FACTORS ASSOCIATED WITH ASYMMETRIC SYMPTOMS OF PARKINSON'S DISEASE IN SOUTH AFRICA

Priyantha Naicker

A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine

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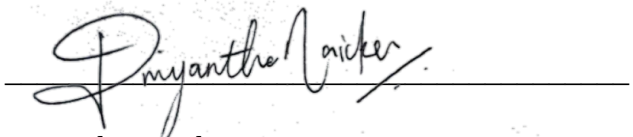
I, Priyantha Naicker, declare that this Thesis is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Priyantha Naicker

21 day of June 2022

Dedicated to my mother, father and brother

And to the rest of my family both on earth and in heaven.

ABSTRACT

Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder resulting from the death of dopamine-producing neurons in the substantia nigra pars compacta and from the development of Lewy bodies in the neuronal cell body. The motor symptoms of PD usually develop asymmetrically and is often predated by non-motor symptoms.

Aims and objectives: This study identified the potential predictive factors (demographics, handedness and non-motor symptoms) that are associated with asymmetric symptoms in South African PD patients.

Methods: Diagnosed PD patients were recruited from Sandton Mediclinic and Wits Donald Gordon Medical Centre in Johannesburg, South Africa. Relevant inclusion and exclusion criteria were applied to obtain an appropriate sample (n=59). A questionnaire was created on REDCap and distributed via email. The data was captured and analysed on Microsoft Excel and STATA.

Results: Asymmetry changes over time and with severity of disease as there were associations between current laterality and age ($p=0.003$), between stage of PD and initial laterality ($p=0.023$), and between current laterality ($p<0.0001$) and change in symptom asymmetry ($p<0.0001$). Asymmetry is related to non-motor symptoms of PD as daytime sleepiness was associated with current asymmetry ($p=0.010$) and change in symptom asymmetry ($p=0.005$). Current asymmetry was associated with pain ($p = 0.042$) and constipation was associated with current asymmetry ($p=0.016$) and change in symptom asymmetry ($p=0.008$). Depression was associated with change in symptom asymmetry ($p=0.034$).

Conclusion: The importance of symptom asymmetry in PD patients is undeniable, therefore, further research is needed as it could be the key to the future management and treatment of this neurodegenerative disorder.

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Firstly, I would like to thank Dr Tanya Calvey for all her direction, assistance and advice throughout my master's year. Not only for the support with this dissertation but also for the guidance that she has given me in terms of my career path and future. I would also like to like to acknowledge the great assistance of Dr Marcelle Smith for her time and effort in recruiting participants and the expert knowledge that she has willingly provided.

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Recognition must be given to the Sandton Mediclinic and the Wits Donald Gordon Medical Centre in Johannesburg, South Africa for permitting me access to their Parkinson's Disease patient base.

My sincere appreciation goes out to my family for giving me the motivation, hope and the determination to continue when I had none. I cannot express how grateful I am to you for never giving up on me. Every time I achieve, your love and pride are what fuels me to go even further.

Last, but certainly not least, I thank the Gods for their abundant blessings that they have bestowed upon me. I turn to them when I feel lost and not once have I been disappointed. They have shown me that everything happens for a reason and that I am on the right path - my path.

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GLOSSARY

Nomenclature

PD: Parkinson's Disease

SNpc: Substantia nigra pars compacta

GPi: Globus Pallidus internus

GPe: Globus Pallidus externus

SMA: Supplementary Motor Area

STN: Subthalamic Nucleus

MDS-UPDRS: Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale

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1. INTRODUCTION

Parkinson's Disease (PD) is a neurodegenerative disorder that is characterized by a loss of motor control resulting in bradykinesia (slowness of movement), resting tremor, muscle rigidity and postural instability (Tolosa, Wenning and Poewe, 2006). PD patients may also develop non-motor symptoms such as loss of smell, bladder problems and depression. Parkinsonian disorders may be caused by an undetermined degenerative disease process, genetic predisposition or may result from toxins and drugs (Dickson, 2012).

PD is the second most widespread neurodegenerative disorder after Alzheimer's disease and results from the death of dopamine-producing neurons in the substantia nigra pars compacta (SNpc) (Radhakrishnan and Goyal, 2018). The SNpc, which is located in the midbrain, contains dopaminergic projections which synapse on to the striatum. These pathways regulate the initiation of motor output (Sonne *et al.*, 2021). The dopamine neurotransmitter (3-Hydroytramine) is a catecholamine that regulates the functioning of certain extrapyramidal structures of the brain such as the substantia nigra and striatum where it may either have an excitatory or inhibitory effect (Marsden, 2006). As there is a decrease in the number of dopaminergic neurons, the consequential drop in dopamine levels results in the inability of the substantia nigra to regulate motor movement. Both the peripheral and central nervous systems are involved in the pathogenic process of PD (Radhakrishnan and Goyal, 2018).

The development of Lewy bodies in the neuronal cell body may also be the cause of PD (refer to figure 1 below). Lewy bodies are an abnormal build-up of protein such as α-synuclein and ubiquitin which results in the dysfunctionality and degeneration of neurons seen in PD (Gómez-Benito *et al*., 2020). Lewy bodies appear first in the brainstem and olfactory neurons. As the disease progresses, Lewy bodies are also found in the limbic and neocortical regions of the brain.

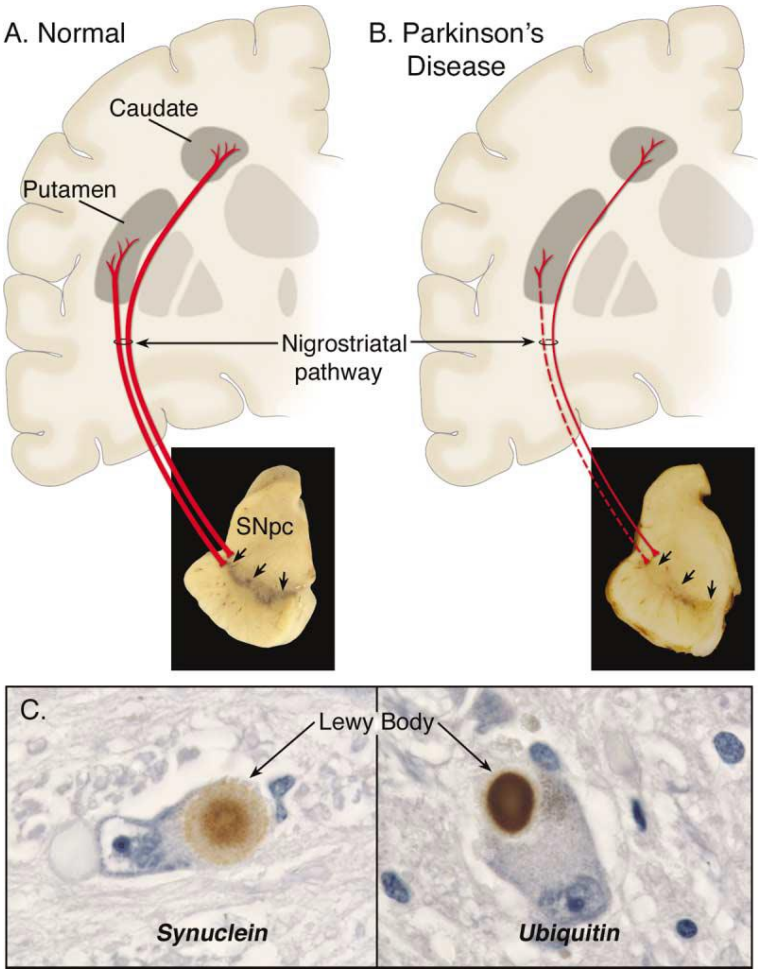


Figure 1: The Neuropathology of PD (Darden, 2007)

1.1. Physiology of PD

The pathway that is affected in PD is the nigrostriatal pathway in which dopaminergic neurons project from the substantia nigra to the striatum (Darden, 2007). They do this via the direct and the indirect pathways – The direct pathway results in movement whereas the indirect pathway results in the inhibition of movement. (Mathai and Smith, 2011). When the activation and inhibition of movement via these pathways are unbalanced, it results in movement disorders such as PD (more activation of the indirect pathway) and Huntington's disease (more activation of the direct pathway) (Albin *et al*., 1989 found in Mathai and Smith, 2011).

1.2. Aetiology of PD

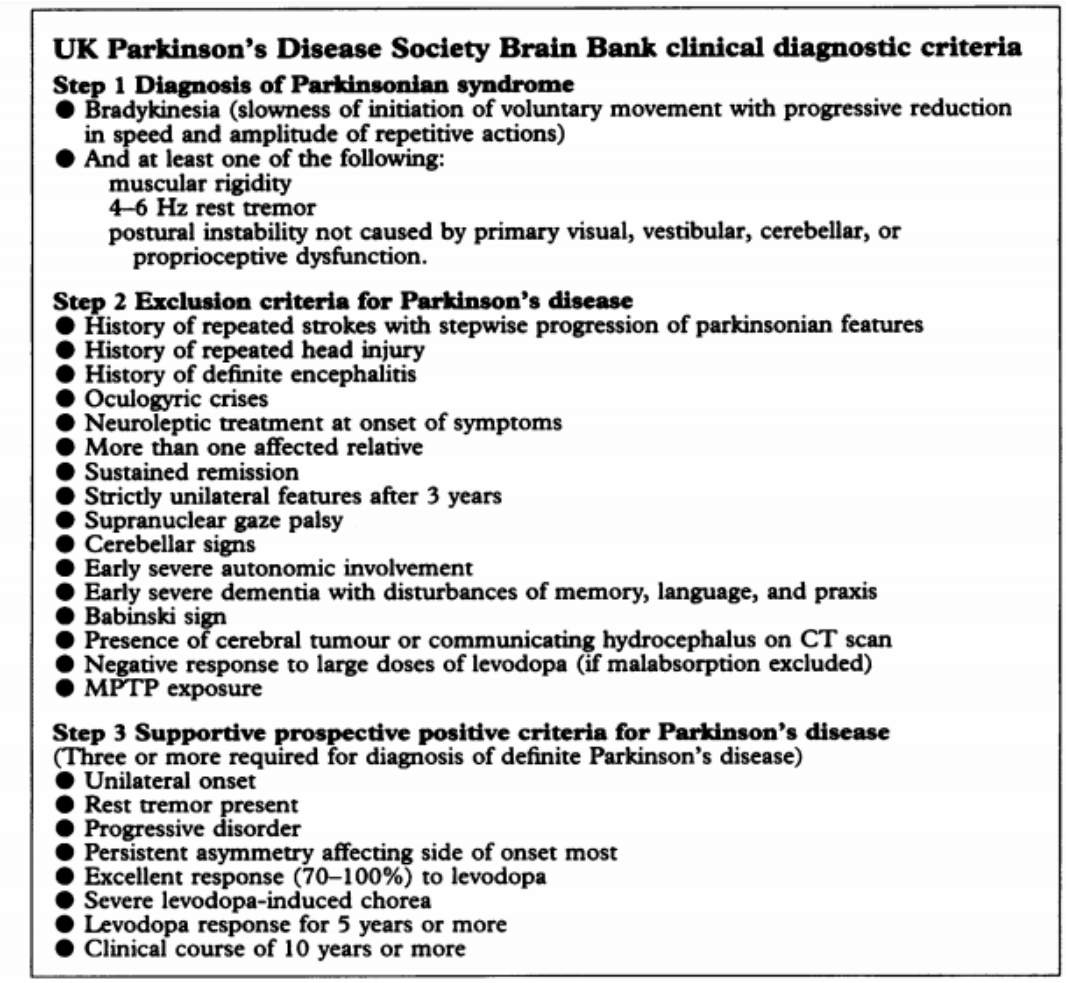
The exact process that causes dopaminergic neuron loss is still unknown. "Current thinking is that mitochondrial dysfunction, oxidative stress, and protein misfolding have a

central role in PD pathogenesis" (Chen and Tsai, 2010). It is also believed that interaction with susceptibility genes may be the cause in the case of sporadic PD. Environmental factors that could be potential triggers to PD are occupational exposures (pesticides, herbicides, and heavy metals), tobacco, coffee, alcohol, dietary factors (antioxidants, fat and fatty acids and dietary iron) and inflammation. These factors have not yet been proven to cause PD as further research is required.

According to Tran *et al*. (2020), around 85% of PD cases occur sporadically but a few occur due to genetic predisposition resulting in neurodegeneration of dopaminergic neurons. The autosomal dominant genes linked with PD are α-synuclein (PARK 1 and PARK 4) and LRRK2 (PARK8) whereas the autosomal recessive genes linked with PD are Parkin (PARK 2), PINK1 (PARK 6) and DJ-1 (PARK 7). Other genes linked to PD include UCHL1 (PARK5), ATP13A2 (PARK 9), GIGYF2 (PARK 11), Omi/HtrA2 (PARK 13), PLA2G6 (PARK 14), FBXO7 (PARK 15) and VPS35 (PARK 17) (Chai and Lim, 2014).

