Cognitive impairment in Parkinson's disease and its effect on patients and their carers

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Abstract

Background

The progression of Parkinson's disease (PD), including cognitive decline, is linked to quality of life (QoL), which may subsequently impact on the QoL of their informal carer. This thesis aimed to investigate how cognitive changes affected the QoL of newly diagnosed PDs over 36 months, and the QoL of their carers, using a mixed methods approach.

Methods

Newly diagnosed PD participants (n=219) completed a schedule of neuropsychological assessments, medical history and QoL measures; these were repeated after 18 months (n=195) and 36 months (n=158). Carers (n=66) completed questionnaires evaluating mood and QoL at 36 months. Purposeful sampling identified participants and their carers with normal cognition, mild cognitive impairment (PD-MCI) and dementia (PDD), who completed qualitative interviews.

Results

Using the Movement Disorder Society criteria, PD-MCI was a small but significant contributor to QoL in newly diagnosed PD. Over 36 months, most participants were cognitively stable and cognition did not impact on QoL; for the minority who developed PDD and their carers, cognition had a greater impact on QoL. Brief tests, such as MoCA score, modestly predicted declining QoL; attentional deficits had a stronger predictive power.

The qualitative analysis revealed three principal themes: the experience of living with PD and cognitive impairment, changes in identity, and coping mechanisms and adjustment. Across these inter-linked themes, the effects of cognitive impairment and the differences between PD and carer experiences were important overarching issues.

Conclusions

This mixed methods study showed that the determinants of QoL were complex, as was its relationship with cognition. Cognitive impairment, particularly attentional impairment, played a significant role in predicting QoL of PDs and carers. However,

there was significant individual variation with some people adjusting better than others over time. The qualitative analysis revealed awareness of cognitive decline, changes in roles and anticipatory grief disrupted emotional equilibrium. However protective factors, including optimism, mutually supportive relationships and finding meaning mitigated these factors.

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Statement of Work Undertaken

Professor David Burn was the Chief Investigator for the Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's Disease (ICICLE-PD) study and was responsible for the study design and grant application. The baseline data collection commenced prior to starting my PhD, and was collected by Dr Alison Yarnall, Dr Gordon Duncan and Dr Tien Khoo at Newcastle University. Dr Yarnall, Dr Duncan, Dr Fionnuala Johnston, Leanne Thompson, Victoria Foster and I contributed to 18 and 36 month data collection. The data checking and cleaning was completed by me, Dr Alison Yarnall, Dr Duncan, Dr Fionnuala Johnston, Dr Tien Khoo and Rosie Morris. Professor Roger Barker was the Principal Investigator at the University of Cambridge. Dr David Breen collected the Cambridge data at baseline and 18 month follow up assessments; his colleagues Dr Gemma Cummings, Dr Caroline Williams-Grey and Dr Natalie Valle Guzman contributed to the at 36 month assessment data collection.

As part of this study, I have completed over 400 participant assessments, the vast majority of which involved multiple participant visits, plus additional participant assessments for 54 month and 72 month evaluation which are not part of this thesis. Since starting as a PhD student, I have co-ordinated and managed the wider ICICLE-PD study as well as the work in this thesis. I have submitted amendments to the protocol to the NHS Local Research Ethics Committee to include additional questionnaires for carers of Parkinson's disease participants and qualitative interviews; I have also submitted amendments not related to this thesis for the wider ICICLE-PD study.

Performing statistical analysis and interpretation of results were completed independently by me. Statistical advice was sought from my supervisors Professor David Burn, Dr Daniel Collerton and Dr John-Paul Taylor, and Dr Shirley Coleman from the School of Mathematics, Newcastle University. The design of the qualitative study as part of this thesis was a collaborative effort with Dr Katie Brittain. All interviews with Parkinson's participants and their carers were undertaken by me. I transcribed the initial interviews; the majority were transcribed by Angela Mattison from the Institute of Health and Society, Newcastle University. Data coding and analysis was

completed by me with support from Dr Brittain. I was responsible for the writing of this thesis.

Chapter 4 of this thesis has been published as two papers of original research in peer review journals:

Lawson, R.A., Yarnall, A.J., Duncan, G.W., Khoo, T.K., Breen, D.P., Barker, R.A., Collerton, D., Taylor, J.-P. and Burn, D.J. (2014) 'Severity of mild cognitive impairment in early Parkinson's disease contributes to poorer quality of life', *Parkinsonism & Related Disorders*, 20(10), pp. 1071-1075.

