort model using the adjusted Rand index.

Dyskinesia persistence.

Among patients with dyskinesia recorded within the 12-year window, we estimated cumulative incidence of sustained dyskinesia from the first dyskinetic visit, with device-aided therapy and death treated as competing events. We compared cumulative incidence between patients above and below the median OFF burden at that visit, using items 4.3 + 4.4 + 4.5. As a positive control, we compared tertiles of age at diagnosis. Both comparisons used Gray's test.

Baseline subtype classification.

We classified each patient at baseline according to the Fereshtehnejad criteria(26). These criteria combine a motor composite with three non-motor domains: probable REM sleep behaviour disorder (RBD), autonomic dysfunction and cognition. The motor composite was the mean of the raw MDS-UPDRS Part II, OFF-state Part III and postural instability and gait difficulty scores. Probable RBD was assessed using the RBD Screening Questionnaire, and autonomic dysfunction using the SCOPA-AUT total score. Cognition was represented by a six-test, externally normed neuropsychological composite; the Montreal Cognitive Assessment was used in a sensitivity analysis(41). Each domain was dichotomised at the 75th percentile of the complete-case sporadic cohort at baseline. We compared subtype with trajectory group using the chi-square test under both definitions of cognition.

Trajectory-model stability.

We refitted the three-group model in 100 random 80% subsamples drawn without replacement. For patients included in each subsample, we compared their group assignments with those from the full-cohort model using the adjusted Rand index. We then decomposed agreement into two components: separation of the combined group from the other two groups, and division of the remaining patients into the low-burden and OFF-predominant groups. Groups were identified using the same trajectory-profile

rule in every refit. We also refitted the model using 10- and 14-year windows and calculated the proportion of patients who remained on the same side of the combined-group division.

Paired-intensity comparisons.

Within the multistate model, we compared pairs of transition intensities that differed only according to whether the other complication was already present. Rate ratios are reported with 95% confidence intervals and two-sided P values derived from the transition-intensity bootstrap. Supplementary Table S10 gives the three paired comparisons and the median disease duration at which each origin state was occupied.

Statistics and reproducibility

Analyses used R (version 4.5.3) with msm, minqa, numDeriv, survival, cmprsk, flexsurv, flexsurvcure, ordinal and gbmt. Continuous variables are summarised as median (interquartile range) and categorical variables as n (%). Groups were compared by the Kruskal–Wallis test for continuous variables, the chi-square test for categorical variables and Gray's test for cumulative incidence. Tests were two-sided at $\alpha = 0.05$, and P values are reported exactly or as $P < 0.001$.

Each objective had one primary analysis. The others were descriptive, sensitivity, falsification or positive-control analyses (Supplementary Table S1), so no adjustment for multiple comparisons was made.

Apart from carrying LEDD forward between assessments, missing data were not imputed. Each model used complete cases, and Supplementary Table S2 gives the patients contributing to each analysis. Large language model tools (Anthropic Claude) assisted with analysis-code development and manuscript drafting. All analyses were designed, executed, verified and interpreted by the authors, who take responsibility for the content.

Declarations

Ethics and consent

The PPMI 2.0 study was approved by the London – City & East Research Ethics Committee (reference 20/LO/0900) on 7 September 2020, and all participating sites obtained ethical approval. The research was conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent. The study is registered on ClinicalTrials.gov (NCT01141023).

Data and code availability

Data used in this article were obtained on 26 June 2026 (curated data cut of 11 May 2026) from the PPMI database (www.ppmi-info.org/access-data-specimens/download-data), RRID:SCR_006431, and comprised PPMI Tier 1 clinical data. The data are available to qualified researchers from PPMI on

application, under the PPMI data use agreement (www.ppmi-info.org). The authors are not permitted to share them. Statistical analysis code is available on Zenodo at 10.5281/zenodo.23645833.

Competing Interests

The authors declare no competing interests.

Author Contribution

DL and NP conceptualised the study with MRB. DL designed the methodology, curated the data, performed the formal analysis, produced the figures and wrote the original draft. DL and NP are the principal investigators of the Newcastle PPMI site. DL, RI, SS, VF, MM, DG and NP carried out study procedures and data collection, and RI, VF, MM and DG coordinated the study at the site. SS checked the data. MRB and NP supervised the work. DL, MRB and NP reviewed and edited all drafts. DL acquired open-access funding through the ASAP programme. All authors read and approved the final manuscript. DL is the guarantor of this work.

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Protocol information for The Parkinson's Precision Medicine Initiative (PPMI) Clinical - Establishing a Deeply Phenotyped PD Cohort can be found on protocols.io or by following this link: https://dx.doi.org/10.17504/protocols.io.n92ldmw6ol5b/v2.