1.3. Diagnosis and Measurement of PD

PD is routinely diagnosed using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (also known as the Queen Square Brain Bank diagnostic criteria) in order to acquire accurate and unbiased results (Massano and Bhatia, 2012). It consists of the following three steps shown in figure 2 below:



UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
  - muscular rigidity
  - 4–6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Figure 2: UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Massano and Bhatia, 2012)

PD is diagnosed when the patient's minor symptoms become progressively worse so much as to affect their daily activities.

In the 1980s, the Unified Parkinson's Disease Rating Scale (UPDRS) was developed to monitor the progression of PD. The MDS-UPDRS is a modified version of the original scale that was sponsored by the International Movement Disorder Society. It is used to evaluate motor and non-motor experiences during the patient's daily life as a way to monitor the disease progression and burden. It assesses the following 4 areas each of which contain multiple sub-questions (Opara *et al.*, 2017).

I) Nonmotor Aspects of Experiences of Daily Living

II) Motor Aspect of Experiences of Daily Living

III) Motor Examination

IV) Motor Complications

Fifty questions are included in the MDS-UPDRS with each answer being scored on a scale from 0 – 4 (0 being mild and 4 being severe). PD severity can be categorised into three main stages: Hoehn-Yahr stage I for newly diagnosed PD, stages II and III for moderately severe PD and stages IV and V for advanced PD (Wood and Calne, 1993). During the motor examination, both sides are rated separately observing the speed, amplitude, hesitations, halts and the decrementing amplitudes at which each movement is done. This can be used to determine the asymmetry of the patient's motor symptoms.

Other diagnostic tests include the DaTSCAN which is an imaging technique that can be used to visualise and localize dopamine activity in the brain (Deeb *et al*., 2010). This is done by injecting a radioactive substance, ioflupane, into the bloodstream to assess dopaminergic neurons. F-DOPA PET scans can also be used as a PD diagnostic tool in which the PET (positron emission tomography) scan uses the radiotracer, F-DOPA, to measure dopamine in the neurons of the brain (Ibrahim et al., 2016).

1.4. Symptoms of PD

In a study done by Kempster *et al.* (1989), it was found that there was asymmetry in the deterioration of the substantia nigra. There was greater neuronal death found contralateral to the side of the body where the initial symptoms appeared. Asymmetry of symptoms is common in PD patients where motor features usually occur unilaterally at the onset of symptoms but with disease progression, symptoms become bilateral and, with more advanced forms of the disease, motor fluctuations occur (Kempster *et al.*, 1989). This study also found that in the initial stages of the disease, the frontal regions of the brain are more prone to degeneration while in later stages of the disease, the posterior regions tend to exhibit these changes. A study done by Claassen and colleagues (2016), indicated that patients with PD present with an initial predominant left cortical atrophy and a predominant posterior right cortical atrophy in later stages of the disease.

Patients with PD experience both motor and non-motor symptoms. Primary motor symptoms include bradykinesia (slowness of movement), rigidity (stiffness of muscle) and tremor (shaking movement of hands or feet). While symptoms such as akinesia and rigidity occur due to a decrease in dopamine levels in the basal ganglia, the cause of a tremor remains

unclear but is thought to be associated with abnormal cerebellar, thalamic, and subthalamic nucleus (STN) functioning (Moustafa *et al.*, 2016). Another motor feature of PD is gait impairment. A shuffling gait occurs when the patient struggles with elevating their feet off the ground when walking. This is due to the incoordination between the basal ganglia, thalamus and cerebral cortex. Micrographia is a small handwriting technique that prominently occurs in PD patients as handwriting utilises an extensive brain network including Broca's area (the language centre of the brain). Precision grip deficit is a motor symptom of PD that occurs due to damage to the dentate nucleus or due to changes sensorimotor processing which results in mistiming of grip force generation (Fellows *et al*., 2001 found in Moustafa *et al.*, 2016). Speech problems (hypophonic, monotonic and dysarthria) are found to correlate with other PD motor symptoms such as akinesis, bradykinesia and gait problems. It is the result of basal ganglia abnormalities similar to those seen in Broca's aphasia. Studies have shown that factors such as duration of disease, younger age of symptom onset and being treated initially with Levodopa, enhance the possibility for motor complications (Kadastik-Eerme *et al.*, 2017).

Non-motor features are referred to as pre-motor symptoms as they are known to develop well before the onset of motor features. Many PD patients are greatly impacted by these non-motor features but they are not as appreciated as the motor symptoms (Salawu *et al.*, 2010). Non-motor symptoms include sleep disorders (excessive daytime sleepiness, insomnia and REM sleep behaviour disorder), restless legs syndrome, fatigue, sleep apnoea, autonomic dysfunction (dizziness, constipation, bladder dysfunction, erectile dysfunction and hyperhidrosis), cognitive impairment and dementia, neuro-behavioural disturbances, olfactory dysfunction and impulse control disorders (Salawu *et al.*, 2010).

1.5. Handedness and PD

In a study done by Yust-katz, Tesler and Treves (2008), a relationship between a patient's dominant hand and side of PD symptom onset was found. Fifty two percent of left-handed patients experienced symptom onset on the left side of their body whereas most right handed patients (53%) experienced symptom onset on their non-dominant side. A study done by Uitti *et al*. (2005) exhibited similar results and concluded that patients with a left dominant hand tend to have a more severe form of PD on the left side of their body compared to right-handed individuals. There is a need for additional research on this topic.

1.6. Treatment of PD

Dopamine is not lipid soluble and therefore cannot cross the blood-brain barrier (BBB) rendering it ineffective in the treatment of PD. However, when its precursor, Levodopa, is administered, it is able to cross the BBB where it then undergoes a process known as aromatic L-amino acid decarboxylase and is converted to dopamine (Wood and Calne, 1993). PD is an incurable disease but there are symptomatic and protective therapies that can be implemented to prolong life and improve quality of life. The foundation for the treatment of PD symptoms is Levodopa. Although Levodopa works on all dopamine receptors and is the most effective treatment for PD, it causes the patient to experience involuntary noticeable movements. These unsolicited actions progressively worsen as the disease advances. Other symptomatic treatment for PD include anticholinergic agents, amantadine and synthetic dopamine agonists. Protective therapies can be implemented to prevent the onset or advancement of neurodegeneration. Some of the hypotheses of neuroprotective therapies include: the free radical hypothesis, selegiline and the theory of autoimmunity (Wood and Calne, 1993).

1.7. Ethnicity and PD

In a study done by Sauerbier *et al*. (2017), in which research addressing the non-motor symptoms in Asian PD patients are summarised, it was found that the occurrence of non-motor symptoms in Asian PD patients is high which is analogous to studies consisting of Caucasian PD patients. It was also found that constipation, urinary problems and memory are the non-motor symptoms most reported in these Asian populations (Sauerbier *et al*., 2017). In another study by Ben-Joseph *et al.* (2020), the clinical signs and symptoms of PD in different ethnic groups were reviewed as well as the different response to treatments. It was found that Black PD patients had a higher mortality rate and higher rates of cognitive decline and dementia. Hispanic PD patients also show the same high rates of cognitive decline while Asian PD patients have more inconsistent findings. The possible causes for these differences between ethnicity could be due to genetics, co-morbidities, healthcare inequalities and socio-cultural factors (Ben-Joseph *et al.*, 2020).

1.8. PD in South Africa

The data acquired for PD in South Africa is limited. In a study done by Amod and Bhigjee (2019) that looked at PD in Kwa-Zulu Natal, it was found that the median age of

onset was 60 years, most patients were male and 20% of patients had early onset PD. Dyskinesia and neuropsychiatric symptoms were prominently exhibited by Indian and White patients. Furthermore, it was found that there was an increase in referral centre prevalence from the last study done by Cosnett and Bill in 1988. In a South African study done by Smith and Modi (2016), it was found that the majority of the sample presented with a classic idiopathic PD phenotype where 59% of males and 94% of females presented with a resting tremor. The study also found that within the Black South African sample, 31% had early onset of idiopathic PD (mostly female), 29% had symptoms that were akinetic (mostly male) and 74% presented with cognitive impairment (mostly male). It is evident that more data is needed on PD that is specific to South Africans, with a large sample size to incorporate the different ethnicities, thereby bringing attention to this often neglected neurodegenerative disease.

2. AIMS AND OBJECTIVES

As very little research exists on asymmetric symptoms in PD, we aimed to identify the predictive factors that are associated with the asymmetric symptoms seen in Parkinson's Disease patients in South Africa by distributing a survey to PD patients in Johannesburg, South Africa.

2.1. Specific aims

1. To determine the percentage prevalence of asymmetric PD versus generalised PD in a sample of PD patients in Johannesburg
2. To determine how patient's demographics and disease history influence PD asymmetry
3. To determine the correlation between initial symptom laterality and handedness in PD patients
4. To determine if non-motor symptoms of PD have an impact on the asymmetry found in PD patients

3. METHODS

3.1. Ethical clearance

An ethics application was submitted (Protocol number: M210442) to the Human Research Ethics Committee (medical) at the University of the Witwatersrand and ethical clearance was granted (see Appendix C).

3.2. Research Design

This study is a prospective cross-sectional survey. An online questionnaire was administered.

3.3. Sample

The inclusion criteria consisted of patients in any of the 5 stages of PD that experienced bradykinesia and at least one of the following: rigidity, tremor, postural instability. The exclusion criteria consisted of patients with cognitive impairment who were not able to give consent to the questionnaire. This decision was made by Dr Marcelle Smith who is a qualified neurologist that is currently treating these patients and therefore was able to determine which patients were unable to give consent and participate in the survey. From the 107 links sent to willing participants, 60 patients responded to the questionnaire. After cleaning the data, it was found that 1 patient responded twice to the questionnaire and was therefore excluded. Thus, the sample size consisted of 59 PD patients recruited from Sandton Mediclinic and Wits Donald Gordon Medical Centre in Johannesburg, South Africa.

3.4. Data collection

Due to the Covid-19 pandemic, no face-to-face interaction was allowed in order to prevent the spread of the virus. Therefore, a questionnaire (see Appendix B) was created using an online survey program known as REDCap. Study data were collected and managed from 20 July 2021 to 31 October 2021 using this electronic data capture tool hosted at the University of the Witwatersrand. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for data integration and interoperability with external sources. Dr Marcell Smith acted as the gate keeper and made a phone call to each patient with diagnosed PD to request for their participation in this study. The patients who agreed to participate were sent the participant information sheet (see Appendix A) and the link to the questionnaire via email. Patients were able to complete the survey on their phone or computer without having to print it out. This program was easy to use and allowed patients to give responses that were anonymous thereby protecting patient’s identity during the data capturing procedure.

Survey questions were designed to establish information related to the objectives: patient demographics, disease history, presence of asymmetrical symptoms, presence of non-motor symptoms and handedness. Patients who knew of a biological family member that had been diagnosed with PD were taken to have a genetic predisposition to PD. Questions related to disease severity were taken from the Unified PD Rating Scale (UPDRS). Questions related to sleep quality were taken from the Queen Square Brain Bank (QSBB) criteria and Pittsburgh Sleep Quality Index (PSQI) and questions related to anxiety and depression were taken from the Mini International Neuropsychiatric Interview (MINI) Screen. Questions were taken from these sources because they have a high test-rested reliability and good validity (Skorvanek *et al*., 2017; Sheehan *et al*., 1997 and Backhaus *et al*., 2002). These sources were also used because they have been included in studies done on South African patients or in the African setting as seen in Mahne *et al*. (2016), Smith and Modi (2016), Olley *et al*. (2004), (Ndlovu *et al*., 2021) and Gelaye *et al*. (2014). The Alcohol Use Disorders Identification Test (AUDIT) and the Drug Abuse Screening Test (DAST) was used to assess patient's alcohol and drug use, respectively. These tools are widely recognized and frequently used on South African patients (Smook *et. al.*, 2014).

The following are variables that were assessed in the demographic section of the survey: gender (male, female or other); age and race (Black, White, Indian, Coloured or other). Questions on the patient's initial laterality of symptoms (right, left or both sides) and current laterality of symptoms (right, left or both sides) were asked to determine if there was a change in asymmetry from the onset of the disease until the time that the questionnaire was completed. Questions on handedness, which was the patient's dominant hand (right-handed, left-handed or ambidextrous) and writing hand, which was the hand the patient wrote with (right-handed or left-handed) were asked to determine if there was a differentiation between the patient's dominant and writing hand and which of these is related to the asymmetric symptoms. Genetic predisposition was assessed in which patients were asked if they knew of a biological family member that had PD, if they answered yes, it was taken as the patient having a genetic predisposition to developing PD. Non-motor symptoms of PD according to the MDS-UPDRS were examined in this study. Patients were asked to assess their non-motor symptoms where 'normal' indicated that there was no problem, 'moderate' indicated that the patient experienced the symptom, but it did not affect their day-to-day living and 'severe' indicated that the symptom affected the patient's ability to carry out their normal activities. The patient's state of PD symptoms was assessed using the Hoehn and Yahr scale. This was

done by patients selecting the number that best described their symptoms where 1=one sided symptoms only with minimal disability; 2=both sides affected but balance is stable; 3=mild to moderate disability but balance is affected; 4=severe disability but able to walk and stand without help and 5=confinement to bed or wheelchair unless aided.