Lawson, R.A., Yarnall, A.J., Duncan, G.W., Khoo, T.K., Breen, D.P., Barker, R.A., Collerton, D., Taylor, J.P. and Burn, D.J. (2014) 'Quality of Life and Mild Cognitive Impairment in Early Parkinson's Disease: Does Subtype Matter?', *Journal of Parkinson's Disease*, 4(3), pp. 331-336.

I have also presented results from this thesis, both complete and preliminary, at national and international conferences, which are listed in Appendix A. Publications and presentations from my wider involvement in the ICICLE-PD study are listed in Appendix A.

Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
ANOVA	Analysis of variance
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDR	Cognitive Drug Research battery
CI	Confidence interval
CRT	Choice Reaction Time
DLB	Dementia with Lewy bodies
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders Revised 3rd Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
EQ-5D	EuroQol health questionnaire
ESS	Epworth Sleepiness Scale
FAB	Frontal Assessment Battery
GDS-15	Geriatric Depression Scale, short form
GT	Grounded Theory
HADS	Hospital Anxiety and Depression Scale
HADS-A	Anxiety subscale of the Hospital Anxiety and Depression Scale
HADS-D	Depression subscale of the Hospital Anxiety and Depression Scale
HR-QoL	Health related quality of life
ICICLE-PD	Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's Disease
IQ	Intelligence quotient
LED	Levodopa equivalent dose
MCI	Mild cognitive impairment
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MOT	Motor Screening Test

MRI	Magnetic resonance imaging
NART	National Adult Reading Test
NHS	National Health Service
NMS	Non-motor symptoms
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory with Carer Distress
OARS	Older Americans Resources and Services
OTS	One Touch Tower of London
PAL	Paired Associate Learning
PCA	Principal component analysis
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PD-MCI	Mild cognitive impairment in Parkinson's disease
PD-NC	Parkinson's disease with normal cognition
PDQ-39	Parkinson's Disease Questionnaire
PDQ-8	Parkinson's Disease Questionnaire, short form
PDQ-Carer	Parkinson's Disease Questionnaire - Carer
PDQL	Parkinson’s Disease Quality of Life Questionnaire
PET	Positron emission tomography
PIGD	Postural instability gait difficulty
PIMS	Parkinson’s Impact Scale
PoA	Power of Attention
PRM	Pattern Recognition Memory
PROMS-PD	Prospective Study of Mood States in Parkinson's Disease study
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of life
RBD	Rapid Eye Movement sleep behaviour disorder
REM	Rapid Eye Movement
SAI	Short latency afferent inhibition
SCOPA-Cog	Scales for Outcomes in Parkinson’s Disease–Cognition
SCOPA-PS	Scales for Outcomes in Parkinson’s Disease–Psychosocial
SD	Standard deviation

SES	Socioeconomic status
SF-36	Short-Form Health Survey
SI	Single index
SPSS	Statistical Package for the Social Sciences
SQLC	Scale of Quality of Life of Care-Givers
SRM	Spatial Recognition Memory
SRT	Simple Reaction Time
UK	United Kingdom
WHO	World Health Organization
WHO-DAS III	World Health Organization Disability Assessment Schedule World Health Organization Disability Assessment Schedule
WTAR	Wechsler Test of Adult Reading

Chapter 1 Introduction and Literature Review

The progression of Parkinson's disease (PD), including cognitive decline, is linked to patient wellbeing and quality of life (QoL), which subsequently impacts on the health and QoL of their informal carers (i.e. spouse, partner or family member). This thesis aimed to investigate cognitive changes in newly diagnosed PD patients over 36 months, and how these changes affect their QoL and the QoL of those who care for them, using a mixed methods approach. The latter enabled me to explore the differences between QoL specific to PD, using PD specific measures, and the overall experience of QoL of people with PD.

In this chapter I will outline QoL in the context of PD and how it has been quantified in previous studies. I will then discuss contributing factors to QoL, including cognitive impairment, and protective factors, including support from informal carers.