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Data Availability

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References

1. Gandhi SE, Zerenner T, Nodehi A, Lawton MA, Marshall V, Al-Hajraf F, et al. Motor Complications in Parkinson's Disease: Results from 3343 Patients Followed for up to 12 Years. Movement Disorders Clinical Practice. 2024;n/a(n/a).
2. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord. 2001;16(3):448–58.
3. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord. 2005;20(2):224–30.
4. Péchevis M, Clarke CE, Vieregge P, Khoshnood B, Deschaseaux-Voinet C, Berdeaux G, et al. Effects of dyskinesias in Parkinson's disease on quality of life and health-related costs: a prospective European study. Eur J Neurol. 2005;12(12):956–63.
5. Antonini A, Stoessl AJ, Kleinman LS, Skalicky AM, Marshall TS, Sail KR, et al. Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach. Curr Med Res Opin. 2018;34(12):2063–73.
6. Ledingham D, Sathyanarayana S, Stewart CB, Iredale R, Foster V, Galley D, et al. Tracking Motor Progression and Device-Aided Therapy Eligibility in Parkinson's Disease. Ann Clin Transl Neurol. 2025.
7. Ledingham D, Stewart CB, Sathyanarayana S, Foster V, Iredale R, Galley D, et al. Timing of device-aided therapy initiation in Parkinson's disease: reference estimates for healthcare planning and biological heterogeneity. Clinical Parkinsonism & Related Disorders. 2026;14:100458.
8. Mazzella L, Yahr MD, Marinelli L, Huang N, Moshier E, Di Rocco A. Dyskinesias predict the onset of motor response fluctuations in patients with Parkinson's disease on L-dopa monotherapy. Parkinsonism Relat Disord. 2005;11(3):151–5.
9. Bjornestad A, Forsaa EB, Pedersen KF, Tysnes OB, Larsen JP, Alves G. Risk and course of motor complications in a population-based incident Parkinson's disease cohort. Parkinsonism Relat Disord. 2016;22:48–53.
10. Olanow CW, Obeso JA, Stocchi F. Drug insight: Continuous dopaminergic stimulation in the treatment of Parkinson's disease. Nat Clin Pract Neurol. 2006;2(7):382–92.

11. Calabresi P, Di Filippo M, Ghiglieri V, Tambasco N, Picconi B. Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. Lancet Neurol. 2010;9(11):1106–17.
12. Cenci MA. Dopamine dysregulation of movement control in L-DOPA-induced dyskinesia. Trends Neurosci. 2007;30(5):236–43.
13. Pavese N, Evans AH, Tai YF, Hotton G, Brooks DJ, Lees AJ, et al. Clinical correlates of levodopa-induced dopamine release in Parkinson disease. Neurology. 2006;67(9):1612–7.
14. de la Fuente-Fernández R, Sossi V, Huang Z, Furtado S, Lu J-Q, Calne DB, et al. Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. Brain. 2004;127(12):2747–54.
15. Politis M, Wu K, Loane C, Brooks DJ, Kiferle L, Turkheimer FE, et al. Serotonergic mechanisms responsible for levodopa-induced dyskinesias in Parkinson's disease patients. The Journal of Clinical Investigation. 2014;124(3):1340–9.
16. Kelly MJ, Lawton MA, Baig F, Ruffmann C, Barber TR, Lo C, et al. Predictors of motor complications in early Parkinson's disease: A prospective cohort study. Mov Disord. 2019;34(8):1174–83.
17. Warren Olanow C, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, et al. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov Disord. 2013;28(8):1064–71.
18. Pellecchia MT, Picillo M, Russillo MC, Amboni M, Arabia G, Avanzino L, et al. Gender Is the Main Predictor of Wearing-Off and Dyskinesia in Levodopa-Naïve Patients with Parkinson's Disease. Mov Disord Clin Pract. 2025;12(11):1774–83.
19. Hauser RA, McDermott MP, Messing S. Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. Arch Neurol. 2006;63(12):1756–60.
20. Kim HJ, Mason S, Foltynie T, Winder-Rhodes S, Barker RA, Williams-Gray CH. Motor complications in Parkinson's disease: 13-year follow-up of the CamPaIGN cohort. Mov Disord. 2020;35(1):185–90.
21. Chou KL, Stacy M, Simuni T, Miyasaki J, Oertel WH, Sethi K, et al. The spectrum of "off" in Parkinson's disease: What have we learned over 40 years? Parkinsonism Relat Disord. 2018;51:9–16.
22. LeWitt PA, Hauser RA, Pahwa R, Isaacson SH, Fernandez HH, Lew M, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Neurol. 2019;18(2):145–54.
23. Olanow CW, Factor SA, Espay AJ, Hauser RA, Shill HA, Isaacson S, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Neurology. 2020;19(2):135–44.
24. Marek K, Chowdhury S, Tropea TF, the Parkinson's Progression Markers I. From Parkinson's Progression Markers Initiative to Parkinson's Precision Medicine Initiative: Still PPMI. Annals of Neurology. 2026;n/a(n/a).
25. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol. 2011;95(4):629–35.

26. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. Brain. 2017;140(7):1959–76.
27. Cilia R, Akpalu A, Sarfo FS, Cham M, Amboni M, Cereda E, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain. 2014;137(Pt 10):2731–42.
28. Dadu A, Satone V, Kaur R, Hashemi SH, Leonard H, Iwaki H, et al. Identification and prediction of Parkinson's disease subtypes and progression using machine learning in two cohorts. NPJ Parkinsons Dis. 2022;8(1):172.
29. Severson KA, Chahine LM, Smolensky LA, Dhuliawala M, Frasier M, Ng K, et al. Discovery of Parkinson's disease states and disease progression modelling: a longitudinal data study using machine learning. The Lancet Digital Health. 2021;3(9):e555-e64.
30. Hähnel T, Raschka T, Sapienza S, Klucken J, Glaab E, Corvol JC, et al. Progression subtypes in Parkinson's disease identified by a data-driven multi cohort analysis. NPJ Parkinsons Dis. 2024;10(1):95.
31. Ledingham D, Sathyanarayana S, Iredale R, Stewart CB, Foster V, Galley D, et al. Beyond motor fluctuations: Understanding the clinical correlates of OFF burden in Parkinson's disease. Journal of Parkinson’s Disease. 2026:1877718X261442857.
32. Regensburger M, Csoti I, Jost WH, Kohl Z, Lorenzl S, Pedrosa DJ, et al. Motor and non-motor fluctuations in Parkinson's disease: the knowns and unknowns of current therapeutic approaches. J Neural Transm (Vienna). 2026;133(2):309–24.
33. de la Fuente-Fernández R, Schulzer M, Mak E, Calne DB, Stoessl AJ. Presynaptic mechanisms of motor fluctuations in Parkinson's disease: a probabilistic model. Brain. 2004;127(Pt 4):888–99.
34. Stewart CB, Ledingham D, Foster VK, Anderson KN, Sathyanarayana S, Galley D, et al. The longitudinal progression of autonomic dysfunction in Parkinson's disease: A 7-year study. Front Neurol. 2023;14:1155669.
35. Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol. 2000;23(2):75–81.
36. LeWitt PA. The persisting puzzle of OFF time in advanced Parkinson’s disease. Brain. 2026;149(4):1137–43.
37. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Movement Disorders. 2008;23(15):2129–70.
38. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649–53.
39. Jackson C. Multi-State Models for Panel Data: The msm Package for R. Journal of Statistical Software. 2011;38(8):1–28.

40. Magrini A. Assessment of agricultural sustainability in European Union countries: a group-based multivariate trajectory approach. AStA Advances in Statistical Analysis. 2022;106(4):673–703.
41. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–9.