3.5. Data Capturing and Analysis

REDCap allowed for the hassle-free capturing of data as patient answers were automatically distributed into the various categories. After the data capturing process, all the data were transferred to Microsoft Excel and STATA for statistical analysis. STATA is a statistical software programme used for the statistical analysis and visualisation of data.

When analysing the data, the prevalence of asymmetric PD was determined by the percentage of patients that presented with asymmetry at the start of the disease (initially) and at the current stage of the disease. This was compared with the percentage of patients that presented with generalised idiopathic PD in which symptoms presented on both sides of the body. Descriptive statistics, such as measures of central tendency and dispersion, was used to summarize the data collected. All variables were placed into frequency distribution tables. From this, contingency tables were drawn up for all categorical variables and hypothesis testing was done in which a null hypothesis (H_O) and an alternate hypothesis (H_A) were constructed. The null hypothesis proposed that there was no statistically significant association between the variables and the alternate hypothesis proposed that there was a statistically significant association between the variables. Then, Chi-squared tests were done to determine the p-value and therefore determine if H_O or H_A should be accepted. This was done if 50% or more of the expected frequencies in the contingency table were above or equal to 5.

The Chi-squared test was done in STATA using the following method:

First, the expected value was calculated using the following formula:

$$Expected\ value = \frac{(row\ total)(column\ total)}{total\ number}$$

Next, Degrees of Freedom was calculated using the following formula:

$$df = n-1$$

Where:

df = degrees of freedom

n = number of categories

The df was then used to calculate the critical value. The critical value is the value that divides a graph into two regions, one where you reject H_O and one where you accept it. This was calculated using the following table:

χ^2 (Chi-Squared) Distribution: Critical Values of χ^2

	Significance level		
Degrees of freedom	5%	1%	0.1%
1	3.841	6.635	10.828
2	5.991	9.210	13.816
3	7.815	11.345	16.266
4	9.488	13.277	18.467
5	11.070	15.086	20.515
6	12.592	16.812	22.458
7	14.067	18.475	24.322
8	15.507	20.090	26.124
9	16.919	21.666	27.877
10	18.307	23.209	29.588

Figure 3: Critical values of chi-squared distribution (David and Brambilla, 1958)

The Chi-squared value was calculated using the following formula:

$$x^2 = \Sigma \frac{(O_i - E_i)^2}{E_i}$$

Where:

x^2 = Chi squared

O_i = Observed value

E_i = Expected value

If x^2 fell onto the left side of the critical value, H_O cannot be rejected. If x^2 fell into the right side of the critical value, H_O is rejected and H_A is accepted.

A Fisher's exact test was also used to determine if variables were statistically associated with one another. This was done in cases where less than 50% of the expected frequencies in the contingency table were above or equal to 5.

The Fisher's exact test was done in STATA using the following formula:

$$p = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{a!\,b!\,c!\,d!\,n!}$$

Where:

p = p-value

a, b, c, d = values in a contingency table

n = total frequency

The p-value is the probability that the association between two variables occurred by chance (under the null hypothesis). A significance level of $\alpha = 0.05$ was used, therefore, if the p-value ≤ 0.05, there is a statistically significant difference between the variables so that H_O can be rejected and H_A can be accepted. If the p-value > 0.05, then there is no statistically significant difference between the variables, and H_O must be accepted.

4. RESULTS

The STATA statistical programme and Microsoft Excel was used for all the data analysis conducted in this study. This study consisted of a sample size of 59 participants with diagnosed PD of which 30 were male and 29 were female. The mean age was 65.19±1.28 years old [95% Cl = 62.63-67.74] (SD = 9.81, min = 44, max = 83) and the mean age of onset of the disease was 57.32±1.48 years old [95% Cl = 54.35-60.29] (SD = 11.39, min = 36, max = 81). The mean duration of illness was 7.86±0.77 years [95% Cl = 6.33-9.40] (SD = 5.90,

min = 1, max = 22). The sample consisted of 5 Black patients, 49 White patients and 6 Indian patients.

4.1. Demographic Data

The demographic data of the patients used in this study can be found in Table 1 below. It can be seen that only age has a p-value that is ≤ 0.05, therefore it is the only variable that has a significant statistical association with current laterality. The variables are further statistically analysed below.

Demographics	**Current Asymmetry**		**Generalised PD**	**Total**	**p-values**
	Right	Left			
Sex					0.813
Male	7	11	12	30	
Female	6	9	14	29	
Age					0.003
40 – 49	3	0	1	4	
50 – 59	0	6	2	8	
60 – 69	2	9	16	27	
70 – 79	7	5	5	17	
80 – 89	1	0	2	3	
Race					1.000
Black	1	2	2	5	
White	11	16	22	49	
Indian	1	2	2	5	
Coloured	0	0	0	0	
Other	0	0	0	0	
Age of Onset					0.483
30 – 39	2	2	1	5	

40 – 49	1	7	5	13	
50 – 59	4	4	6	14	
60 – 69	4	6	11	21	
70 – 79	2	0	2	4	
80 – 89	0	0	2	2	
Genetic predisposition					0.241
Yes	3	2	8	13	
No	10	17	17	44	
Chronic medication					0.499
Yes	13	20	24	57	
No	0	0	2	2	

Table 1: Demographic data of PD patients used in this study

4.2. Asymmetry of symptoms

4.2.1. Asymmetry Vs Generalised PD

Table 2 indicates patient's asymmetry of symptoms (either right or left) at the onset of the disease and currently and how many of the patients either changed laterality, remained asymmetric or remained with generalised PD (symptoms on both sides of the body).

Asymmetry of Symptoms		Number of Patients	Percent of patients (%)
Initial Laterality	Current Laterality		
Right	Right	11	18.64
Right	Left	0	0.00
Right	Generalised PD	9	15.25
Left	Right	2	3.39
Left	Left	19	32.20

Left	Generalised PD	10	16.95
Generalised PD	Right	0	0.00
Generalised PD	Left	1	1.69
Generalised PD	Generalised PD	7	11.86
Total		59	99.98

Table 2: Initial vs current laterality of PD patients in this sample

Table 2 indicates the number of patients that have sustained laterality of symptoms and those where symptom laterality has changed from the initial onset of the disease until the current stage of PD. From this sample, 18.64% (11 patients) continued to have a right laterality of symptoms while 32.20% (19 patients) continued to have left laterality of symptoms. It can be seen that 0.00% (0 patients) have changed from right laterality to left laterality of symptoms whereas 3.39% (2 patients) changed from left laterality to right laterality of symptoms. From this sample, 15.25% (9 patients) changed from right laterality to generalised PD and 16.95% (10 patients) changed from left laterality to generalised PD. Therefore, 32.20% (19 patients) changed from having symptom laterality to generalised PD. Table 3 indicates that 0.00% (0 patients) changed from generalised PD to right laterality, 1.69% (1 patient) changed from generalised PD to left laterality and 11.86% (7 patients) continued to have generalised PD.

The findings indicate that more patients presented with asymmetry both at the onset of PD and currently compared to generalised PD. However, the amount of PD patients presenting with asymmetry decreased by 30.51% from the onset of the disease to the present day whereas the number of patients with Generalised PD increased by 31.51%.

4.2.2. Initial vs Current Laterality

Table 3 indicates the number of patients in this study that presented with right laterality of symptoms, left laterality of symptoms and generalised PD (both sides affected) at the onset of the disease (initial laterality) and at the time the survey was conducted (current laterality).

Laterality	Initial Frequency (N)	Initial Percentage (%)	Current Frequency (N)	Current Percentage (%)
Right	20	33.90	13	22.03
Left	31	52.54	20	33.90
Both	8	13.56	26	44.07
Total	59	100.00	59	100.00

Table 3: Initial and Current laterality of PD patients in this sample

From this sample, 33.90% (20 patients) presented with initial right laterality of symptoms and 52.54% (31 patients) presented with initial left laterality of symptoms. Therefore, 86.44% (51 patients) presented with initial asymmetric PD while 13.56 (8 patients) presented with initial generalised PD. It was seen that 22.03% (13 patients) presented with current right laterality of symptoms and 33.90% (20 patients) presented with current left laterality of symptoms. Therefore 55.93% (33 patients) presented with current asymmetric PD while 45.07% (26 patients) presented with current generalised PD.

This indicates that with regards to generalised PD, more patients exhibited symptoms on both sides of their body currently compared to at the onset of the disease. More people exhibited asymmetry (right or left laterality) at the onset of the disease but as time progressed, more patients exhibited symptoms on both sides of their body suggesting that patients move from an initial laterality to a generalised PD as the disease progresses.

4.3. Asymmetry Is Not Related to Sex, Age of Onset, Genetics or Handedness

4.3.1. Sex

Initial laterality according to sex of the PD patients is shown in Table 4 below.

Sex	Initial Laterality			Total
	Right Laterality	Left Laterality	Generalised PD	

Male	11	18	1	30
	36.67	60.00	3.33	100.00
Female	9	13	7	29
	31.03	44.83	24.14	100.00
Total	20	31	8	59
	33.90	52.54	13.56	100.00

Table 4: Sex vs initial laterality in PD patients

Table 4 shows that in a sample of 30 males and 29 females, 36.67% of males (11 males) and 60.00% of females (18 females) presented with right asymmetry whereas 31.03% of males (9 males) and 44.83% of females (13 females) presented with left asymmetry. In total, 96.67% of males (29 males) and 75.86% of females (22 females) presented with asymmetric PD. 3.33% of males in this sample (1 male) and 24.14% of females (7 females) presented with generalised PD.

This indicates that initial left laterality is prominent in both males and females but more males present with initial left laterality than females. Right laterality of symptoms is more prominent in males than females and initial generalised PD is more prominent in females.

A Pearson's chi-square test was done and it was found that the sex of a patient is not associated with the initial laterality of PD symptoms (p=0.064).

Table 5 indicates how a patient's sex influences current laterality. It was seen that generalised PD is the most prominent laterality in both males and females, but more females exhibit generalised PD than males whereas more males exhibit left laterality and right laterality of symptoms.

	Current Laterality			
Sex	Right laterality	Left Laterality	Generalised PD	Total
Male	7	11	12	30

	23.33	36.67	40.00	100.00
Female	6	9	14	29
	20.69	31.03	48.28	100.00
Total	13	20	26	59
	22.03	33.90	44.07	100.00

Table 5: Sex vs current laterality in PD patients

In a sample of 30 males and 29 females, 23.33% of males (7 males) and 20.69% of females (6 females) presented with right asymmetry whereas 36.66% of males (11 males) and 31.03% of females (9 females) presented with left asymmetry. In total, 59.88% of males (18 males) and 51.72% of females (15 females) presented with asymmetric PD. 40.00% of males in this sample (12 males) and 48.28% of females (14 females) presented with generalised PD.

A Pearson's chi-square test was done and it was found that the sex of a patient is not associated with the current laterality of PD symptoms (p=0.813).

4.3.2. Age of Onset

Table 6 shows the initial laterality of symptoms of PD patients in this sample according to their age of onset. Most patients in the 30 – 39, 40 – 49, 50 – 59 and 60 – 69 year age of onset category initially presented with left laterality of symptoms. Most patients in the 70 – 79 year age of onset category presented with initial right laterality of symptoms while all the patients in the 80 – 89 year age of onset category presented with right laterality of symptoms and generalised PD.