1.1 Parkinson's Disease

Parkinson's disease is a neurodegenerative disease that is defined by the presence of motor symptoms: bradykinesia, tremor and rigidity. It was first described by James Parkinson in 1817 as a shaking palsy (Parkinson, 2002). PD symptoms become apparent as dopaminergic neurotransmission in the brain decreases; up to 80% of dopamine can be lost before the physical symptoms of PD are manifest (Marsden, 1990).

Idiopathic PD is defined by the Queen's Square Brain Bank clinical diagnostic criteria (Hughes *et al.*, 1992). Bradykinesia must be present; this is an abnormal slowing of movement, either in spontaneously starting a movement or the progressive slowing of repetitive movement, where reduced speed and amplitude would be observed. In addition to bradykinesia, one of the following core symptoms must be present: a resting tremor, muscular rigidity or postural instability. Other causes of a Parkinsonian syndrome, such as vascular PD, drug induced PD or dementia with Lewy bodies (DLB), excluded a diagnosis of idiopathic PD.

1.1.1 Non-motor symptoms

Controlling the motor symptoms of PD has long been the main focus of research and treatment. However, non-motor symptoms (NMS) are currently receiving increased attention as the treatment of motor symptoms has improved (Martinez-Martin *et al.*, 2011b; Khoo *et al.*, 2013). James Parkinson originally listed: sleep disturbances, constipation, problems with speech, excess saliva, incontinence, excessive sleep and delirium as features of PD (Parkinson, 2002). However, these symptoms do not form part of the Queen's Square Brain Bank Criteria clinical diagnostic criteria (Hughes *et al.*, 1992).

Since James Parkinson's original essay, many NMS have been linked with PD. Mood disorders such as depression, anxiety and apathy have been shown to be significant NMS of PD (Brown *et al.*, 2011; Starkstein and Brockman, 2011; Ziropadja *et al.*, 2012), although the prevalence of these symptoms varies between studies. Cognitive decline in PD has also become a key focus, as PD with dementia (PDD) has a high cumulative prevalence (Hely *et al.*, 2008). However, in his original essay James Parkinson did not identify cognition as part of idiopathic PD and stated that the "sense and intellect" were unaffected in PD (Parkinson, 2002). Furthermore, PDD can have a major impact on the QoL of the person with PD and their family, and is associated with nursing home placement and shorter survival time (Galvin, 2006).

1.2 Quality of Life

1.2.1 Defining quality of life

There is no current consensus on the definition of QoL; therefore theories and findings vary. The term is often used as an umbrella to capture a broad concept, which varies widely between disciplines. Quality of life is subjective, which can also make it difficult to define. The World Health Organization (1993) defines QoL as:

> *"…an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment."*
>
> The World Health Organization (1993)

This definition has been criticised by others as being too broad and holistic to be used in practice (Koller and Lorenz, 2002). An alternative definition is that QoL:

> *"…integrates objective and subjective indicators, collectively reflecting a broad range of life domains, through an individual ranking of the relative importance of each domain."*
>
> Felce and Perry (1995)

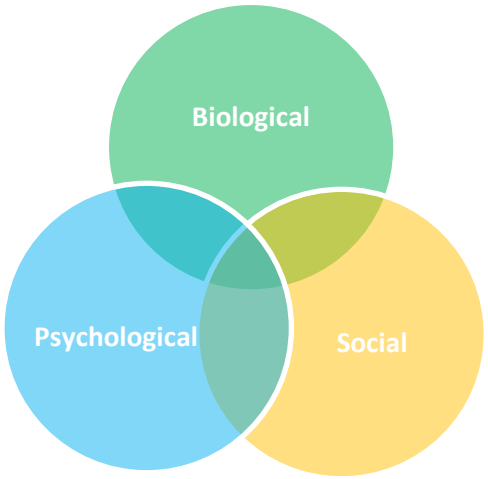
There is much philosophical debate about the definition of QoL and whether it is subjective or objective (Glozman, 2004). There are multiple measures across the disciplines that try to capture and quantify QoL; however with such a varied definition the measures are often not comparable as they focus on different concepts within the construct of "QoL." Concepts measured include: wellbeing, stress, strain, psychological health, physical health and spirituality, to name but a few.

