

# Symptom Clusters in Individuals with Parkinson’s Disease with Motor Fluctuations

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## BACKGROUND

Parkinson's Disease (PD) manifests with a multitude of motor and non-motor features compounded by intra-individual fluctuation, which makes diagnosis and management of specific PD manifestations challenging.

There are clear indications that demographics, including age of onset, sex, and race/ethnicity heavily influence the expression of PD.

Knowledge of which patients are more likely to manifest specific symptoms clusters can improve symptom detection and management and may be considered in clinical trial design.

There remain critical gaps in our understanding of the relationship between patient demographics and symptom clusters.

## OBJECTIVES

Identify symptom clusters in a large group of PD patients who experience fluctuations in symptoms.

Examine the relationship of symptom fluctuations with age, age at PD onset, and gender.

## METHODS

Cross-sectional online questionnaire was administered to the Fox Insight Study cohort. Fox Insight (FI) is an online observational study that includes individuals with self-reported PD (foxinsight.org).

Sample criteria for survey participation:

- i. Enrolled in the PD cohort of Fox Insight based on self-report of PD diagnosis
- ii. On Levodopa therapy

Of 13,359 eligible FI participants, 2681 initiated the survey. 2,107 endorsed experiencing OFF periods in which symptoms are not controlled.

The 19-item Wearing Off Questionnaire (WOQ-19) was administered. It presents 19 symptoms and asks the patients to indicate presence or absence of each symptom “once a day recently”, then asks if each symptom is alleviated or remains the same after taking Levodopa (medication-responsive=MR).

233 participants endorsed >12 symptoms on the WOQ-19 and were excluded as outliers. The final sample considered in this analysis was n=1874.

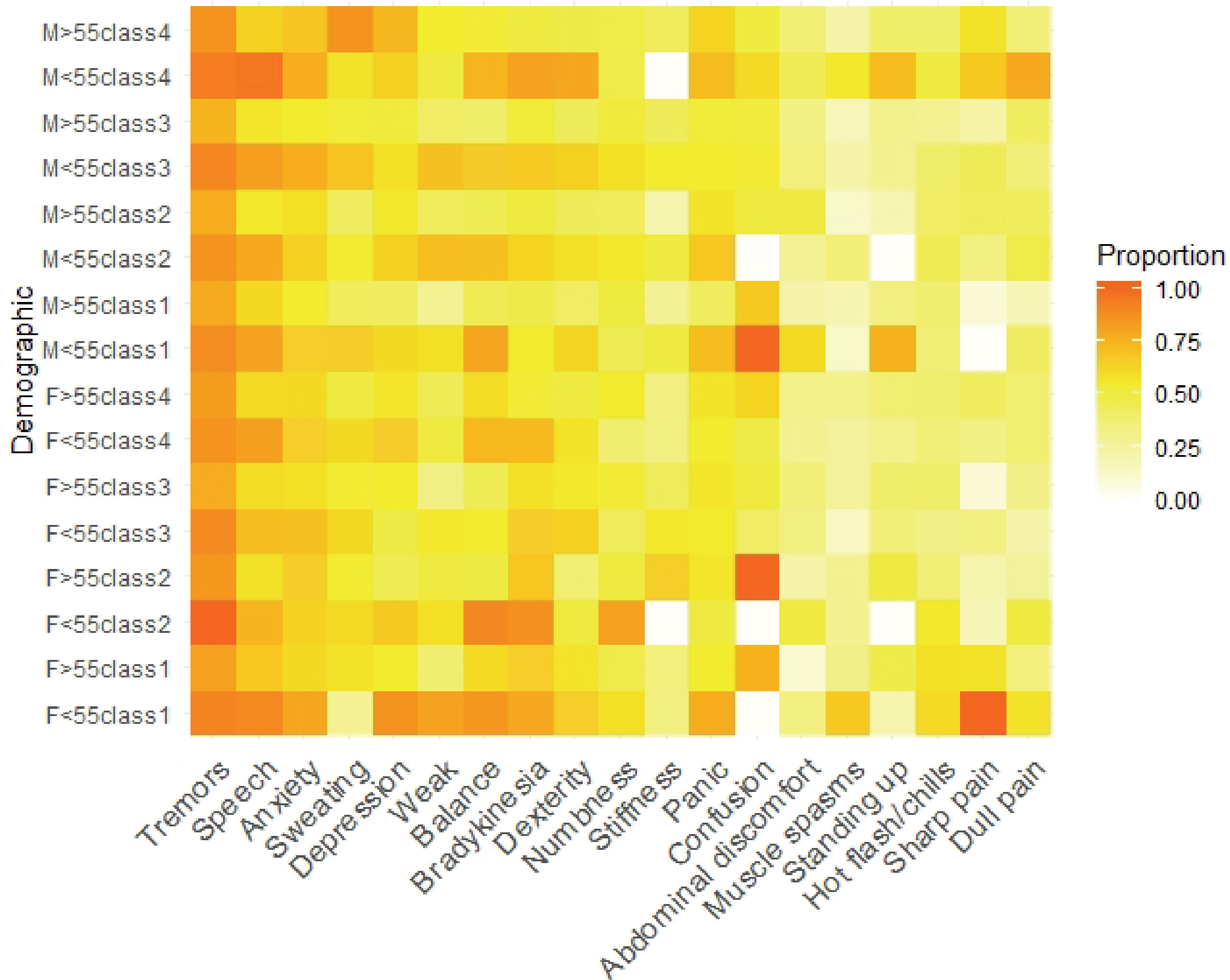
A latent class analysis (LCA) was fit using poLCA package in R. Models were estimated for 2 to 6 classes. Tremor, bradykinesia, and rigidity are core features of PD, and any attempts to include them overwhelmed the model. LCA was then attempted using the remaining 16 of the 19 questions from the WOC 19 questionnaire as latent class indicators. Bayesian information criterion (BIC) statistic indicated a 4 class model was optimal fit. Each model was estimated 10 times with different starting values in order to find the global maximum for class membership probabilities.