Figures

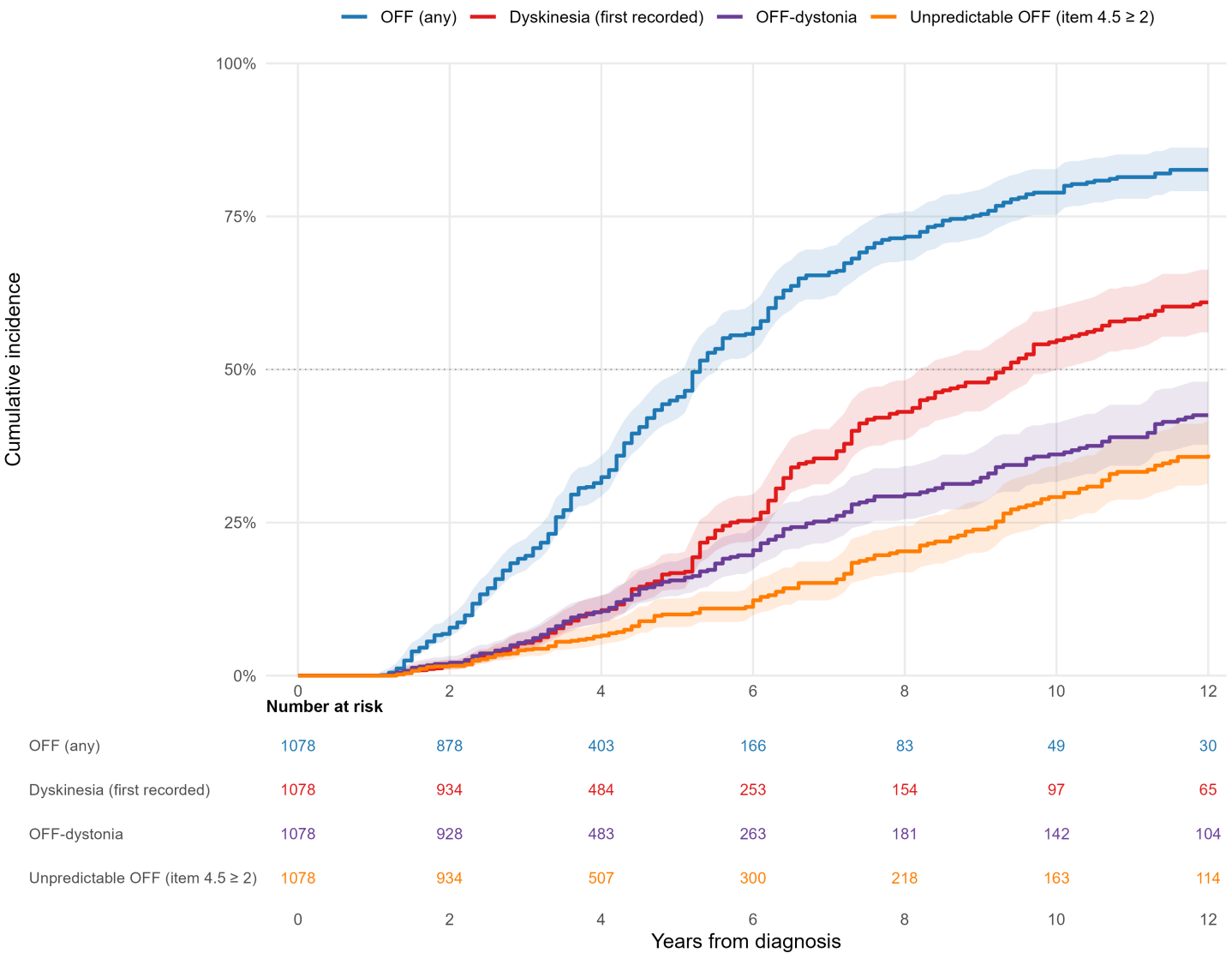

Figure 1

Emergence of motor complications from diagnosis.

Cumulative incidence from diagnosis in the 1,078 patients with at least one rated MDS-UPDRS Part IV assessment. The endpoints are first OFF (item 4.3 > 0), first dyskinesia (item 4.1 > 0), first OFF-dystonia (item 4.6 > 0) and first unpredictable OFF (item 4.5 ≥ 2). Device-aided therapy and death were treated as

competing events, so each curve estimates the probability of reaching that complication before either. Dyskinesia is dated at its first recorded occurrence. The conversion analysis of Fig. 4a uses sustained dyskinesia, a dyskinetic state at two or more visits, and is not comparable with this curve. Shaded bands are 95% confidence intervals and the dotted line marks 50%. Curves end at 12 years, the pre-specified analysis window, and the number at risk is shown beneath the panel. Cumulative incidence reached 50% at 5.3 years for any OFF and 9.3 years for dyskinesia.