Quality of life is often used as an impact measure of health problems or illness, where chronic illness or poor health leads to reduced QoL. Health related quality of life (HR-QoL) has been defined as a "patient's own perception and self-evaluation regarding the effects of an illness and its consequences on her or his life," (Martinez-Martin, 1998). Some argue that HR-QoL is a "narrow" view of QoL as it often focuses on health, illness and treatment, while neglecting emotional and social functioning (Soh *et al.*, 2011). This is also not consistent with the World Health Organisation's view of health which states:

> *"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."*
>
> World Health Organization (1946)

This view of health was also proposed by George Engel who described the biopsychosocial model of health (Engel, 1977). He proposed that health was not merely the absence of disease but the interaction and combination of medical, psychological and social factors that are illustrated in Figure 1-1.

Figure 1-1: Diagram of the Biopsychosocial model of health



Engel, 1977

Consequently, if health is not just the absence of disease, it could be inferred that a person with a chronic illness does not necessarily have reduced QoL as psychological and social wellbeing are also contributing factors and may be intact despite illness or disease (Bond and Corner, 2004). This has also been suggested by Farquhar (1995), who stated that social contact was as important to QoL as health status. She found that social contact in older adults was an important determinant of QoL and that family and activities were important contributors to QoL. Other factors, such as personality, coping mechanisms, resilience, self-esteem and identity can also impact on QoL (Shaw, 2001; Hagberg *et al.*, 2002; Corner *et al.*, 2007; Hildon *et al.*, 2010).

Thus, defining QoL in a chronic illness like PD is complex since it can be affected by motor symptoms and NMS like mood disorders, cognitive impairment plus wider issues such as their relationships with family, friends and their place in society. Furthermore, as people with PD tend to be older adults, there are also the broader issues associated with ageing that impacts on QoL. Loneliness, social isolation, changing role and other physical or health comorbidities that are common in older adults can also impact on QoL (Farquhar, 1995; Victor *et al.*, 2000; Bond and Corner, 2004; Corner *et al.*, 2007).

1.2.2 Quality of life in Parkinson's disease

1.2.2.1 Measuring quality of life in Parkinson's disease

As discussed, there is no agreement as to the definition on QoL, similarly agreeing on how to measure QoL is likewise problematic, comprising different views as to what

constitutes 'good' or 'bad' QoL (Bond and Corner, 2004). Thus, measures of QoL in PD vary between studies (Table 1-1). However, many of these measures are general and aimed at a broad spectrum of populations. Therefore, many of the more generic QoL measures do not take into account features or symptoms specific to PD; this makes them less sensitive for measuring QoL in PD (Jenkinson *et al.*, 1997b; Martinez-Martin *et al.*, 2011a). Conversely, specific measures could over-estimate the effect of disease on overall QoL and may not include other factors, such as personality, socioeconomic factors and culture (Corner *et al.*, 2007). However, using a more generic measure has the advantage of covering wider issues relating to QoL and for comparison across populations with different health concerns or disorders, including healthy controls (Martinez-Martin *et al.*, 2011a).

Table 1-1: Measures of quality of life in Parkinson's disease

Measure	Description of Measure
Parkinson's Disease Questionnaire (PDQ-39)[a]	Parkinson's disease specific questionnaire with 39 items measuring eight domains: mobility, activities of daily living, emotional wellbeing, stigma, social support, cognitive impairment, communication and bodily discomfort
Parkinson's Disease Questionnaire - Short Form (PDQ-8)[b]	Parkinson's disease specific questionnaire with one item measuring each of the domains in PDQ-39
Parkinson's Disease Quality of Life Questionnaire (PDQL)[c]	Parkinson's disease specific questionnaire with 37 items measuring: parkinsonian symptoms, systemic symptoms, social function, and emotional function
Parkinson's Impact Scale (PIMS)[d]	Parkinson's disease specific questionnaire with 10 items completed three times one month apart.
Scales for Outcomes in Parkinson's Disease–Psychosocial (SCOPA-PS)[e]	Parkinson's disease specific questionnaire with 11 items measuring psychosocial functioning
Short-Form Health Survey (SF-36)[f]	General measure with 36 items measuring eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health
World Health Organization Disability Assessment Schedule (WHO-DAS II)[g]	General measure of disability composed of a total score and of six sub-scores: understanding and communication, getting around, self-care, getting along with people, life activities and participation in society
Euroqol (EQ-5D)[h]	General measure of QoL, five questions on: mobility, self-care, usual activities, pain/discomfort, anxiety/depression

a Jenkinson et al. (1997b); b Jenkinson et al. (1997a); c de Boer et al. (1996); d Calne et al. (1996); e Marinus et al. (2003); f Ware Jr and Sherbourne (1992); g Rehm et al. (1999); h EuroQol (1990)