	Initial Laterality			
Age of Onset	Right laterality	Left Laterality	Generalised PD	Total
30 – 39	1	4	0	5
	20.00	80.00	0.00	100.00
40 - 49	4	7	2	13

	30.77	53.85	15.38	100.00
	4	9	1	14
50 – 59	28.57	64.29	7.14	100.00
	7	11	3	21
60 – 69	33.33	52.38	14.29	100.00
	3		1	4
70 – 79	75.00	0.00	25.00	100.00
	1	0	1	2
80 – 89	50.00	0.00	50.00	100.00
	20	31	8	59
Total	33.90	52.54	13.56	100.00

Table 6: Age of onset vs initial laterality

Table 6 indicates that from the 5 patients in the 30 – 39 year age of onset category, 20.00% (1 patient) presented with initial right laterality of symptoms, 80.00% (4 patients) presented with initial left laterality of symptoms and 0.00% (0 patients) presented with initial generalised PD. From the 13 patients in the 40 – 49 year age of onset category, 30.77% (4 patients) presented with initial right laterality of symptoms, 53.85% (7 patients) presented with initial left laterality of symptoms and 15.83% (2 patients) presented with initial generalised PD. From the 14 patients in the 50 – 59 year age of onset category, 28.57% (4 patients) presented with initial right laterality of symptoms, 64.29% (9 patients) presented with initial left laterality of symptoms and 7.14% (1 patient) presented with initial generalised PD. From the 21 patients in the 60 – 69 year age of onset category, 33.33% (7 patients) presented with initial right laterality of symptoms, 52.38% (11 patients) presented with initial left laterality of symptoms and 14.29% (3 patients) presented with initial generalised PD. From the 4 patients in the 70 – 79 year age of onset category, 75.00% (3 patients) presented with initial right laterality of symptoms, 0.00% (0 patients) presented with initial left laterality of symptoms and 25.00% (1 patient) presented with initial generalised PD. From the 2 patients in the 80 – 89 year age of onset category, 50.00% (1 patient) presented with initial right

laterality of symptoms, 0.00% (0 patients) presented with initial left laterality of symptoms and 50.00% (1 patient) presented with initial generalised PD.

A Fisher's exact test was done and it was found that the age of onset of PD symptoms is not associated with the initial laterality of PD symptoms (p=0.384).

4.3.3. Genetic Predisposition

The initial laterality of symptoms according to the PD patient's genetic predisposition to PD can be seen in Table 7 below. Most patients presented with left laterality of symptoms in both patients that had a family member with PD and those that did not have a family member with PD. Patients that had a genetic predisposition to PD had a higher percentage of patients with left laterality of symptoms and generalised PD whereas patients without a genetic predisposition had a higher percentage of patients with right laterality of symptoms.

Genetic Predisposition	Initial Laterality			Total
	Right laterality	Left Laterality	Generalised PD	
Yes	3	8	2	13
	23.08	61.54	15.38	100.00
No	16	22	6	44
	36.36	50.00	13.64	100.00
Total	19	30	8	57
	33.33	52.63	14.04	100.00

Table 7: Genetic predisposition vs initial laterality

In this sample, 13 patients had family members with PD of which 23.08% (3 patients) had initial right laterality of symptoms, 61.54% (8 patients) had initial left laterality of symptoms and 15.38% (2 patients) had initial generalised PD. The sample consisted of 44 patients that had no known family members with PD. From this, 36.36% (16 patients) had initial right

laterality of symptoms, 50.00% (22 patients) had initial left laterality of symptoms and 13.64% (6 patients) had initial generalised PD. Two patients were not sure if they had a family member with PD or not and were therefore excluded.

A Pearson's chi-square test was done and it was found that the genetic predisposition of a patient to PD is not associated with the initial laterality of PD symptoms (p=0.668).

The current laterality of symptoms according to genetic predisposition can be seen in Table 8 below. Most patients that had a family member with PD presented with current generalised PD whereas most patients that did not have family members with PD presented with current left laterality of symptoms and generalised PD.

Family member with PD	Current Laterality			Total
	Right Laterality	Left Laterality	Generalised PD	
Yes	3	2	8	13
	23.08	15.38	61.54	100.00
No	10	17	17	44
	22.73	38.64	38.64	100.00
Total	13	19	25	57
	22.81	33.33	43.86	100.00

Table 8: Genetic predisposition vs current laterality in PD patients

In this sample, 11 patients had family members with PD of which 23.08% (3 patients) had right laterality of symptoms, 15.38% (2 patients) had left laterality of symptoms and 61.54% (8 patients) had generalised PD. The sample consisted of 44 patients that had no known family members with PD. From this, 22.73% (10 patients) had right laterality of symptoms, 38.64% (17 patients) had left laterality of symptoms and 38.64% (17 patients) had generalised PD. 2 patients were not sure if they had a family member with PD or not and were therefore excluded.

A Pearson's chi-square test was done and it was found that the genetic predisposition of a patient to PD is not associated with the current laterality of PD symptoms (p=0.243).

4.3.4. Handedness

Figure 4 shows the initial laterality of PD symptoms according to the patient's handedness (writing hand). Most right- and left-handed patients presented with left laterality of symptoms. More right-handed patients presented with right laterality of symptoms than left-handed patients, whereas more left-handed patients presented with left laterality that right-handed patients. No left-handed patients presented with initial generalised PD.

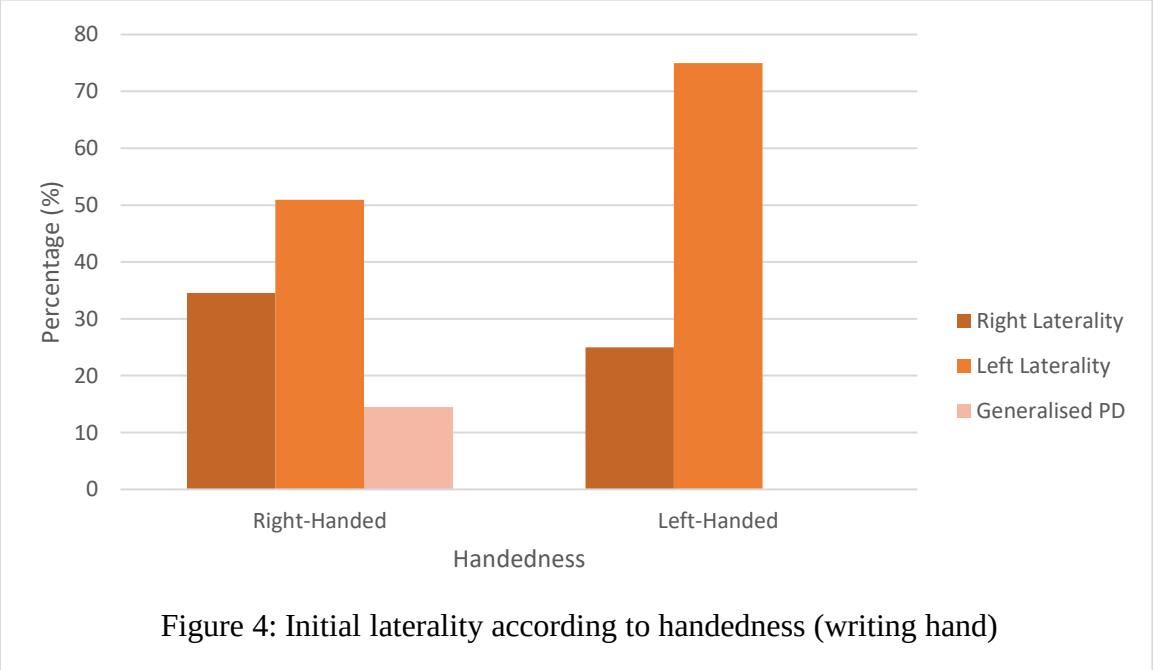


Figure 4: Initial laterality according to handedness (writing hand)

Table 10 below shows the initial laterality of PD symptoms according to the patient's dominant hand (right-handed, left-handed, ambidextrous). More right-handed patients presented with right laterality of symptoms than the other two groups whereas more left-handed and ambidextrous patients presented with left laterality of symptoms. No left-handed patients presented with initial generalised PD and no ambidextrous patients presented with initial left laterality of symptoms or initial generalised PD.

Handedness	Initial Laterality	Total

	Right Laterality	Left Laterality	Generalised PD	
Right-Handed	19	26	8	53
	35.85	49.06	15.09	100.00
Left-Handed	1	3	0	4
	25.00	75.00	0.00	100.00
Ambidextrous	0	2	0	2
	0.00	100.00	0.00	100.00
Total	20	31	8	59
	33.90	52.54	13.56	100.00

Table 9: handedness vs initial laterality in PD patients

The sample consisted of 53 right-handed patients of which 35.85% (19 patients) presented with initial right laterality and 49.06% (26 patients) presented with left laterality while 15.09% (8 patients) presented with initial generalised PD. With regards to the 4 left-handed patients, 25.00% (1 patient) presented with initial right laterality and 75.00% (3 patients) presented with initial left laterality. The sample consisted of 2 ambidextrous patients who both presented with initial left laterality.

A Fisher's exact test was done and it was found that the handedness of a patient is not associated with the initial laterality of PD symptoms ($p=0.747$).

4.4. Asymmetry Changes Over Time and With Severity of Disease

4.4.1. Age vs current laterality

Figure 5 shows the age of the PD patients used in this sample. Most of the sample included patients in the 60 – 69 year age category with the 80 – 89 year age category making up the minority. The mean age of the sample was 65.19 ±1.28 years old [95% Cl = 62.63-67.74].

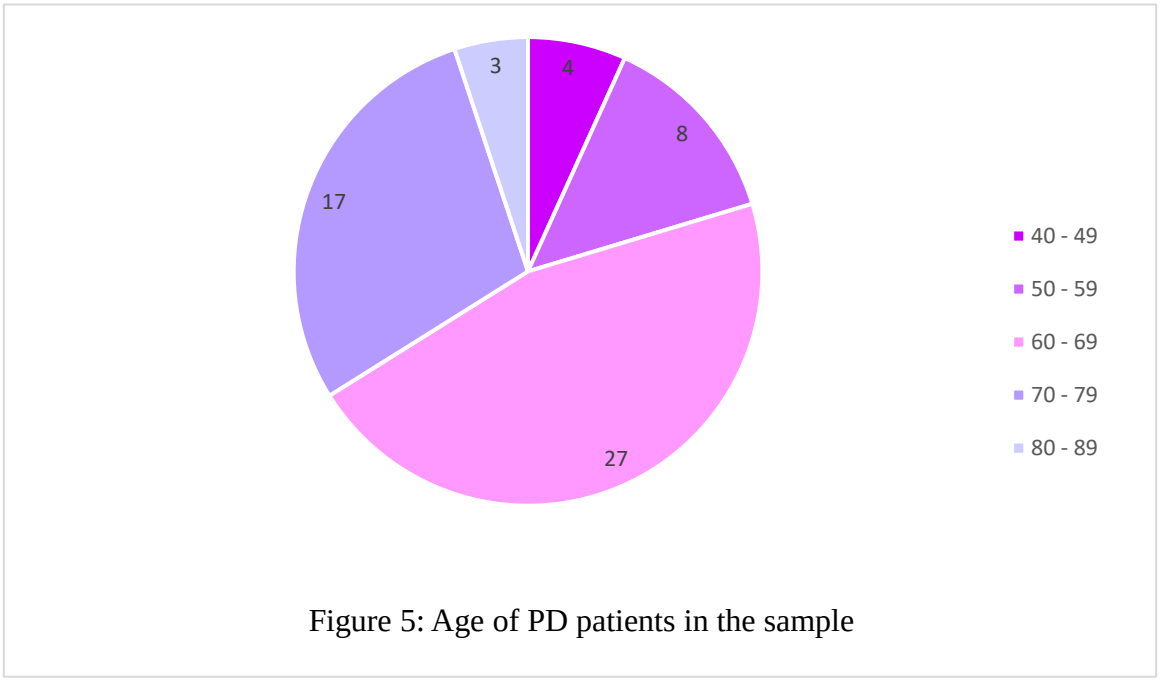


Figure 5: Age of PD patients in the sample

Patients were grouped in 10-year age categories. Figure 5 indicates that 6.78% (4 patients) were between the ages of 40 – 49, 13.56% (8 patients) were between the ages of 50 – 59, 45.76% (27 patients) were between the ages of 60 – 69, 28.81% (17 patients) were between the ages of 70 – 79 and 5.08% (3 patients) were between the ages of 80 – 89.

Age groups of the PD patients used in this sample and their current laterality are shown in Table 10 below. It indicates that right laterality of symptoms is most common in the age groups 40 – 49 and 70 - 79, left laterality of symptoms is most common in age group 50 – 59 and generalised PD is most common in age groups 60 – 69 and 80 – 89. There were no patients in the 40 - 49 and 80 – 89 that presented with left laterality of symptoms.