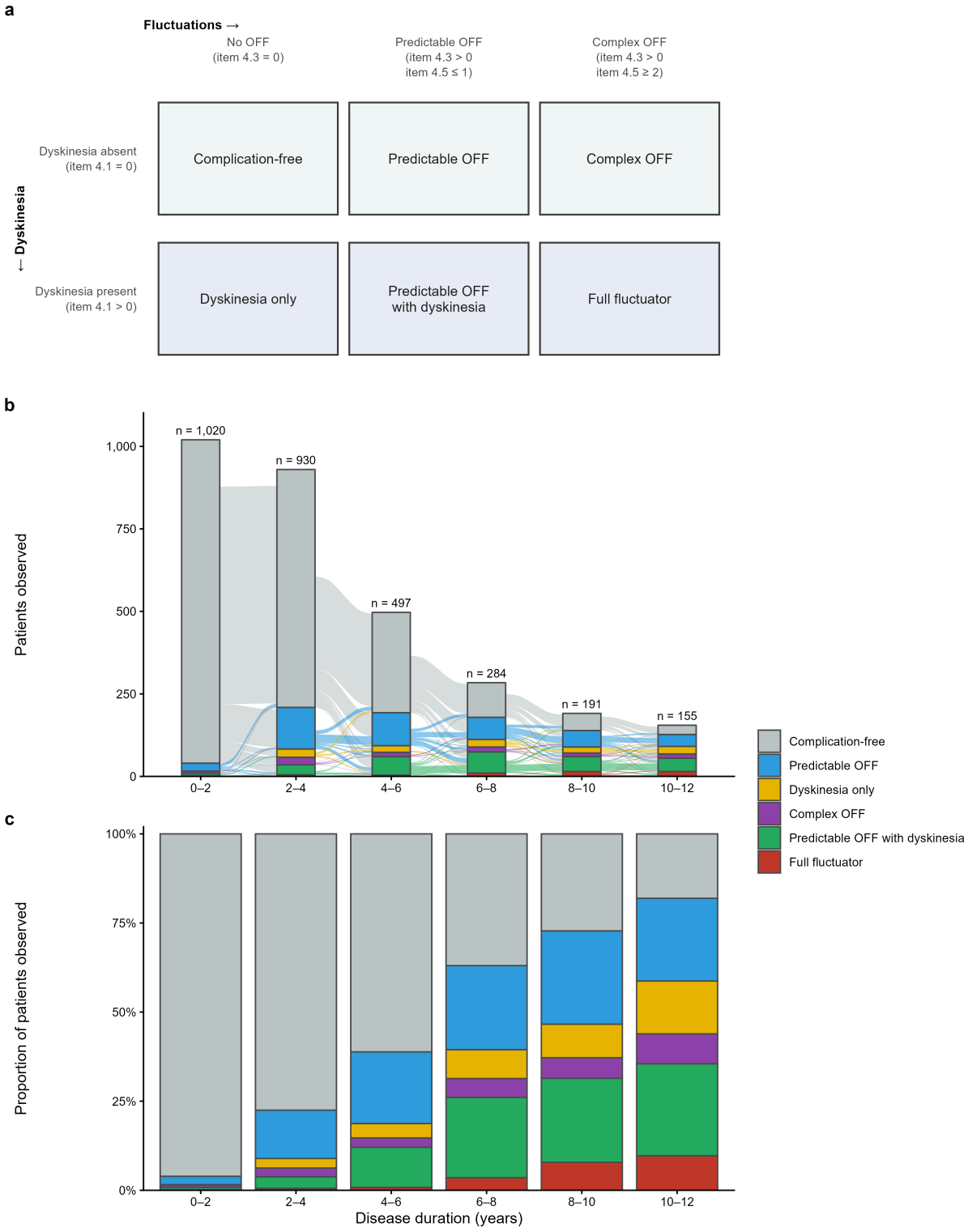

Figure 2

Motor complication states and their occupancy across disease duration.

a, The six mutually exclusive motor-complication states, assigned at each visit from MDS-UPDRS Part IV. OFF is present when time spent OFF (item 4.3) is scored above zero. Complex, or unpredictable, OFF requires a complexity score (item 4.5) of 2 or more; otherwise OFF is predictable. Dyskinesia is present when time with dyskinesia (item 4.1) is scored above zero. The complication-free state also requires no OFF-dystonia (item 4.6), and visits confirmed as untreated were assigned to it. Visits with OFF-dystonia but neither OFF nor dyskinesia were left unclassified. Device-aided therapy and death are two further absorbing states, giving the eight states used for transition modelling (Fig. 3).

b, State of each patient observed alive and before device-aided therapy, in two-year bands of disease duration. Bar height and flow width are proportional to the number of patients, and flows show movement between adjacent bands. Each patient contributes at most one state per band, taken from the visit nearest the band midpoint.

c, The same states as a proportion of the patients observed in each band. Bands run from 0–2 to 10–12 years, the analysis window. The number observed fell from 1,020 in the first band to 155 in the last, so the proportions are conditional on continued observation and are not cohort prevalences. Patients who left through device-aided therapy, death, withdrawal or loss to follow-up are not shown (Supplementary Fig. S1b).

