Supplementary Materials

Associations between individual limb rigidity scores and monthly or more frequent falls

In addition to the primary rigidity subscores discussed in the main text, secondary analyses considered additional rigidity subscores calculated for individual limbs as follows: lower limb lesser (/4), the lesser of UPDRS-III[4] items 22d-e; lower limb greater (/4), the greater of items 22d-e; upper limb lesser (/4), the lesser of items 22b-c; and, upper limb greater (/4), the greater of items 22b-c.

As in the main text, multivariate logistic regressions were performed to identify associations between secondary rigidity subscores and faller status while controlling for age, gender, PD duration, total UPDRS-III score, and presence of FOG. Associations between rigidity subscores and fall history were expressed as Odds Ratios (OR) +/- 95% Confidence Intervals. In order to control for overall UPDRS-III score, the remainder of each UPDRS-III total score after subtracting the rigidity subscore of interest was entered as a covariate into logistic regression analyses. Prior to entry into multivariate analyses, age and disease duration were converted into z-scores.

Multivariate logistic regression results using individual limb rigidity subscores indicated that the association between lower limb rigidity and fall history described in the main text is primarily driven by a strong association between rigidity on the more affected side and falls. When individual limb rigidity scores were entered into models, we found that rigidity in each of the lower limbs – both the lesser and more affected sides – were positively associated with fall history, although the identified associations were no longer statistically significant (Table S2). In particular, the magnitude of association for the more affected side was increased (24%), whereas the magnitude of association for the less affected side was reduced (23%). This demonstrates that rigidity in the less-affected limb is much less strongly associated with fall history. Changes in associations among the upper limbs were minimal (2.8%).

Table S1. Rigidity subscores assembled from sub-items of the UPDRS-III motor scale, overall and stratified on presence of previous monthly falls.

Rigidity Subscore	All Participants (N=216)	Non-Fallers (N=181)	Fallers (N=35)	P value
Total rigidity (/20)	3.7 ± 3.0	3.5 ± 2.8	5.0 ± 3.8	0.03
Lower limb sum (/8)	0.9 ± 1.4	0.7 ± 1.2	1.7 ± 1.9	<0.01
Lower limb lesser (/4)	0.3 ± 0.6	0.3 ± 0.5	0.7 ± 0.9	0.03
Lower limb greater (/4)	0.6 ± 0.8	0.5 ± 0.7	1.0 ± 1.0	<0.01
Upper limb sum (/8)	1.9 ± 1.4	1.8 ± 1.4	2.1 ± 1.6	0.19
Upper limb lesser (/4)	0.7 ± 0.7	0.6 ± 0.7	0.8 ± 0.8	0.25
Upper limb greater (/4)	1.2 ± 0.8	1.2 ± 0.8	1.3 ± 0.9	0.22
Neck (/4)	1.0 ± 0.8	0.9 ± 0.8	1.2 ± 0.9	0.09

P values reflect univariate tests of central tendency (*t*-tests or chi-squared tests) between Fallers and Non-Fallers.

Table S2. Odds ratios (OR) describing associations between individual limb rigidity subscores and fall history in the study sample.

Rigidity Subscore	OR	95% CI	P value	Change from main model
Lower limb lesser	1.24	0.38–4.03	0.73	-23.0%
Lower limb greater	1.99	0.75–5.28	0.17	+23.6%
Upper limb lesser	0.70	0.27–1.81	0.46	-1.4%
Upper limb greater	0.74	0.31–1.72	0.48	+4.2%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, and presence of FOG.

Associations between rigidity and less frequent falls

In addition to the associations with frequent falls discussed in the main text, additional analyses considered associations between rigidity subscores and less frequent falls. For these analyses, participants were classified as “Fallers” if they scored ≥1 on item 12 of the gait and falls questionnaire (GF-Q), “How often do you fall?” corresponding to annual or more frequent falls, and as Non-Fallers otherwise. Multivariate logistic regressions were performed to identify associations between rigidity subscores and faller status while controlling for age, sex, total UPDRS-III, PD duration, and presence of FOG as discussed in the main text.