Age	Current Laterality	Total

	Right laterality	Left Laterality	Generalised PD	
40 – 49	3	0	1	4
	75.00	00.00	25.00	100.00
50 – 59	0	6	2	8
	0.00	75.00	25.00	100.00
60 – 69	2	9	16	27
	7.41	33.33	59.26	100.00
70 – 79	7	5	5	17
	41.18	29.41	29.41	100.00
80 – 89	1	0	2	3
	33.33	0.00	66.67	100.00
Total	13	20	26	59
	22.03	33.90	44.07	100.00

Table 10: Age vs current laterality in PD patients

Table 10 indicates that from the 4 individuals in the 40 – 49 age group, 75.00% (3 patients) had right laterality of symptoms, 0.00% (0 patients) had left laterality of symptoms and 25.00% (1 patient) had generalised PD. From the 8 patients in the 50 – 59 age group, 0.00% (0 patients) had right laterality, 75.00% (6 patients) had left laterality and 25.00% (2 patients) had generalised PD. From 27 patients in the 60 – 69 age group, 7.41% (2 patients) had right laterality of symptoms, 33.33% (9 patients) had left laterality of symptoms and 59.26% (16 patients) presented with generalised PD. From the 17 patients in the 70 – 79 age group, 41.18% (7 patients) presented with right laterality of symptoms, 29.41% (5 patients) presented with left laterality of symptoms, 29.41% (five patients) presented with generalised PD. From the 3 patience in the 80 – 89 age group, 33.33% (1 patient) presented with right laterality of symptoms, 0.00% (0 patients) presented with left laterality of symptoms and 66.67% (2 patients) presented with generalised PD.

A Fisher's exact test was done and it was found that the age of a patient is associated with the current laterality of PD symptoms (p=0.003).

4.4.2. Stage of PD symptoms vs initial laterality

The relationship between the stage of PD symptoms and the initial laterality of symptoms found in the PD patients used in this sample can be seen in Table 11 below. It is seen that most patients with stage 1 and 3 of PD symptoms presented with initial left laterality, most patients with stage 2 of PD symptoms and all patients with stage 5 of PD symptoms presented with initial right laterality and most patients with stage 4 of PD symptoms presented with initial generalised PD. No patients with stage 1 of PD symptoms presented with initial generalised PD, no patients with stage 4 of PD symptoms presented with initial right laterality and no patients with stage 5 of PD symptoms presented with initial left laterality or initial generalised PD.

Stage of PD symptoms	Initial Laterality			Total
	Right Laterality	Left Laterality	Generalised PD	
1	7	12	0	19
	36.84	63.16	0.00	100.00
2	4	2	2	8
	50.00	25.00	25.00	100.00
3	7	16	4	27
	25.93	59.26	14.81	100.00
4	0	1	2	3
	0.00	33.33	66.67	100.00
5	2	0	0	2
	100.00	0.00	0.00	100.00
Total	20	31	8	59

	33.90	52.54	13.56	100.00

Table 11: Symptoms of PD vs initial laterality

Table 11 indicates that from the 19 patients in stage 1 of PD symptoms, 36.84% (7 patients) had initial right laterality of symptoms, 63.16% (12 patients) presented with initial left laterality of symptoms and 0.00% (0 patients) presented with initial generalised PD. From the 8 patients in stage 2 of PD symptoms, 50.00% (4 patients) presented with initial right laterality of symptoms, 25.00% (2 patients) presented with initial left laterality of symptoms and 25.00% (2 patients) presented with initial generalised PD. From the 27 patients in stage 3 of PD symptoms, 25.93% (7 patient) presented with initial right laterality of symptoms, 59.26% (16 patients) presented with initial left laterality of symptoms and 14.81% (4 patients) presented with initial generalised PD. From the 3 patients in stage 4 of PD symptoms, 0.00% (0 patients) presented with initial right laterality of symptoms, 33.33% (1 patient) presented with initial left laterality of symptoms and 66.67% (2 patients) presented with initial generalised PD. From the 2 patients in stage 5 of PD symptoms, 100.00% (2 patients) presented with initial right laterality of symptoms, 0.00% (0 patients) presented with initial left laterality of symptoms and 00.00% (0 patients) presented with initial generalised PD.

A Fisher's exact test was done and it was found that the patient's stage of PD symptoms is associated with the initial laterality of PD symptoms (p=0.023).

4.4.3. Stage of PD symptoms vs current laterality

Table 12 below indicate the stage of PD symptoms seen in PD patients in this sample in relation to their current laterality of symptoms. The data shows that most patients with stage 1 and 4 of PD symptoms presented with current left laterality, most patients with stage 2 and 3 of PD symptoms presented with current generalised PD, most patients with stage 5 of PD symptoms presented with current right laterality and generalised PD.

	Current Laterality			Total

Stage of PD symptoms	Right Laterality	Left Laterality	Generalised PD	
1	8	11	0	19
	42.11	57.89	0.00	100.00
2	1	0	7	8
	12.50	0.00	87.50	100.00
3	3	7	17	27
	11.11	25.93	62.96	100.00
4	0	2	1	3
	0.00	66.67	33.33	100.00
5	1	0	1	2
	50.00	0.00	50.00	100.00
Total	13	20	26	59
	22.03	33.90	44.07	100.00

Table 12: Stage of PD symptoms vs current laterality

Table 12 indicates that from the 19 patients in stage 1 of PD symptoms, 42.11% (8 patients) had right laterality of symptoms, 57.89% (11 patients) presented with left laterality of symptoms and 0.00% (0 patients) presented with generalised PD. From the 8 patients in stage 2 of PD symptoms, 12.50% (1 patient) presented with right laterality of symptoms, 0.00% (0 patients) presented with left laterality of symptoms and 87.50% (7 patients) presented with generalised PD. From the 27 patients in stage 3 of PD symptoms, 11.11% (3 patient) presented with right laterality of symptoms, 25.93% (7 patients) presented with left laterality of symptoms and 62.96% (17 patients) presented with generalised PD. From the 3 patients in stage 4 of PD symptoms, 0.00% (0 patients) presented with right laterality of symptoms, 66.67% (2 patients) presented with left laterality of symptoms and 33.33% (1 patient) presented with generalised PD. From the 2 patients in stage 5 of PD symptoms, 50.00% (1 patient) presented with right laterality of symptoms, 0.00% (0 patients) presented with left laterality of symptoms and 50.00% (1 patient) presented with generalised PD.

A Fisher's exact test was done and it was found that the patient's stage of PD symptoms is associated with the current laterality of PD symptoms ($p<0.0001$).

4.4.4. Stage of PD symptoms vs change in symptom asymmetry

Table 13 below indicates the relationship between the stage of PD symptoms and the change in symptom asymmetry seen in PD patients in this sample. The data indicates that in stage 1 of PD symptoms, most patients had symptoms that remained asymmetric, in stage 2 and 3 of PD symptoms, most patients had symptoms that changed from asymmetric to generalised, in stage 4 of PD symptoms, most patients had symptoms that either remained asymmetric, changed from asymmetric to generalised or changed from generalised to asymmetric. In stage 5 of PD symptoms, most patients either had symptoms that remained asymmetric or symptoms that changed from asymmetric to generalised.

	Change in symptom Asymmetry				
Stage of PD Symptoms	Asymmetry to Asymmetry	Asymmetry to Generalised	Generalised to Asymmetry	Generalised to Generalised	Total
1. One-sided symptoms only – minimal disability	19 100.00	0 0.00	0 0.00	0 0.00	19 100.00
2. Both sides affected but balance is stable	1 12.50	5 62.50	0 0.00	2 25.00	8 100.00
3. Mild to moderate disability, balance is affected	10 37.04	14 51.85	0 0.00	3 11.11	27 100.00
4. Severe disability, able to walk and stand without help	1 33.33	0 0.00	1 33.33	1 33.33	3 100.00

5. Confinement to bed or wheelchair unless aided	1 50.00	1 50.00	0 0.00	0 0.00	2 100.00
Total	32 54.24	20 33.90	1 1.69	6 10.17	59 100.00

Table 13: Stage of PD symptoms vs change in symptom asymmetry

Table 13 shows that from the 19 patients with stage 1 of PD symptoms, 100.00% (19 patients) had symptoms that remained asymmetric, 0.00% (0 patients) had symptoms that changed from asymmetric to generalised, changed from generalised to asymmetric and remained generalised. From the 8 patients with stage 2 of PD symptoms, 12.50% (1 patient) had symptoms that remained asymmetric, 62.50% (5 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 25.00% (2 patients) had symptoms that remained generalised. From the 27 patients with stage 3 of PD symptoms, 37.04% (10 patients) had symptoms that remained asymmetric, 51.85% (14 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 11.11% (3 patients) had symptoms that remained generalised. From the 3 patients with stage 4 of PD symptoms, 33.33% (1 patient) had symptoms that remained asymmetric, 0.00% (0 patients) had symptoms that changed from asymmetric to generalised, 33.33% (1 patient) had symptoms that changed from generalised to asymmetric and 33.33% (1 patient) had symptoms that remained generalised. From the 2 patients with stage 5 of PD symptoms, 50.00% (1 patient) had symptoms that remained asymmetric, 50.00% (1 patient) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 0.00% (0 patients) had symptoms that remained generalised.

A Fisher's exact test was done and it was found that the patient's change in symptom asymmetry is associated with their stage of PD symptoms ($p<0.0001$).

4.5. Asymmetry is Related to Non-Motor Symptoms Of PD

Table 14 below indicates the number and percentage of the PD patients that present with each non-motor symptom.

Non-motor symptoms	Severity	Freq.	Percentage (%)
	Normal	29	49.15
Cognitive Impairment	Moderate	26	44.07
	Severe	4	6.78
	Normal	43	72.88
Hallucination	Moderate	16	27.12
	Severe	0	0.00
	Normal	37	62.71
Depressed1	Moderate	17	28.81
	Severe	5	8.47
	Normal	33	55.93
Depressed2	Moderate	22	37.29
	Severe	4	6.78
	Normal	36	61.02
Anxious1	Moderate	20	33.90
	Severe	3	5.08
	Normal	44	74.58
Anxious2	Moderate	12	20.34
	Severe	3	5.08
	Normal	44	74.58
Anxious3	Moderate	13	22.03
	Severe	2	3.39
Apathy	Normal	34	57.63

	Moderate	21	35.59
	Severe	4	6.78
	Normal	14	23.73
Sleep Problems	Moderate	38	64.41
	Severe	7	11.86
	Normal	32	55.17
Day time sleepiness	Moderate	24	41.38
	Severe	2	3.45
	Normal	14	23.73
Pain	Moderate	41	69.49
	Severe	4	6.78
	Normal	39	66.10
Loss of smell	Moderate	11	18.64
	Severe	9	15.25
	Normal	24	40.68
Urinary Problems	Moderate	31	52.54
	Severe	4	6.78
	Normal	27	45.76
Constipation	Moderate	28	47.46
	Severe	4	6.78
	Normal	35	59.32
Light Headedness	Moderate	24	40.68
	Severe	0.00	0.00
	Normal	27	45.76
Fatigue	Moderate	30	50.85

Severe	2	3.39

Table 14: PD patients with non-motor symptoms

Table 14 indicates that most PD patients have the normal cognitive impairment, no symptoms of hallucinations, depression, loss of interest, anxiety attacks, quick anxiety peaks, unexpected anxiety, apathy, daytime sleepiness, loss of smell and light headedness. Most PD patients experience moderate sleep problems, pain, urinary problems, constipation and fatigue. Not many patients reported severe symptoms, but many patients reported severe sleep problems and loss of smell.

4.5.1. Current Asymmetry and Change in Symptom Asymmetry vs Daytime Sleepiness

Current Asymmetry vs Daytime Sleepiness

Table 15 below shows current asymmetry of symptoms according to severity of daytime sleepiness seen in PD patients. It was seen that most patients that presented with asymmetry had normal daytime sleepiness while those that presented with generalised PD had moderate daytime sleepiness. No patients that presented with generalised PD had severe daytime sleepiness.

Current Asymmetry	Daytime Sleepiness			Total
	Normal	Moderate	Severe	
Yes	22	8	2	32
	68.75	25.00	6.25	100.00
No	10	16	0	26
	38.46	61.54	0.00	100.00
Total	32	24	2	58
	55.17	41.38	3.45	100.00

Table 15: Current asymmetry vs daytime sleepiness in PD patients

In this sample, 32 patients presented with asymmetry of which 68.75% (22 patients) did not present with daytime sleepiness, 25.00% (8 patients) presented with moderate daytime sleepiness and 6.25% (2 patients) presented with severe daytime sleepiness. From the 26 patients that presented with generalised PD, 38.46% (10 patients) did not present with daytime sleepiness, 61.54% (16 patients) presented with moderate daytime sleepiness and 0.00% (0 patients) presented with severe daytime sleepiness.

A Pearson's chi-square test was done and it was found that the patient's daytime sleepiness is associated with the current asymmetry of PD symptoms (p=0.013).

Change in symptom asymmetry vs Daytime Sleepiness

The relationship between daytime sleepiness and change in symptom asymmetry can be seen in Table 16 below. This shows that most patients with no daytime sleepiness presented with symptoms that remained asymmetric, most patients that had moderate daytime sleepiness presented with symptoms that changed from asymmetric to generalised and patients with severe daytime sleepiness presented with symptoms that changed from asymmetric to generalised or generalised to asymmetric. No patients in the normal and moderate categories presented with symptoms that changed from generalised to asymmetric and no patients in the severe category presented with symptoms that changed from asymmetric to generalised or remained generalised.