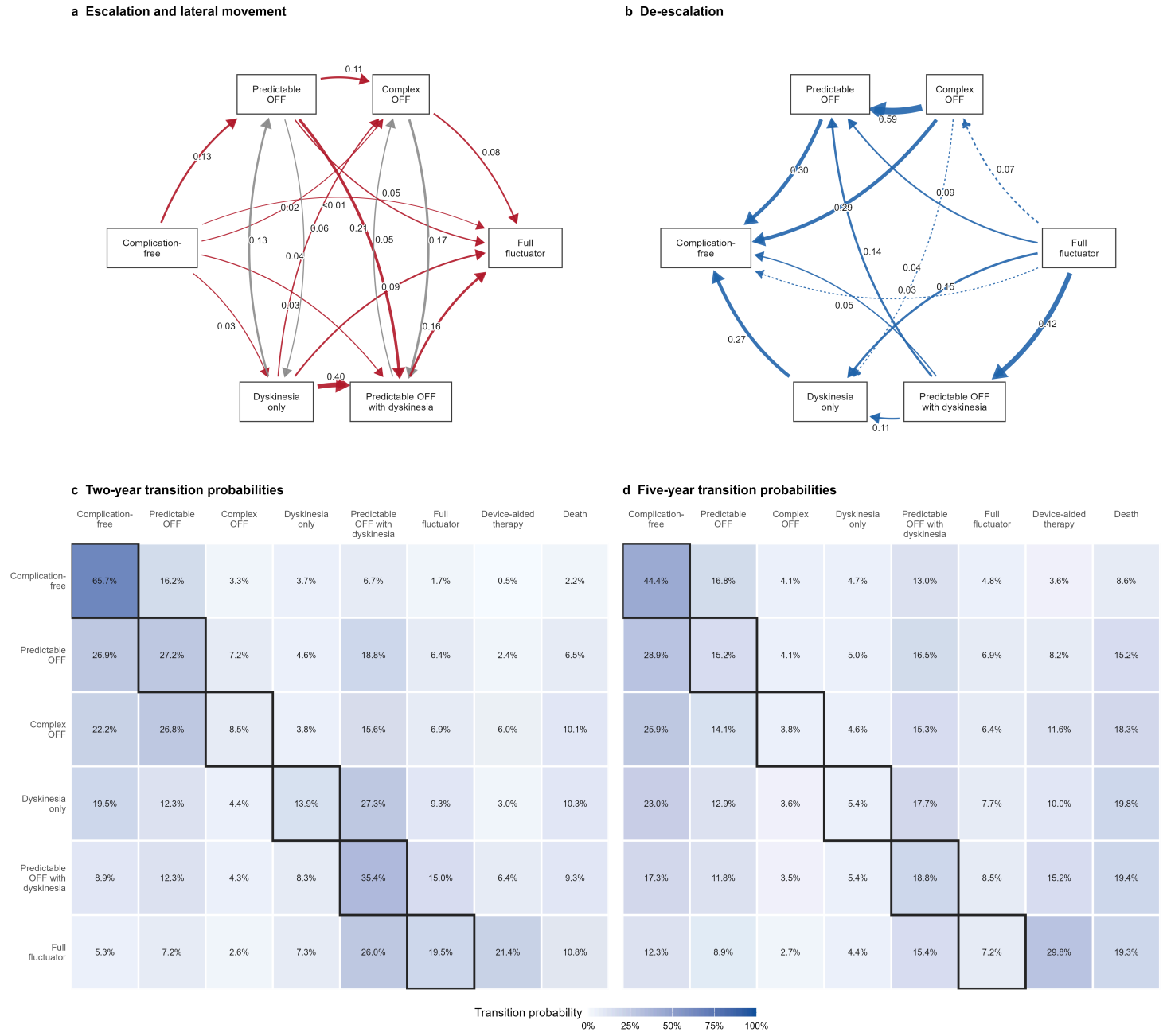

Figure 3

The transition structure of motor-complication states.

a,b, Observed movement between the six living motor-complication states defined in Fig. 2a: escalation and lateral movement (a) and de-escalation (b). Nodes are positioned by burden, which increases from left to right, with dyskinesia-positive states on the lower row. Node positions and arrow widths share one scale across both panels. Each rate is the number of moves observed between consecutive assessments divided by the person-years spent in the origin state, using the midpoint exposure rule. Rates are conditional on occupying the origin state and are not cohort proportions. Movement that occurred and reversed between two assessments is not observable. Red, escalation to a higher-burden state; grey, lateral movement between states of equal burden; blue, de-escalation. Dashed arcs were

observed five or fewer times and were fixed at zero in the multistate model. Exits to device-aided therapy (*n* = 62) and death (*n* = 115) are not drawn. Rates under the full-interval rule are given in Supplementary Table S3, one-year first-move probabilities in Supplementary Table S4 and the fitted intensities in Supplementary Table S5.

c,d, Probabilities of occupying each state two years (c) and five years (d) later, from the fitted multistate model and allowing for movement through intermediate states. Rows give the state occupied at a given time and columns the state occupied later; each row sums to 100%. Outlined diagonal cells give the probability of occupying the same state, including patients who left and returned. Both panels share one colour scale. Both matrices assume that the next move depends only on the current state and that transition rates are constant across the 12-year window. Rates in fact changed with disease duration (Supplementary Table S7), and the effect of this accumulates over longer intervals, so the five-year probabilities are less certain than the two-year probabilities.