Among the study sample, 93/216 (43%) fell annually or more often. Multivariate logistic regression results of the model with history of annual or more frequent falls as the outcome (rather than history of monthly or more frequent falls) indicated that the association between lower limb rigidity and fall history described in the main text only holds for frequent falls. Multivariate logistic regression results (Table S3) demonstrated that the association between lower limb rigidity and history of annual or more frequent falls was significantly attenuated (-21.7%) from that of the main model, and was no longer statistically significant (P=0.119). Changes in associations between other rigidity subscores and fall history were also substantial (11-26%).

Consistent with the literature, these logistic regression models also identified significant effects of female sex (Odds Ratio [95% CI] 2.1 [1.1–4.1], P=0.031), FOG (2.5 [1.2–5.1]; P=0.016), disease duration (1.1 [1.0–1.2]; P=0.021), and total UPDRS score (1.1 [1.1–1.2]; P=0.021).

Table S3. Odds ratios (OR) describing associations between rigidity subscores and history of annual or more frequent falls in the study sample.

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	0.97	0.85–1.10	0.62	-11.0%
Lower limb sum	1.26	0.94–1.69	0.12	-21.7%
Upper limb sum	0.82	0.60–1.12	0.21	+15.5%
Neck	0.74	0.47–1.17	0.74	-26.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, and presence of FOG.

Associations between rigidity and fall history while controlling for the presence of postural instability

To test whether associations between rigidity and fall history described in primary models were affected by the presence of postural instability (UPDRS-III item 30, the "retropulsion test"), additional multivariate logistic regression models were calculated that controlled for this variable as well as for age, gender, PD duration, total UPDRS-III score, and presence of FOG. UPDRS-III item 30 was dichotomized as ≥2 or <2 and entered as a dichotomous predictor variable. Among the study sample, 14/216 (6%) exhibited postural instability as defined above.

Multivariate logistic regression results of the further adjusted model indicated that the associations between rigidity subscores and fall history described in the main text hold when controlling for the presence of postural instability. Numerical results (Table S4) were essentially unchanged from those of the main model, with average changes in identified OR of 1.2%, including a slight strengthening (+3.7%) for the association between lower limb rigidity and fall history.

Table S4. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls in the study sample, further adjusted for presence of Postural Instability (UPDRS-III item 30 ≥2).

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	1.10	0.94–1.29	0.24	+0.9%
Lower limb sum	1.67	1.13–2.47	<0.01	+3.7%
Upper limb sum	0.70	0.45–1.09	0.12	-1.0%
Neck	1.01	0.55–1.89	0.96	+1.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, presence of FOG, and presence of Postural Instability.

Associations between rigidity and fall history while controlling for the presence of impaired gait

To test whether associations between rigidity and fall history described in primary models were affected by the presence of impaired gait (UPDRS-III item 29), additional multivariate logistic regression models were calculated that controlled for this variable as well as for age, gender, PD duration, total UPDRS-III score, and presence of FOG. UPDRS-III item 29 was dichotomized as ≥2 or <2 and entered as a dichotomous predictor variable. Among the study sample, 32/216 (15%) exhibited impaired gait as defined above.

Multivariate logistic regression results of the further adjusted model indicated that the associations between rigidity subscores and fall history described in the main text hold when controlling for the presence of gait impairment. Numerical results (Table S5) were essentially unchanged from those of the main model, with average changes in identified OR of 1.0%, including a slight reduction (-8.1%) for the association between lower limb rigidity and fall history. We note that the association between lower limb rigidity and fall history was reduced to borderline statistical significance (P=0.060) when this control was added.

Table S5. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls in the study sample, further adjusted for presence of impaired gait (UPDRS-III item 29 ≥2).

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	1.09	0.92–1.28	0.31	+0.0%
Lower limb sum	1.48	0.98–2.23	0.06	-8.1%
Upper limb sum	0.81	0.51–1.84	0.12	+14.1%
Neck	0.97	0.55–1.89	0.96	-3.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, presence of FOG, and presence of impaired gait.