	Change in symptom Asymmetry				
Daytime Sleepiness	Asymmetry to Asymmetry	Asymmetry to Generalised	Generalised to Asymmetry	Generalised to Generalised	Total
Normal	22	7	0	3	32
	68,75	21.88	0.00	9.38	100.00
Moderate	8	13	0	3	24
	33.33	54.17	0.00	12.50	100.00
Severe	1	0	1	0	2

	50.00	0.00	50.00	0.00	100.00
Total	31	20	1	6	58
	53.45	34.48	1.72	10.34	100.00

Table 16: Daytime sleepiness vs change in symptom asymmetry

Table 16 indicates that from the 32 patients that did not present with daytime sleepiness, 68.75% (22 patients) had symptoms that remained asymmetric, 21,88% (7 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 9.38% (3 patients) had symptoms that remained generalised. From the 24 patients that presented with moderate daytime sleepiness, 33.33% (8 patients) had symptoms that remained asymmetric, 54.17% (13 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 12.50% (3 patients) had symptoms that remained generalised. From the 2 patients that presented with severe daytime sleepiness, 50.00% (1 patient) had symptoms that remained asymmetric, 0.00% (0 patients) had symptoms that changed from asymmetric to generalised, 50.00% (1 patient) had symptoms that changed from generalised to asymmetric and 0.00% (0 patients) had symptoms that remained generalised.

A Fisher's exact test was done and it was found that the patient's daytime sleepiness is associated with the change in symptom asymmetry found in PD patients (p=0.005).

4.5.2. Current Asymmetry vs Pain

The relationship between the current asymmetry of symptoms and pain found in PD patients can be seen in Table 17 below. This shows that both patients that presented with asymmetry and generalised PD had moderate pain. No patients that presented with asymmetry had severe pain.

Current Asymmetry	Pain			Total
	Normal	Moderate	Severe	

Yes	7	26	0	33
	21.21	78.79	0.00	100.00
No	7	15	4	26
	26.92	57.69	15.38	100.00
Total	14	41	4	59
	23.73	69.49	6.78	100.00

Table 17: Current asymmetry vs pain in PD patients

In this sample, 33 patients presented with asymmetry of which 21.21% (7 patients) did not present with pain, 78.79% (26 patients) presented with moderate pain and 0.00% (0 patients) presented with severe pain. From the 26 patients that presented with generalised PD, 26.92% (7 patients) did not present with pain, 57.69% (15 patients) presented with moderate pain and 15.38% (4 patients) presented with severe pain.

A Fisher's exact test was done and it was found that the pain reported by PD patients is associated with the current asymmetry of PD symptoms (p=0.042).

4.5.3. Current Asymmetry and Change in Symptom Asymmetry vs Constipation

Current Asymmetry vs Constipation

The relationship between current asymmetry of symptoms and constipation found in PD patients in this sample can be seen in Table 18 below.

Current Asymmetry	Constipation			Total
	Normal	Moderate	Severe	
Yes	19	14	0	33
	57.58	42.42	0.00	100.00
No	8	14	4	26
	30.77	53.85	15.38	100.00

Total	27	28	4	59
	45.76	47.46	6.78	100.00

Table 18: Current asymmetry vs constipation in PD patients

In this sample, 33 patients presented with asymmetry of which 57.58% (19 patients) did not present with constipation, 42.42% (14 patients) presented with moderate constipation and 0.00% (0 patients) presented with severe constipation. 26 patients presented with generalised PD of which 30.77% (8 patients) did not present with constipation, 53.85% (14 patients) presented with moderate constipation and 15.38% (4 patients) presented with severe constipation.

A Fisher's exact test was done and it was found that the constipation reported by PD patients is associated with the current asymmetry of PD symptoms (p=0.016).

Change in symptom asymmetry vs Constipation

Table 19 below indicates the relationship between constipation and the change in symptom laterality in the PD patients in this sample. The data shows that most patients with no constipation and with moderate constipation presented with symptoms that remain asymmetric. All patients that presented with severe constipation presented with symptoms that changed from asymmetry to generalised. No patients in the normal category had symptoms that changed from generalised to asymmetric and no patients in the severe category remained asymmetric, changed from generalised to asymmetric or remained generalised.

	Change in symptom Asymmetry				
Constipation	Asymmetry to Asymmetry	Asymmetry to Generalised	Generalised to Asymmetry	Generalised to Generalised	Total
Normal	19	4	0	4	27
	70.37	14.81	0.00	14.81	100.00

Moderate	13	12	1	2	28
	46.43	42.86	3.57	7.14	100.00
Severe	0	4	0	0	4
	0.00	100.00	0.00	0.00	100.00
Total	32	20	1	6	59
	54.24	33.90	1.69	10.17	100.00

Table 19: Constipation vs change in symptom asymmetry

Table 19 indicates that from the 27 patients that did not present with constipation, 70.37% (19 patients) had symptoms that remained asymmetric, 14.81% (4 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 14.81% (4 patients) had symptoms that remained generalised. From the 28 patients that presented with moderate constipation, 46.43% (13 patients) had symptoms that remained asymmetric, 42.86% (12 patients) had symptoms that changed from asymmetric to generalised, 3.57 (1 patient) had symptoms that changed from generalised to asymmetric and 7/14% (2 patients) had symptoms that remained generalised. From the 4 patients that presented with severe constipation, 0.00% (0 patients) had symptoms that remained asymmetric, 100.00% (4 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 0.00% (0 patients) had symptoms that remained generalised.

A Fisher's exact test was done and it was found that the constipation reported by PD patients is associated with the change in symptom asymmetry seen in PD (p=0.008).

4.6. Depression and PD

4.6.1. Apathy vs Current Asymmetry

Current asymmetry of PD symptoms according to severity of Apathy can be seen in Table 20 below.

	Apathy	Total

Current Asymmetry	Normal	Moderate	Severe	
Yes	19	14	0	33
	57.58	14.42	0.00	100.00
No	15	7	4	26
	57.69	26.92	15.38	100.00
Total	34	21	4	59
	57.63	35.59	6.78	100.00

Table 20: Current asymmetry vs apathy in PD patients

In this sample, 33 patients presented with asymmetry of which 57.58% (19 patients) did not present with apathy, 14.42% (14 patients) presented with moderate apathy and 0.00% (0 patients) presented with severe apathy. From the 26 patients that presented with generalised PD, 57.69% (15 patients) did not present with apathy, 26.92% (7 patients) presented with moderate apathy and 15.38% (4 patients) presented with severe apathy.

A Fisher's exact test was done and it was found that the apathy reported by PD patients is not associated with the current asymmetry of PD symptoms (p=0.055). However, this p-value is trending significance, thus with a bigger sample size, this association might be significant and therefore it is worth mentioning.

4.6.2. Depression vs Change in symptom asymmetry

Table 21 below indicates the relationship between the change in symptom asymmetry and depression found in PD patients. The data shows that most patients with no depression and moderate depression present with symptoms that remain asymmetric while most patients with severe depression present with symptoms that change from asymmetric to generalised. No patients in the normal group and moderate group presented with symptoms that changed from generalised to asymmetric while no patients in the severe group presented with symptoms that remained asymmetric or that remained generalised.

Depression	Change in symptom Asymmetry				
	Asymmetry to Asymmetry	Asymmetry to Generalised	Generalised to Asymmetry	Generalised to Generalised	Total
Normal	22	11	0	4	37
	59.46	29.73	0.00	10.81	100.00
Moderate	10	5	0	2	17
	58.82	29.41	0.00	11.76	100.00
Severe	0	4	1	0	5
	0.00	80.00	20.00	0.00	100.00
Total	32	20	1	6	59
	54.24	33.90	1.69	10.17	100.00

Table 21: Depression vs change in asymmetry in PD patients

Table 21 indicates that from the 37 patients that did not present with symptoms of depression, 59.46% (22 patients) had symptoms that remained asymmetric, 29.73% (11 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 10.81% (4 patients) had symptoms that remained generalised. From the 17 patients that presented with moderate symptoms of depression, 58.82% (10 patients) had symptoms that remained asymmetric, 29.41% (5 patients) had symptoms that changed from asymmetric to generalised, 0.00% (0 patients) had symptoms that changed from generalised to asymmetric and 11.76% (2 patients) had symptoms that remained generalised. From the 5 patients that presented with severe symptoms of depression, 0.00% (0 patients) had symptoms that remained asymmetric, 80.00% (4 patients) had symptoms that changed from asymmetric to generalised, 20.00% (1 patient) had symptoms that changed from generalised to asymmetric and 0.00% (0 patients) had symptoms that remained generalised.

A Fisher's exact test was done and it was found that the depression reported by PD patients is associated with the change in symptom asymmetry found in PD ($p=0.034$).

4.6.3. Apathy vs Genetic Predisposition

Table 22 below indicate the severity of apathy and the genetic predisposition of PD patients in this sample to PD. The data shows that most patients in the normal and moderate 'apathy' categories did not have a genetic predisposition to PD whereas most patients in the severe 'apathy' category had a genetic predisposition to PD.

Apathy	Genetic Predisposition		Total
	Yes	No	
Normal	8	24	32
	25.00	75.00	100.00
Moderate	2	19	21
	9.52	90.48	100.00
Severe	3	1	4
	75.00	25.00	100.00
Total	13	44	57
	22.81	77.19	100.00

Table 22: Apathy vs genetic predisposition of PD

Table 22 indicates that from the 32 patients that did not present with apathy, 25.00% (8 patients) knew of a biological family member that has PD and 75.00% (24 patients) did not know of a biological family member with PD. From the 21 patients that presented with moderate apathy, 9.52% (2 patients) knew of a biological family member with PD and 90.48% (19 patients) did not know of a biological family member with PD. From the 4 patients that presented with severe apathy, 75.00% (3 patients) knew of a biological family member with PD and 25.00% (1 patient) did not know of a biological family member with PD.

A Fisher's exact test was done and it was found that the apathy reported by PD patients is associated with the genetic predisposition of patients to PD ($p=0.023$).

4.6.4. Depression vs Stage of PD Symptoms

The relationship between depression and sate of PD symptoms found in PD patients in this sample can be seen in Table 23 below. This shows that most patients in stage 1, 2 and 3 of PD symptoms did not experience depression while most patients in stage 4 and 5 of PD symptoms experienced moderate depression.

Stage of PD Symptoms	Depression			Total
	Normal	Moderate	Severe	
1. One-sided symptoms only – minimal disability	13	6	0	19
	68.42	31.58	0.00	100.00
2. Both sides affected but balance is stable	6	1	1	8
	75.00	12.50	12.50	100.00
3. Mild to moderate disability, balance is affected	18	6	3	27
	66.67	22.22	11.11	100.00
4. Severe disability, able to walk and stand without help	0	2	1	3
	0.00	66.67	33.33	100.00
5. Confinement to bed or wheelchair unless aided	0	2	0	2
	0.00	100.00	0.00	100.00
Total	37	17	5	59
	62.71	28.81	8.47	100.00

Table 23: Stage of PD symptoms vs Depression in PD Patients

From the 19 patients in stage 1 of PD symptoms, 68.42% (13 patients) had no depression symptoms, 31.58% (16 patients) had moderate depression and 0.00% (0 patients) had severe depression. From the 8 patients in stage 2 of PD symptoms, 75.00% (6 patients) had no depression symptoms, 12.50% (1 patient) had moderate depression and 12.50% (1 patient) had severe depression. From the 27 patients in stage 3 of PD symptoms, 66.67% (18 patient had no depression symptoms, 22.22% (6 patients) had moderate depression and 11.11% (3

patients) had severe depression. From the 3 patients in stage 4 of PD symptoms, 0.00% (0 patients had no depression symptoms, 66.67% (2 patients) had moderate depression and 33.33% (1 patient) had severe depression. From the 3 patients in stage 5 of PD symptoms, 0.00% (0 patients) had no depression symptoms, 10.00% (2 patients) had moderate depression and 0.00% (0 patients) had severe depression.

A Fisher's exact test was done and it was found that the depression reported by PD patients is associated with the patient's stage of PD symptoms (p=0.043).