**Table 1.** Symptom classes and characteristics of subjects in each class; unique symptoms were those symptoms predicted to occur in >50% of only a single class

	Class 1 N=684 (%)	Class 2 N= 451 (%)	Class 3 N=406 (%)	Class 4 N=333 (%)
Mean age in years (SD)	67.35 (8.02)	68.61 (7.56)	66.54 (9.26)	64.63 (7.95)
Mean age of PD onset (SD) in years	61.83 (8.77)	62.08 (8.94)	59.96 (10.59)	58.44 (8.56)
Mean disease duration (SD) in years	5.48 (4.59)	6.53 (5.31)	6.57 (5.87)	6.41 (4.52)
M : F N (%)	386 (56.43) : 298 (43.57)	282 (62.53) : 169 (37.47)	280 (68.97) : 126 (31.03)	50 (15.02) : 283 (84.98)
Unique symptom (%)	None	Mood swings/depression (76%)	Difficulty standing from chair (73%)	Sweating (62%) Muscles spasms (70%) Hot flashes/chills (57%) Dull pain (59%)

**Figure 1.** Heat map depicting proportion with symptoms based on age and sex in each class.

M>55 = Males ≥55 years age ; M<55 = Males <55 years age;  
F>55 = Females ≥55 years age; F<55 = Females <55 years age



## RESULTS

The final sample of 1874 individuals with PD had a mean age of 66.9 (SD 8.3). 998 (53%) males. Mean age of PD onset was 60.8 (SD 9.3), with a 4.8 mean years disease duration.

The LCA yielded four groups, arbitrarily numbered classes 1, 2, 3, and 4. Predicted demographics are shown in table 1. Predicted class probabilities by gender and age are shown in figure 1.

### Class 1

- Low symptom burden
- None were predicted to report any symptoms in proportions greater than 50% (excluding tremor, rigidity, bradykinesia)
- No demographic characteristics more likely to be predicted in class members
- A significantly shorter disease duration as compared to all other classes

### Class 2

- Defined by mood swings/depression (endorsed in 50% or more of members)
- Other symptoms predicted in >50%: feeling weak, impaired balance, difficulty doing detailed work with the hands, numbness, and mood swings and/or depression
- Significantly older (mean 68.61, SD 7.56 years) and had the oldest age of onset (mean 62.08, SD 8.94 years) compared to all other classes

### Class 3

- Defined by difficulty arising from a chair (endorsed in 50% or more of members)
- Other symptoms predicted in >50%: feeling weak, impaired balance, difficulty doing detailed work with hands and fingers, and numbness.
- More likely to be male ( $\beta=0.376$ , OR=1.46,  $p=0.037$ )

### Class 4

- Defined by persistent dull pain, hot flashes/chills, sweating, and muscle spasms (predicted 50% or more of group members)
- Other symptoms reported in >50%: feeling weak, impaired balance, difficulty doing detailed work with hands and fingers (table 2)
- More likely to be female ( $\beta=-1.77$ , OR=0.170,  $p<0.001$ )

Observed prevalence of symptoms were concordant with that predicted across symptoms (table 2).