Associations between rigidity and fall history while controlling for overall cognition

To test whether associations between rigidity and fall history described in primary models were affected by the presence of reduced overall cognition, additional multivariate logistic regression models were calculated that controlled for MoCA score as well as for age, gender, PD duration, total UPDRS-III score, and presence of FOG using the subset of cases (N=194) for whom MoCA scores were available. MoCA score was dichotomized around the sample median as ≥25 or <25 and entered as a dichotomous predictor variable. Among cases for whom MoCA scores were available (N=194), 86 (44%) exhibited reduced overall cognition as defined above.

Multivariate logistic regression results of the further adjusted model indicated that the associations between rigidity subscores and fall history described in the main text hold when controlling for the presence of reduced overall cognition. Numerical results for total, lower limb, and neck rigidity (Table S6) were essentially unchanged from those of the main model, with average changes in identified OR of 0.7%, including a slight increase (+4.3%) for the association between lower limb rigidity and fall history. The inclusion of MoCA as a covariate substantially impacted the association between neck rigidity and fall history (-20.6% change), which may indicate some interaction between neck rigidity and cognition as risk factors for falls.

Table S6. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls in the study sample, further adjusted for presence of impaired gait (UPDRS-III item 29 ≥2).

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	1.07	0.91–1.26	0.43	-2.0%
Lower limb sum	1.68	1.13–2.52	0.01	+4.3%
Upper limb sum	0.71	0.43–1.17	0.18	-0.3%
Neck	0.79	0.38–1.68	0.55	-20.6%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, presence of FOG, and dichotomized MoCA score.

Effect of medication state during exam on associations between rigidity and fall history

Additional analyses considered whether medication state at testing (ON vs. OFF medications) affected associations between rigidity subscores and fall history. Among the 212/216 patients for whom medication information was available, 131 were taking carbidopa/levodopa (37 as monotherapy); 88, 50, 31, and 31 were taking dopamine agonists, MAO-B inhibitors, COMT inhibitors, and amantadine, respectively. Although the majority of participants (197/216) were ON medications during UPDRS assessments, some who were prescribed antiparkinsonian medications (19/216) were assessed in the practically-defined 12-hour OFF state according to the protocol of the study in which they participated.

In order to assess whether medication state affected the main study results, additional multivariate logistic regression analyses were performed considering only those patients in the ON medication state during testing. Changes in identified OR between rigidity subscores and fall history from those calculated in the main model were compared qualitatively. Because of the small number of patients in the OFF state, multivariate logistic regressions were inappropriate among these participants.

Multivariate logistic regression results considering only those patients assessed in the ON medication state indicated that the associations between rigidity subscores and fall history described in the main text hold when limited to the ON state typically observed clinically. In particular, the association between leg rigidity and fall history was only slightly attenuated (-4.3%) and remained statistically significant (P=0.045) at the reduced sample size (Table S7).

Table S7. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls among those in the study sample assessed in the ON medication state.

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	1.09	0.91–1.30	0.36	+0.0%
Lower limb sum	1.54	1.01–2.36	<0.05	-4.3%
Upper limb sum	0.70	0.43–1.13	0.14	-1.4%
Neck	1.22	0.62–2.37	0.57	+22.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, and presence of FOG.

Effect of dopamine agonist monotherapy on associations between rigidity and fall history

Recently, a large observational study in early PD[30] identified dopamine agonist monotherapy as a significant fall risk factor in early PD patients. In this sample, among the 212/216 patients for whom medication information was available, 21 were taking dopamine agonists as monotherapy. Therefore, in order to assess whether the presence of dopamine agonist monotherapy affected the main study results, additional multivariate logistic regression analyses were performed with a dichotomized indicator variable coding for the presence of dopamine agonist monotherapy included as a covariate. Changes in identified OR between rigidity subscores and fall history from those calculated in the main model were compared qualitatively.

Multivariate logistic regression results indicated that the associations between rigidity subscores and fall history described in the main text were insensitive to the presence of this dopamine agonist monotherapy (average change in OR, -0.7%; Table S8). There was a small positive association between dopamine agonist monotherapy and fall history in this sample (OR: 1.40), however, the identified confidence interval was wide (0.28–6.98). A significantly larger sample would be required to assess whether associations between agonist monotherapy and falls identified previously would hold in this more advanced group.