The most widely used measure of QoL in PD is the 39 item version of the Parkinson's Disease Questionnaire (PDQ-39) (Jenkinson *et al.*, 1997b). This is a PD specific measure

of QoL and so is better equipped to detect subtle differences or changes in PD over time, making it useful for longitudinal studies (Reuther *et al.*, 2007; McGhee *et al.*, 2013). A Movement Disorders Society (MDS) Task Force systematically reviewed QoL measures used in PD (Martinez-Martin *et al.*, 2011a); the PDQ-39 was a recommended scale, along with Parkinson's Disease Questionnaire Short Form (PDQ-8) (Jenkinson *et al.*, 1997a), Parkinson's Disease Quality of Life Questionnaire (PDQL)(de Boer *et al.*, 1996), Parkinson's Impact Scale (PIMS)(Calne *et al.*, 1996), and Scales for Outcomes in Parkinson's Disease–Psychosocial (SCOPA-PS)(Marinus *et al.*, 2003). However, they found the PDQ-39 was the most widely used measure of QoL in PD and had been thoroughly tested for validity and reliability (Jenkinson *et al.*, 1997b; Hagell and Nygren, 2007; Martinez-Martin *et al.*, 2011a).

Another review also evaluated QoL instruments used for studies involving people with PD but instead examined the clinimetric properties (the measurement of clinical or medical phenomena) of the instruments (Marinus *et al.*, 2002). They found the PDQ-39 was the most appropriate measure for measuring QoL in people with PD as it has been tested the most thoroughly compared to other measures, it scored highly on all clinimetric properties and was available in many languages. Furthermore, it covers many psychometric properties that are important attributes to QoL, which are measured using eight subscales: mobility, activities of daily living (ADL), emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort (Jenkinson *et al.*, 1995; Jenkinson *et al.*, 1997b; Marinus *et al.*, 2002). However, Hagell and Nygren (2007) argue the PDQ-39 is biased towards more severe problems. It also has been criticised for lacking items that address nocturnal sleep problems and sexuality (Marinus *et al.*, 2002; Martinez-Martin *et al.*, 2011a).

1.2.2.2 Motor symptoms and non-motor symptoms: equal impact on quality of life?

There is some debate about which aspects of PD have the greatest effect on QoL, and whether motor or non-motor symptoms are the most significant factors. Disease severity, duration and disability have been previously associated with poorer QoL in people with PD (Schrag *et al.*, 2000; Pontone *et al.*, 2011; Soh *et al.*, 2011). Motor complications have been associated with poorer QoL, including unpredictable "off" periods, dyskinesia and motor fluctuations (Marras *et al.*, 2004; Chapuis *et al.*, 2005). Fung *et al.* (2009) found that early PD patients treated with

levodopa/carbidopa/entacapone (Stalevo) had fewer motor fluctuations and improved QoL, compared to patients treated with levodopa/carbidopa (Sinemet). Rahman *et al.* (2008) reported that poorer QoL was related to unpredictable on/off fluctuations and gait problems, including festination, freezing and falling. Conversely, they found that non-motor, autonomic symptoms, including incontinence, constipation and dizziness, had no significant associations with QoL. A systematic review by Soh *et al.* (2011) found that the motor symptoms most associated with poorer QoL were gait dysfunction and motor complications arising medication therapy. More recently, disease severity was significantly associated with reduced QoL and disability (Leonardi *et al.*, 2012). Additionally, this study found that QoL was correlated with increased number of NMS. However, some studies suggest disease severity contributes little to the total variance when NMS are removed from the model (Schrag *et al.*, 2000). Conversely, another study found that although NMS were significantly associated with QoL, the effect size was small compared to the contribution of motor symptoms (Santos-Garcia and de la Fuente-Fernandez, 2013).