5. DISCUSSION

The asymmetry of symptoms is a familiar aspect seen in PD patients, yet it is still not well understood. The aim of this study was to identify the predictive factors that are associated with the asymmetric symptoms seen in Parkinson's Disease patients in South Africa. This was done by comparing patients who presented with asymmetric PD and generalised PD and by determining how patient demographics, patient history, prevalence of laterality, handedness and non-motor symptoms influence the asymmetry of PD. It was found that most patients in this sample presented with asymmetric symptoms both initially (86.44%) and at the time that the questionnaire was completed (55.93%), however, there was a 31.51% increase in the number of patients that presented with generalised PD from the onset of their disease to the time that the questionnaire was completed. Asymmetry (and more specifically initial laterality) was not found to be related to the sex of the patient (p=0.064), their age of onset of PD (p=0.348), their genetic predisposition to PD (p=0.668) or their handedness (p=0.747). The symptoms of PD were found to change from presenting asymmetrically to bilaterally over time and with severity of disease as age was found to be related to current laterality (p=0.003) and the stage of PD symptoms was found to be related to initial laterality (p=0.023), current laterality (p<0.0001) and change in symptom asymmetry (p<0.0001). Asymmetry was found to be related to some non-motor symptoms such as daytime sleepiness (p=0.013), pain (p=0.042) and constipation (p=0.016) and the patient's genetic predisposition to PD was also found to be related to non-motor symptoms of PD such as urinary problems (p=0.004) and constipation (p=0.026). Interestingly, depression was found to be related to many of the variables in this study such as the patient's change in symptom asymmetry (p=0.034), genetic predisposition to PD (p=0.005), and stage of PD symptoms (p=0.043). The results have been further discussed below:

5.1. Demographic Data

The demographic data of the PD patients in this sample, such as sex, age and race, were captured in this study. There was a non-response rate of 44.86% which could have been due to patients forgetting to complete the questionnaire, not being able to complete it due to their illness or changing their minds about wanting to complete it. From the patients that managed to complete it, there was a similar number of males and females that responded to the questionnaire with 50.85% being male and 49.15% being female. The mean age of onset of PD symptoms was 57 years old which is a young age considering that PD is a degenerative disorder that affects the elderly. Most patients in the sample were between the ages of 60 – 69 with the average age of PD patients being 65 years old. This indicates that PD is present in South Africa's elder population which is consistent with the average age seen in other populations as seen in the study done by Chen and Tsai (2010). The majority of the sample consisted of White patients which does not accurately represent South Africa's population which could be due to the fact that the sample was very small and taken from only two hospitals in Johannesburg.

5.2. Asymmetry of symptoms

The present study indicated that most patients showed asymmetric symptoms of PD, both initially (86.44%) and currently (55.93%). It was found that 52.54% of patients presented with initial left laterality and 33.90% of patients presented with current left laterality. In a study done by Kempster and colleagues (1989), it was found that the side of the body that was initially affected experienced contralateral degeneration of the substantia nigra resulting in the asymmetry of symptoms. The number of patients that presented with asymmetry of symptoms decreased from the onset of the disease until the current time while the number of patients that presented with generalised PD increased from the onset until the current time. This could indicate that as the disease progresses, the PD symptoms tend to present on both sides of the body and not just unilaterally. It was seen that patient's symptoms had a propensity to remain with their initial laterality (right laterality to right laterality: 18.64% and left laterality to left laterality: 32.20%) or change to generalised PD (right laterality to generalised PD: 15.25% and left laterality to generalised PD: 16.94%), but it was rare to observe patients that changed from one laterality of symptoms to the other (right laterality to left laterality: 0.00% and left laterality to right laterality: 3.39%) or that changed from generalised PD to asymmetry of symptoms (generalised PD to right laterality: 0.00% and generalised PD to left laterality: 1.69%).

5.3. Asymmetry is not related to sex, age of onset, genetics or handedness

There was no statistically significant association found between sex and initial or current laterality of symptoms however, this analysis showed that initially, left laterality of symptoms were prominent in both males (60.00%) and females (44.83%) while at the time the survey was conducted, generalised PD was most prominent in both males (40.00%) and females (48.28%).

Most patients in this sample started experiencing symptoms in the 60 – 69 year age category with the average age of onset of PD symptoms being 57 years old. This is consistent with previous studies where it is atypical for the onset of PD to occur in patients before the age of 50 and after the age of 60, the frequency of patients that present with PD increases greatly. (Chen and Tsai, 2010). There was a low incident rate of PD at the early ages of onset (only 5 patients were in the 30-39 year age category) which may be due to patient's being asymptomatic and at the late ages of onset (only 4 patients were in the 70-79 year age category and 2 patients in the 80-89 year age category) which may be due to the small population size at these advanced ages. The average years living with PD seen in this sample was 8 years. This was measured from the onset of the disease until the questionnaire was conducted. There was no significant statistical association between the patient's age of onset and their initial laterality of symptoms.

In this study, 77.19% of the sample were not sure if they had a biological family member with PD. This could be due to family members passing away before the onset of PD or due to patients not keeping in contact with family members. In the 22.81% of the sample that did know of a biological family member with PD, 61.54% presented with initial left laterality and 61.54% presented with current generalised PD. From these findings, there was no statistically significant association between the genetic predisposition of PD and the initial or current asymmetry of symptoms. However, studies indicate that there is a known genetic aspect of PD such as the SNCA gene (encodes the alpha-synuclein protein) and the LRRK2 gene (encodes for the dardarin protein) (Chai and Lim, 2014). How these genes relate to symptom asymmetry is yet to be determined and further research would be of great value to the field.

It was found that 89.83% of the sample used in this study were right-handed individuals which could result in the skewed data. There was no statistically significant association between handedness and laterality of symptoms in this study which could be as a

result of the small sample size. The results indicated that 49.06% right-handed and 75.00% left-handed patients presented with initial left laterality of symptoms. Interestingly, there was a propensity for left-handed PD patients to initially exhibit symptoms on their dominant side. This was seen by 70.00% of left-handed patients who initially presented symptoms on their left-hand side whereas only 34.55% of right-handed patients initially presented symptoms on their right-hand side. This was in consensus with other studies such as Yust-katz, Tesler and Treves (2008) who found that 47.00% of right-handed patients present with initial right laterality and 52.00% of left-handed patients present with initial left laterality. A study done by Uitti *et al*. (2005) exhibited similar results and concluded that left-handed patients tend to have a more severe form of PD on the left side of their body compared to right-handed individuals. However, a study done by Cohen and colleagues (2003), indicated that there is a neuroprotective influence from exercise on the side of the body that receives more physical activity. Thus, the dominant side should have neuroprotection from PD and symptoms should initially appear on the patient's non-dominant side, but this was not the case for left-handed patients in the present study. All ambidextrous patients in this sample presented with left laterality of symptoms. More research is needed regarding asymmetry that is focused on left-handed and ambidextrous PD patients as they make up a small portion of society.

5.4. Asymmetry changes over time and with severity of disease

A statistically significant association was found between the age of the patient and the current laterality of symptoms ($p = 0.003$). It was found that as age increases, symptoms tend to change from presenting unilaterally (on the right or left) to bilaterally with the exception of the 70 – 79 year age category where 41.18% presented with current right laterality.

According to the estimated Hoehn & Yahr scale that comprises of 5 stages, the severity of PD symptoms increases from newly diagnosed to moderately severe and finally to advanced PD with each stage. It was found that the stage of PD symptoms had statistically significant associations with initial laterality of symptoms ($p = 0.023$), current laterality of symptoms ($p < 0.0001$) and the change in symptom asymmetry ($p < 0.0001$).

Initial right laterality was prominent in the stages 2 and 5, initial left laterality was prominent in stage 1 and 3 while generalised PD was prominent in stage 4. This could indicate that patients that exhibit an initial right laterality are likely to develop more severe symptoms of

PD while initial left laterality could lead to more milder symptoms. Further investigation on this finding needs to be conducted with a larger sample size to yield accurate results.

It was seen that 57.89% of patients exhibiting stage 1 and 66.67% of patients exhibiting stage 4 of symptom severity presented with current left laterality. Moreover, 50.00% of patients exhibiting stage 5 of symptoms presented with current right laterality while 0.00% of patients in this stage presented with current left laterality. Generalised PD patients seem to be spread out among the stages but 87.50% of patients in stage 2 presented with generalised PD. These findings could indicate that patients who exhibit current left laterality have more milder symptoms compared to those with current right laterality.

It was found that 59.38% of patients whose symptoms remain asymmetric experience stage 1 of PD symptoms, 70.00% of those that change from asymmetric to generalised PD exhibit stage 3 of PD symptoms, 100.00% of patients that change from generalised PD to asymmetric symptoms exhibit stage 4 of PD symptoms and 50.00% of patients that remained generalised exhibit stage 3 of PD symptoms. This could indicate that exhibiting symptoms that remain asymmetric results in milder PD symptoms than exhibiting symptoms that change (from asymmetric to generalised PD or from generalised PD to asymmetric) or that remain generalised.

5.5. Asymmetry is related to the non-motor symptoms of PD

Non-motor features are referred to as pre-motor symptoms as they are known to develop well before the onset of motor features. Unfortunately, they are not appreciated as much as motor symptoms but impact patient's lives greatly. From this sample, it was found that daytime sleepiness had statistically significant associations with both the presence of current asymmetry ($p=0.010$) and change in symptom asymmetry ($p=0.005$). It was found that 69.75% of patients that presented with current asymmetry had normal daytime sleepiness while 61.56% of patients that presented with current generalised PD had moderate daytime sleepiness. It was also found that 68.75% of patients that had normal daytime sleepiness presented with symptoms that remained asymmetric, 54.17% of patients that had moderate daytime sleepiness presented with symptoms that changed from asymmetric to generalised and 50.00% of patients with severe daytime sleepiness presented with symptoms that either changed from asymmetric to generalised or generalised to asymmetric. This could indicate that patients whose symptoms change (from asymmetry to generalised or from generalised to

asymmetry) experience more severe forms of daytime sleepiness compared to those whose symptoms remain asymmetric.

The presence of constipation also had statistically significant relationships with both the presence of current asymmetry (p=0.016) and change in symptom asymmetry since diagnosis (p=0.008). It was seen that 57.58% of patients that presented with current asymmetry had normal constipation while 53.85% of patients that presented with generalised PD had moderate constipation. The results also indicated that 70.37% of patients that presented with normal constipation and 46.43% of patients that presented with moderate constipation had symptoms that remained asymmetric while 100.00% of patients that presented with severe constipation had symptoms that changed from asymmetric to generalised. Constipation seems to be milder in patient whose symptoms remain asymmetric or remain generalised while more severe forms of constipation are seen in patients whose symptoms changed either from asymmetric to generalised or from generalised to asymmetric.

As seen above, change in asymmetry was also found to be linked to the stage of PD symptoms. This is relevant since development of these early non-motor symptoms – daytime sleepiness and constipation – could result in more severe motor symptoms later on. This is supported by Salawu et al. (2010) who indicates that non-motor symptoms of PD are also known as pre-motor symptoms because they are likely to develop preceding the motor-symptoms of PD.

Pain was only related to current presence of asymmetry (p=0.042) where 78.79% of patients that presented with asymmetry of symptoms and 57.69% of patients that presented with generalised PD had moderate pain. The findings indicate that most patients that presented with current generalised PD also presented with moderate day-time sleepiness (61.56%), moderate pain (57.69%) and moderate constipation (53.85%) whereas most patients that presented with current asymmetry had normal daytime sleepiness (68.75%) and normal constipation (57.58%) but moderate pain (78.79%). An explanation for this could be that these are also symptoms that tend to appear with old age, however patients that exhibit asymmetry are usually in the early stages of the disease. Therefore, moderate pain could be an early indication of PD.

5.6. Depression and PD

Depression is a non-motor symptom of PD that had a statistically significant association with the stage of PD symptoms (p=0.043), change in symptom asymmetry (p=0.034) and genetic predisposition (p=0.005). It was found that none of the patients presented with depression in the early stages of the disease but as the stages increase (and PD symptoms progress), so does the severity of the patient's depression. Depression seems to be milder in patient whose symptoms remain asymmetric or remain generalised. This was seen as 59.46% of patients that presented with normal depression and 58.82% of patients that presented with moderate depression had symptoms that remained asymmetric. It was also found that 10.81% of patients that presented with normal depression and 11.46% of patients that presented with moderate depression had symptoms that remained generalised. Furthermore, both the groups of patients whose symptoms remained asymmetric and remained generalised did not present with severe depression. More severe forms of depression are seen in patients whose symptoms changed either from asymmetric to generalised or from generalised to asymmetric as 80.00% of patients that presented with severe depression had symptoms that changed from asymmetric to generalised PD and the remaining 20.00% of these patients had symptoms that changed from generalised PD to asymmetric. The results indicated that 71.43% of patients that presented with normal depression and 100.00% of patients that presented with moderate depression did not have a genetic predisposition to PD while 60.00% of patients that presented with severe depression had a genetic predisposition to PD. Apathy and loss of interest are symptoms of depression, and it was found that apathy exhibited statistically significant associations with current asymmetry (p=0.055) and genetic predisposition (p=0.023). There was also an association between loss of interest and genetic predisposition (p=0.006) where patients that presented with a genetic predisposition to PD showed a more severe loss of interest.