Table S8. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls, further adjusted for the presence dopamine agonist monotherapy.

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	1.08	0.92–1.27	0.33	-0.9%
Lower limb sum	1.61	1.10–5.97	0.01	+0.0%
Upper limb sum	0.71	0.45–1.11	0.13	+0.0%
Neck	0.98	0.52–1.85	0.94	-2.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, and presence of FOG.

Additional analyses associating rigidity, falls, and FOG

Because of the strong relationship between FOG and falling in PD, we performed additional analyses to evaluate how relationships between rigidity and falls might be impacted by this symptom.

Associations between rigidity and monthly or more frequent falls with a less stringent criterion for fog. First, in addition to analyses in the main text, we also tested whether primary results would be sensitive to the use of a less stringent criterion for identifying "freezers." For these analyses, participants were classified as freezers if they scored ≥1 on FOG-Q item 3, "Do you ever feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?" corresponding to monthly or more frequent freezing.

To identify associations between rigidity subscores and faller status while controlling for age, sex, total UPDRS-III, PD duration, and presence of monthly or more frequent FOG, we repeated the primary analyses discussed in the main text with the presence of monthly or more frequent freezing included as a dichotomized covariate, comparing identified odds ratios to those identified in the primary models. We found that the use of a less stringent criterion for identifying freezers affected the identified odds ratios only moderately, with average changes of -2.2% (Table S9).

Table S9. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls, controlling for monthly or more frequent freezing.

Rigidity Subscore	OR	95% CI	P value	Change from main model
Total rigidity	1.05	0.90–1.22	0.55	-3.7%
Lower limb sum	1.43	1.01–2.03	0.04	-11.2%
Upper limb sum	0.71	0.46–1.09	0.12	+0.0%
Neck	1.06	0.58–1.96	0.84	+6.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, and presence of monthly or more frequent FOG.

Associations between rigidity and monthly or more frequent falls stratified by FOG status. Next, to evaluate for potential interactions between rigidity and freezing status, we 1) performed stratified multivariate logistic regressions to quantify associations between rigidity and falls among those with no self-reported freezing (FOG-Q item 3 score of 0), and among those with freezing (FOG-Q item 3 score>0), as described above, and 2) performed multivariate logistic regressions with interaction terms in order to assess whether differences in associations between the no freezing and freezing groups were greater than could be explained by chance.

For these analyses, 78/216 patients were considered “Freezers” and 138/216 patients were considered “Non-Freezers.” Positive associations were identified between lower-limb rigidity and fall history in patients both with and without FOG, with stronger (and statistically-significant) associations among those patients without FOG (Table S10). Substantially weaker associations between lower limb rigidity and fall history were observed in patients with FOG. However, models with interaction terms demonstrated that there was no statistically-significant association between FOG status and identified associations between lower-limb rigidity and fall history (P=0.42). One interpretation of this is that FOG and rigidity may represent competing risks, so that if a particular patient has FOG, their likelihood of having fall history is not impacted by the presence of rigidity. Importantly, this result suggests that less-affected patients may be most likely to benefit from pharmacotherapeutic approaches to reduce rigidity in order to ameliorate fall risk.

Table S10. Odds ratios (OR) describing associations between rigidity subscores and history of monthly or more frequent falls, stratified by presence of monthly or more frequent freezing.

Rigidity Subscore	OR	95% CI	P value	Change from main model
FOG-Q item 3=0				
Total rigidity	1.36	0.95–1.95	0.10	+24.8%
Lower limb sum	2.19	1.00–4.80	<0.05	+36.0%
Upper limb sum	0.93	0.41–2.12	0.87	+31.0%
Neck	0.98	0.31–3.06	0.97	-2.0%
FOG-Q item 3≥1				
Total rigidity	1.01	0.85-1.21	0.91	-7.3%
Lower limb sum	1.29	0.87-1.93	0.21	-19.9%
Upper limb sum	0.73	0.45-1.22	0.21	+2.8%
Neck	1.08	0.52-2.26	0.84	+8.0%

P values reflect logistic regressions controlling for age, sex, total UPDRS-III, PD duration, and presence of monthly or more frequent FOG.