Nonetheless, Martinez-Martin *et al.* (2011b) argue that NMS are more important than motor symptoms for predicting QoL in people with PD. They substantiated this in a cross-sectional study of 411 participants with PD across several countries, where nocturia, fatigue and drooling of saliva were the most common NMS (Martinez-Martin *et al.*, 2011b). Furthermore, they found that NMS had a stronger correlation with QoL than disease severity and that NMS were a better predictor of poorer QoL. Muller *et al.* (2013) found that in newly diagnosed people with PD, NMS were the most common predictors of poorer QoL, while another study including participants with more advanced PD found NMS to be significantly associated with QoL (Weerkamp *et al.*, 2013). A larger study also reported that NMS were reported as predictors of QoL (Barone *et al.*, 2009). Duncan *et al.* (2014) found both motor and non-motor symptoms negatively impacted on QoL, but that NMS had a stronger association with poorer QoL. The impact of NMS has been observed in other studies; symptoms that have negatively impacted on QoL include: constipation, urinary urgency, excess saliva, leg pain, fatigue, insomnia, depression and anxiety (Barone *et al.*, 2009; Winter *et al.*, 2011; Hinnell *et al.*, 2012; Muller *et al.*, 2013; Elbers *et al.*, 2014; Song *et al.*, 2014). However, an

increased frequency of NMS is also associated with increased disease duration and severity (Leonardi *et al.*, 2012).

Neuropsychiatric symptoms are NMS that have also been associated with reduced QoL in PD populations, independent of motor symptoms (McKinlay *et al.*, 2008). The presence of hallucinations and Rapid Eye Movement (REM) sleep behaviour disorder (RBD) have been associated with poorer QoL (McKinlay *et al.*, 2008; Rahman *et al.*, 2008; Whitehead *et al.*, 2008; Martinez-Martin *et al.*, 2011b). Duncan *et al.* (2014) found that neuropsychiatric and neuropsychological features have the greatest negative impact on QoL; these included depression, anxiety, impaired concentration, memory complaints, and insomnia. Barone *et al.* (2009) described that apathy, fatigue, attention/memory deficits and psychiatric symptoms were associated with reduced QoL, with apathy as the main predictor. Apathy has also been associated with poorer QoL in other studies (Benito-León *et al.*, 2012; Skorvanek *et al.*, 2013). Carod-Artal *et al.* (2008) argued that anxiety and depression were the main predictors of HR-QoL in a cross sectional study in Brazil.

However, depression has been the most commonly reported factor in the literature as affecting QoL (Burn, 2002; Schrag, 2006; Brown *et al.*, 2011; Duncan *et al.*, 2014). This is dominant compared with other motor and non-motor symptoms. In a literature review, depression was consistently listed as a factor which has a negative impact on QoL in PD, despite different outcome measures and rating scales being used (Schrag, 2006). A systematic review also found that the presence of depression was the single, most common, significant determinant of QoL in people with PD (Soh *et al.*, 2011).

It is important to note that, to date, few studies have used the DSM-IV criteria (American Psychiatric Association, 2000), which has now been superseded by the DSM-V criteria (American Psychiatric Association, 2013), to diagnose psychiatric disorders or symptoms. Using the DSM-IV criteria in a research setting is not always practical or appropriate, which may entail many measures or assessments (Schrag *et al.*, 2007). Instead most studies have relied on less burdensome self-reported measures, such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) or Geriatric Depression Scale (GDS-15) (Yesavage *et al.*, 1982), to signify the presence of anxiety and depression. However, these are subjective, open to recall bias and can

only be used as an indication of possible psychiatric disorders, not given a diagnosis. Furthermore, there may also be some inter-correlations with QoL domains; for example the PDQ-39 has a subdomain of emotional wellbeing (Jenkinson *et al.*, 1997b) which may have some overlap in terms of questions.

1.2.2.3 Young vs. later onset: is age a factor?

Age is also an important feature of PD to consider as a potential determinant of QoL. As PD predominantly affects older adults, it is often assumed that older adults with PD have poorer QoL as they may have more severe motor symptoms, have a number of age-related comorbidities and are more frail (Ahmed *et al.*, 2008; Lauretani *et al.*, 2012; Roland *et al.*, 2012). However, it has been proposed that younger people with PD may have poorer perceived QoL. Approximately 5% of people with PD are diagnosed when they are under 50 years old, with 30% being diagnosed before 65 (Murphy *et al.*, 2013), age related factors are important to consider when addressing QoL.