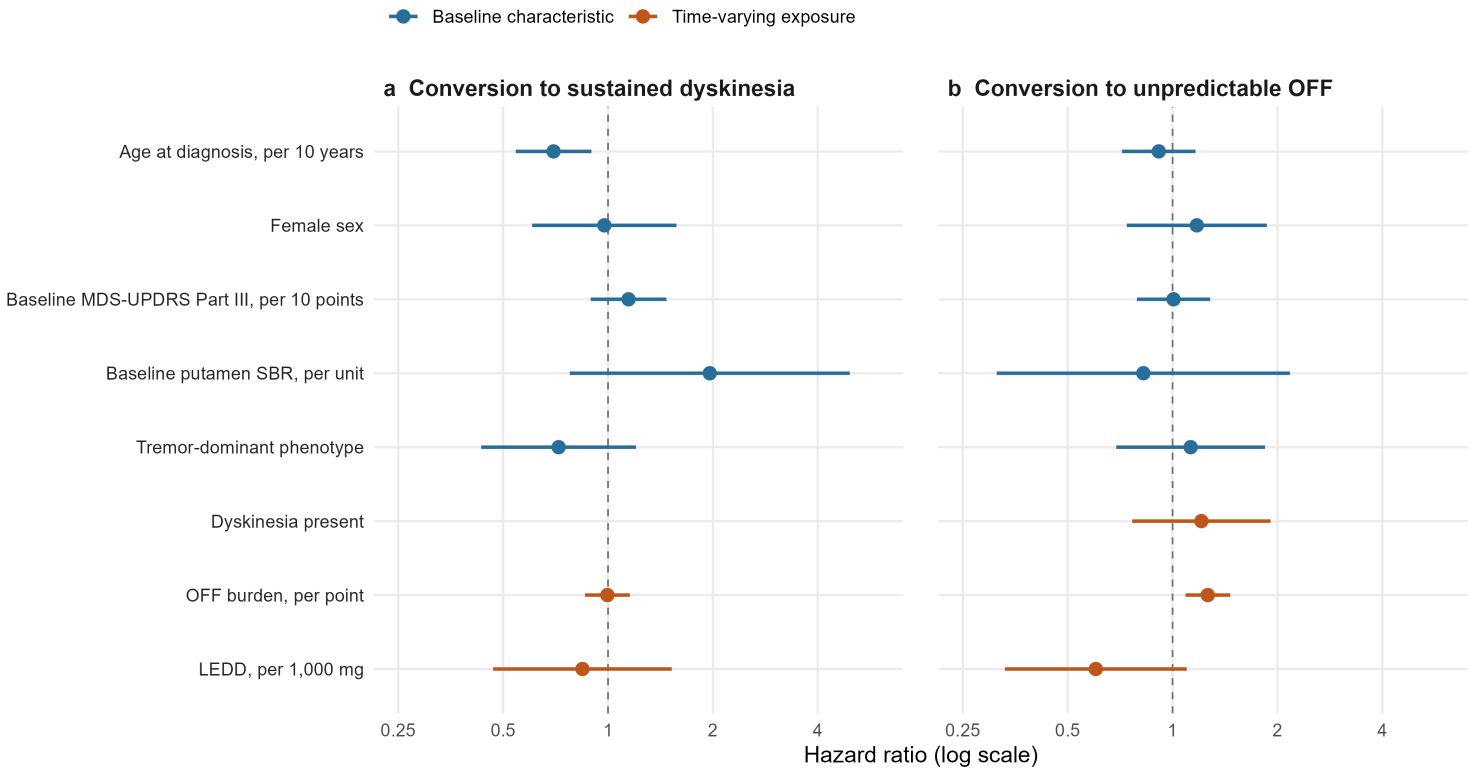

Figure 4

Determinants of sustained dyskinesia and unpredictable OFF measured from each patient's first OFF.

Cox proportional-hazards models timed from each patient's first recorded OFF. **a**, Conversion to sustained dyskinesia, a dyskinetic state at two or more visits (302 patients, 82 events). **b**, Conversion to unpredictable OFF, item 4.5 ≥ 2 (326 patients, 87 events). Points are hazard ratios and horizontal lines 95% confidence intervals; the dashed line marks a hazard ratio of 1. Blue, baseline characteristics; orange, time-varying exposures taken from the most recent assessment. OFF burden is the sum of items

4.3 and 4.4. Motor phenotype compares tremor-dominant with postural instability and gait difficulty or indeterminate. Dyskinesia is the outcome in **a** and is not a covariate there. LEDD, levodopa equivalent daily dose; SBR, striatal binding ratio.