Dopaminergic medication responsiveness was reported by >80% present for tremor, bradykinesia, and rigidity across classes (table 2). Aside from responsiveness of muscle spasms in >60% of class 4, in most classes the unique defining symptom was reported to be medication responsiveness in less than half.

The average observed number of medication-responsive symptoms in classes 1-4 respectively was 2.62, 5.62, 4.92, and 5.39.

**Table 2.** The predicted and observed proportion of symptoms and proportion of those symptoms that were reported to be medication-responsive in the sample subdivided by their predicted class membership. Tremor, slow movement, and stiffness were excluded from the LCA (grey cells).

P = Predicted proportion with symptom

O = Predicted proportion with symptom

MR= % Medication-responsive among observed symptoms

	Class 1			Class 2			Class 3			Class 4		
Symptom	P (%)	O (%)	% MR	P (%)	O (%)	%MR	P (%)	O (%)	%MR	P (%)	O (%)	%MR
Motor												
Tremors		68.6	80.0		72.3	80.0		66.8	86.2		68.5	81.2
Impaired balance	38.7	37.9	54.2	78.2	78.1	52.2	92.0	93.8	58.3	63.9	63.7	57.7
Slow movement		57.2	70.6		86.9	59.8		91.4	69.7		80.2	59.5
Dexterity	45.6	45.0	55.7	85.2	86.0	50.0	87.2	87.9	61.5	70.3	69.7	53.4
Stiffness		56.9	59.6		82.9	60.7		81.5	65.3		83.8	61.1
Difficulty standing from chair	20.6	18.7	45.4	48.9	48.6	45.1	73.1	77.3	49.3	41.0	40.5	39.1
Difficulty speaking	22.5	21.1	47.7	64.7	64.1	53.8	66.1	69.2	53.9	30.6	29.7	48.5
Muscle spasms	22.7	23.1	51.7	42.3	41.2	44.3	42.7	43.1	55.0	70.2	72.4	68.4
Autonomic												
Hot flashes and chills	5.3	4.5	46.0	16.7	16.4	39.4	6.2	4.7	34.1	57.2	63.7	37.6
Sweating	9.0	8.45	27.7	28.5	28.4	39.9	14.8	12.8	29.5	62.5	68.5	26.3
Abdominal discomfort	9.8	9.4	26.5	28.6	29.7	23.8	24.9	24.4	27.1	40.3	41.4	4.0
Neuropsych												
Confusion/bradyphrenia	19.0	18.3	52.9	76.9	78.3	52.8	54.5	55.4	59.4	36.2	33.9	59.6
Anxiety	28.4	28.7	47.2	98.2	99.3	51.7	27.9	25.4	46.4	55.1	55.3	51.7
Mood swings/depression	11.5	10.8	31.8	75.5	80.7	42.7	17.7	13.8	38.7	26.1	24.0	43.1
Panic	1.5	1.2	0.0	36.1	36.8	49.1	1.2	0.7	46.7	15.2	15.0	63.9
Sensory/Other												
Numbness	11.3	11.6	44.4	26.7	25.3	37.3	34.3	36.5	39.2	32.0	31.5	47.4
Sharp pain	3.0	3.1	38.1	11.4	10.6	31.8	14.1	13.6	41.5	33.5	36.6	0.0
Persistent dull pain	13.2	13.0	35.0	32.9	31.0	38.4	39.6	41.9	39.7	58.2	60.4	22.7
Feeling weak	27.7	25.3	59.5	78.7	79.6	57.6	78.5	81.0	58.2	68.0	69.4	59.3

## CONCLUSION

Our findings illustrate motor and non-motor symptom clustering in PD and demographic differences in this regard.

In this latent class analysis, we found 4 classes:

- (1) a shorter disease duration, low symptom burden group
- (2) an older group with a prominence of neuropsychiatric symptoms and feeling weak
- (3) a longer disease duration group with difficulty arising from chairs (indicating axial involvement) and feeling weak and
- (4) a female-predominant group with autonomic symptoms and pain.

Knowledge of these patterns of symptoms and demographic risk factors for symptom clusters could aid in their detection.

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