Although the present study indicated a link between depression and the genetic predisposition to PD, a larger sample size is needed to produce more accurate results. The study done by Schrag, Jahanshahi and Quinn (2001), indicated that a possible reason for depression being associated with PD is that patients develop a negative perception on the hinderance that the disease causes (such as cognitive impairment and stigma caused by society) rather than the disease itself. This reason could also contribute to the apathy and loss of interest that is seen in PD patients in this study.

6. CONCLUSION

Parkinson's Disease is a progressive neurodegenerative disorder that affects the elder population resulting in motor and non-motor symptoms. Initial asymmetry of symptoms is common in PD patients, with left laterality being dominant over right laterality of symptoms. There were no statistically significant associations found between symptom asymmetry and sex, age of onset, genetic predisposition or handedness. The present study found current laterality to be associated with age of the patient – as the patient gets older, and as the disease progresses, symptoms change from being asymmetrical to bilateral. Only 3.39% of the sample had symptoms that changed from one laterality to the other and 1.69% of the sample had symptoms that changed from presenting bilaterally to unilaterally. In this study, the stage of PD symptoms had statistically significant associations with initial laterality of PD symptoms, current laterality of PD symptoms and change in symptom asymmetry. Thus, the generalised pattern seen in PD patients is that symptoms change from presenting asymmetrically to bilaterally over time and with increasing severity of disease. Left-handed patients had a tendency to exhibit symptoms on their dominant side. This is in consensus with some studies but in opposition to others, therefore, a larger sample size which includes more left-handed and ambidextrous patients is needed in order to get a better understanding of handedness and asymmetry.

Daytime sleepiness and constipation were found to have statistically significant associations with both current asymmetry and change in symptom asymmetry while pain was only found to be related to current asymmetry. Patients that presented with generalised PD showed moderate severity of these non-motor symptoms while patients that presented with asymmetry showed normal severity of sleepiness and constipation but moderate pain. The genetic predisposition of patients to PD did not have an association with asymmetry of PD symptoms, however, it did have a relation to non-motor symptoms such as urinary problems and constipation. These non-motor symptoms were found to be severe in patients that knew of a biological family member with PD suggesting a genetic component to these non-motor symptoms. Further research with larger sample sizes might uncover genetic components to asymmetry of symptoms.

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APPENDIX A – PARTICIPANT INFORMATION SHEET

Parkinson's Disease Questionnaire:

Participant Information Sheet

Study title: ***Factors Associated with the Asymmetric Symptoms of Parkinson's Disease in South Africa***

Good day!

My name is Priyantha Naicker and I am a neuroscience Masters student at the University of the Witwatersrand. I am currently undertaking a research project on the topic of Parkinson's Disease (PD). This topic is not well-researched in South Africa and therefore this study may contribute to new knowledge about the disease. In this study, I will be looking at the proportion of individuals with asymmetric PD in South Africa, how demographics and disease history influence asymmetric symptoms and how hand dominance affects these asymmetric symptoms.

I am inviting you to take part in a research study where you would simply answer questions with regards to your PD in an online questionnaire. If you require any assistance with this exercise from other members of your household, that will be fine. The questionnaire will take about 15 minutes to complete and will include questions about your demographics, symptoms, and disease severity. It will be completed online (no face to face interaction is needed) and engaging in the questionnaire will be taken as consent to take part in the study.

There are minimal risks and no direct benefits to participating in this study and while your involvement may contribute to PD research, it is completely voluntary. Whether or not you decide to participate will have no consequence for any ongoing medical treatment for PD which you may be receiving.

Should any of the questions cause you distress please feel free to contact me or my supervisors to make alternative arrangements. For telephonic counselling, please make use of the following contact information:

- LifeLine: (24 hours) 011 728 1347 or 0861 322 322

- South African Depression and Anxiety Group (SADAG) Helpline: 0800 567 567 SMS 31393 Available 08h00 – 20h00
- Akeso Psychiatric Response Unit: (24 Hour) 0861 435787
- Family Life Centre: (011) 788 4784/5 Available 08h00 - 20h00

All personal information will be treated in the strictest confidence and will only be available to myself and my supervisors – Dr Marcelle Smith and Dr Tanya Calvey. Your data will remain anonymous throughout the study. You will not be identified by name in any publication arising out of the study. The data I collect on participants will be destroyed after 2 years, if a publication comes out of the study and after 6 years, if there is no publication.

Please feel free to contact me, Priyantha Naicker, or my supervisors, Drs Smith and Calvey, if you have further questions on tel no. 071 886 8347, or by e-mail on 1658499@students.wits.ac.za; on tel no. 010 549 1267, or by e-mail on Marcelle.Smith@wits.ac.za, or on tel. no. 011 717 2743, or by e-mail on Tanya.Calvey@wits.ac.za). Once I have completed my research, I will be more than happy to send you the written summary upon your request.

Participation in the study involves neither cost nor payment.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research. If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Participant information sheet. If you would like to participate in this study, please click on the link below:

[Link to Questionnaire]

Please note that engaging in the questionnaire will be taken as consent. You may change your mind and discontinue your participation up until the point when you submit your online response.

Date: June 2021

APPENDIX B – PARKINSON'S DISEASE QUESTIONNAIRE

Are you the Parkinson's Disease patient or are you helping the patient to complete the questionnaire?	I am the patient	I am helping the patient
If you are helping the patient, do you agree to keep the all the patient's answers confidential and not share any of the patient's information in any way? (If you do not agree please do not complete the rest of this questionnaire)	I agree	I do not agree

SECTION 1 – Demographics

Please answer the following questions

Patient Demographics			
1.1 Are you male or female?	Male	Female	Prefer not to say
1.2 What is your age?			
1.3 What is your race?			
1.4 What is your first language?			

SECTION 2 - Disease history, presence of asymmetrical symptoms and handedness

Please answer the following questions

Parkinson's Disease Questions			
2.2 At what age did you start experiencing symptoms of Parkinson's disease?			
2.2 Which side of your body did the symptoms start?	Right	Left	Both Sides
2.3 Which side of your body do you experience symptoms now?	Right	Left	Both Sides
2.2 Are you right-handed, left-handed or ambidextrous (which is your dominant hand)?	Right	Left	Ambidextrous (both hands)
2.3 Which hand do you write with?	Right	Left	Ambidextrous (both hands)
2.4 Do you know of a biological family member that has Parkinson's Disease?	Yes	No	Not sure
2.5 Are you on any chronic medication?	Yes	No	
2.6 If so, please list the medication.			

SECTION 3 – Presence of non-motor symptoms and severity of disease

Please choose the best response that describes how you have felt MOST OF THE TIME for the PAST WEEK.

0: Normal – There is no problem

1: Moderate – you experience the problem, but it does not affect your day to day living

2: Severe – The problem affects your ability to carry out normal activities

	Non-Motor Symptoms	Normal	Moderate	Severe
Cognitive impairment	3.1 Over the past week, have you had problems remembering things, following conversations, paying			

	attention, thinking clearly, or finding your way around the house or in town?			
Hallucinations and psychosis	3.2 Over the past week have you seen, heard, smelled, or felt things that were not really there?			
Depressed mood	3.3 Have you been depressed or down, or felt sad, empty or hopeless most of the day nearly every day, for the past two weeks?			
	3.4 In the past week, were you much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?			
Anxious mood	3.5 Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, very frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?			
	3.6 Did the spells surge to a peak, within 10 minutes of starting?			
	3.7 Did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?			
Apathy	3.8 Over the past week, have you felt the lack of interest to doing activities or being with people?			
Sleep problems	3.9 Do you had trouble sleeping because you wake up in the middle of the night and/or early morning?			
Daytime sleepiness	3.10 Do you have trouble staying awake during the day?			

Pain and other sensations	3.11 Over the past week, have you had uncomfortable feelings in your body like pain, aches, tingling, or cramps?			
Loss of Smell	3.12 Over the past week, have you experienced a loss of smell?			
Urinary problems	3.13 Over the past week, have you had trouble with urine control?			
Constipation problems	3.14 Over the past week have you had constipation troubles that cause you difficulty moving your bowels?			
Light headedness on standing	3.15 Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or lying down?			
Fatigue	3.16 Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad.			

Estimated Hoehn & Yahr

The following question is to assess disease severity:

Please select the option that best describes the current stage of your Parkinson's Disease symptoms:	1. One-sided symptoms only - minimal disability 2. Both sides affected but balance is stable 3. Mild to moderate disability, balance is affected 4. Severe disability, able to walk and stand without help 5. Confinement to bed or wheelchair unless aided

The following questions are to assess drug and alcohol use:

Have you used drugs other than those required for medical reasons?	Yes	No
If yes, which drugs have you used? (Please select all that apply)	a. methamphetamines (speed, crystal) b. cocaine c. cannabis (marijuana, pot) d. narcotics (heroin, oxycodone, methadone, etc.) e. inhalants (paint thinner, aerosol, glue) f. hallucinogens (LSD, mushrooms) g. tranquilizers (Valium) h. Other (Please specify) _____	
How often have you used these drugs?	a. Monthly or less b. Weekly c. Daily or almost daily	
How often do you have a drink containing alcohol?	a. Never b. Monthly or less c. 2-4 times a week d. 4 or more times a week	
How many drinks containing alcohol do you have on a typical day when you are drinking?	a. 1 or 2 b. 3 or 4 c. 5 or 6 d. 7 to 9 e. 10+	
Has a relative, friend, doctor or health care worker been concerned about your drinking or suggested you cut down?	a. No b. Yes, but not in the last year c. Yes, during the last year	

APPENDIX C – ETHICAL CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms P Naicker

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210442

NAME: (Principal Investigator) Ms P Naicker

DEPARTMENT: School of Anatomical Sciences
Medical School
University

PROJECT TITLE: *Factors associated with asymmetric symptoms of Parkinson's Disease in South Africa*

DATE CONSIDERED: 2021/04/30

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Drs T Calvey and M Smith

APPROVED BY: CB Penny
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2021/07/13

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **April** and therefore reports and re-certification will be due in the month of **April** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX D – DATA TABLE

Variable	Frequency	Percent
Gender		
Male	30	50.85
Female	29	49.15
Age		
40 – 49	4	6.67
50 – 59	8	13.33
60 – 69	27	46.67
70 – 79	17	28.33
80 – 89	3	5.00
Race		
Black	5	8.33
White	49	81.67
Coloured	6	10.00
Age of Onset		
30 – 39	5	8.33
40 – 49	13	21.67
50 – 59	14	23.33
60 – 69	22	36.67
70 – 79	4	6.67
80 – 89	2	3.33
Initial Laterality		
Right	21	35.00
Left	31	51.67

Both	8	13.33
Current Laterality		
Right	13	21.67
Left	20	33.33
Both	27	45.00
Handedness		
Right	54	90.00
Left	4	6.67
Ambidextrous	2	3.33
Writing Hand		
Right	56	93.33
Left	4	6.67
Genetic Predisposition		
Yes	13	22.41
No	45	77.59
Chronic Medication		
Yes	58	96.67
No	2	3.33
Cognitive impairment		
Normal	29	48.33
Moderate	27	45.00
Severe	4	6.67
Hallucination		
Normal	43	71.67
Moderate	17	28.33

Severe	0	0.00
Depressed		
Normal	38	63.33
Moderate	17	28.33
Severe	5	8.33
Loss of interest		
Normal	34	56.67
Moderate	22	36.67
Severe	4	6.67
Anxiety attacks		
Normal	37	61.67
Moderate	20	33.33
Severe	3	5.00
Quick Anxiety Peak		
Normal	45	75.00
Moderate	12	20.00
Severe	3	5.00
Unexpected Anxiety Attack		
Normal	45	58.33
Moderate	13	35.00
Severe	2	6.67
Apathy		
Normal	35	58.33
Moderate	21	35.00
Severe	4	6.67

Sleep Problems		
Normal	14	23.33
Moderate	39	65.00
Severe	7	11.67
Daytime Sleepiness		
Normal	32	54.24
Moderate	25	42.37
Severe	2	3.39
Pain		
Normal	14	23.73
Moderate	41	69.49
Severe	4	6.78
Loss of Smell		
Normal	39	65.00
Moderate	11	18.33
Severe	10	16.67
Urinary Problems		
Normal	25	41.67
Moderate	31	51.67
Severe	4	6.67
Constipation		
Normal	27	45.00
Moderate	29	48.33
Severe	4	6.67
Light headedness		

Normal	35	58.33
Moderate	25	41.67
Severe	0.00	0.00
Fatigue		
Normal	27	45.00
Moderate	31	51.67
Severe	2	3.33
Stage of PD symptoms		
1	19	31.67
2	8	13.33
3	28	46.67
4	3	5.00
5	2	3.33
Drug Consumption		
Yes	4	6.67
No	56	93.33
Alcohol Consumption		
Never	22	36.67
Monthly or Less	17	28.33
2-4 times a week	10	16.67
4 or more times a week	11	18.33