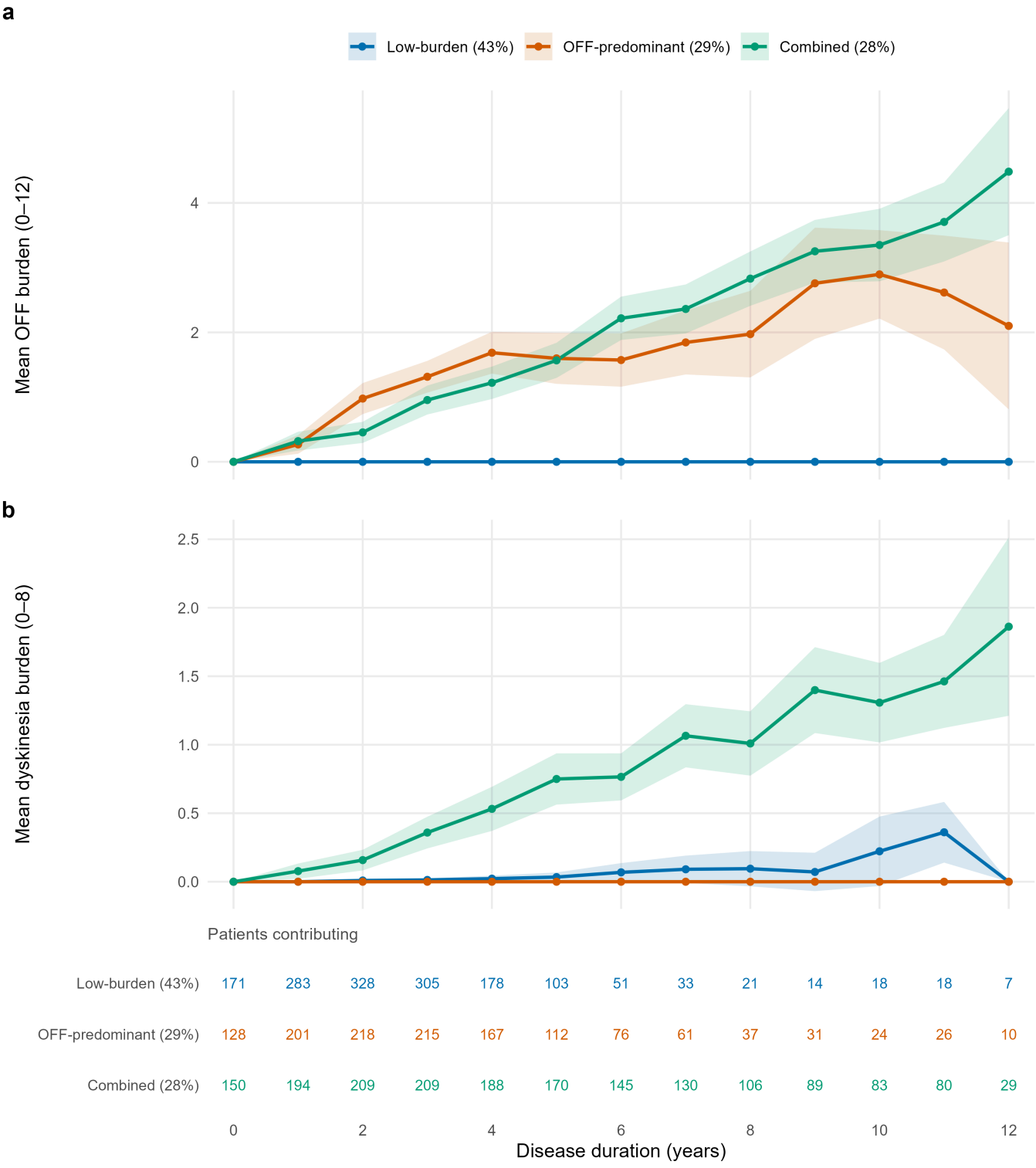

Figure 5

Group-based multitrajectory model of OFF and dyskinesia burden.

Mean OFF burden (**a**; items 4.3 + 4.4 + 4.5, range 0–12) and dyskinesia burden (**b**; items 4.1 + 4.2, range 0–8) in each year of disease duration, by trajectory group. The three groups were identified by group-based multitrajectory modelling in 852 patients: low-burden (n = 366), OFF-predominant (n = 250) and combined (n = 236). Lines join the observed group means and shaded bands are 95% confidence intervals; years with fewer than five patients in a group are not shown. The number of patients contributing in each year is given beneath **b**. Classification within the fitted model was strong (entropy 0.972; lowest group-specific average posterior probability 0.947). Group membership depends on how long a patient was observed (Table 1, footnote), so the groups describe patients within the 12-year window and do not identify fixed subtypes.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplTableS1AnalysisMap.docx
- SupplTableS10Pairedintensitymodifiertests.docx
- SupplTableS2Analysissets.docx
- SupplTableS3EmpericialTransitionrates.docx
- SupplTableS5FittedTransitionIntensities.docx
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