The first study to investigate the differences in QoL between younger and later onset PD as a primary outcome was by Schrag *et al.* (2003). They used the PDQ-39 and EQ-5D as measures of QoL and also had a number of questionnaires relating to psychosocial functioning. They classified younger onset as PD onset before the age of 50. Subjects with young onset PD had poorer QoL, as measured by the PDQ-39, with stigma being the only significantly different sub-sale of the questionnaire after corrections for multiple comparisons. Schrag *et al.* (2003) also found that subjects with young onset scored significantly higher for depression with more meeting the cut-offs for moderate/severe depression compared to later onset subjects (40% vs. 17%). Younger subjects also scored higher for stigma and marital discord in the psychosocial functioning questionnaires.

In the PROMS-PD study, a longitudinal study investigating mood states in PD, the PDQ-8 was used to measure QoL in 462 subjects. In a baseline regression model, younger age was predicted to be a predictor of worse QoL in addition to duration of PD, levodopa equivalent dose (LED), disease severity, anxiety and depression (Hinnell *et al.*, 2012). Knipe *et al.* (2011) investigated the effect of age of onset on of PD on QoL using the PDQ-39, with young onset PD classified as being diagnosed under the age of

45. They found that subjects with younger onset PD had poorer QoL, but suggested that this was probably mediated by depressed mood. The authors proposed that people with younger onset PD would have more emotional consequences compared to those who were older as they would see having PD as "unfair."

These psychosocial consequences have also been observed elsewhere. Singer (1974) suggested that younger people with PD are affected more by PD and thus prematurely age. She proposed that younger people with PD tend to socialise more and so may be exposed more often to stigma from others, leading to social withdrawal and a reduction in activity levels similar to people who are much older than themselves. Stigma has also been suggested as being more problematic for younger people with PD, where the perceptions of PD of others may have a greater effect (Schrag *et al.*, 2003; Calne *et al.*, 2008; Murphy *et al.*, 2013).

Loss of employment is also an important issue relating to QoL in younger people with PD (Singer, 1974; Schrag *et al.*, 2003). Murphy *et al.* (2013) investigated loss of employment in PD and found of those still working, 50% remained working after five years and only 14% after 10 years from time from PD onset. This study found that loss of earnings was a significant factor when considering QoL and that early retirement was associated with social isolation, feelings of futility and lack of purpose.

Thus, there is a range of psychosocial problems that can impact on the QoL, specifically to younger people with PD. These include: stigmatisation, dissatisfaction, lack of purpose, role change, depression, apathy, social isolation, break down of relationships, marital problems, financial strain and addictive behaviours, such as punding (Singer, 1974; Schrag *et al.*, 2003; Calne *et al.*, 2008; Knipe *et al.*, 2011; Hinnell *et al.*, 2012; Murphy *et al.*, 2013). These elements can also impact on how well an individual is able to adjust to living with a chronic disease, particularly one such as PD which is associated with older adults (Calne *et al.*, 2008).

1.2.3 Adjusting to Parkinson's disease: the long term impact of chronic disease on quality of life

As described above, after diagnosis there are often many changes in a person's life. Motor and non-motor symptoms associated with PD, as well as psychological and social consequences, can negatively impact on QoL and wellbeing of people with PD.

After diagnosis, individuals are confronted with new situations and stressors that can be difficult, and which can challenge existing coping mechanisms (Lazarus and Folkman, 1984; Stanton *et al.*, 2007; de Ridder *et al.*, 2008). Finding a new balance or equilibrium to the new circumstance of chronic disease is referred to as adjustment (de Ridder *et al.*, 2008). Individuals with chronic illness often regain or achieve a new equilibrium and return to a state of QoL similar to before the chronic illness began (Moos and Holahan, 2007; Moss-Morris, 2013). However, not all people with chronic illness successfully adjust. Those who do not face psychological disturbance, such as fear, anger and distress (Moos and Holahan, 2007). They also face threats to their self-image, difficulty maintaining a sense of self-efficacy, emotional imbalance, difficulty facing an uncertain future and poorer health outcomes (de Ridder *et al.*, 2000). Suzukamo *et al.* (2006) showed that poor psychological adjustment had a greater impact on QoL in PD than disease severity. However, research into the area is heterogeneous; there are multiple complex conceptualisations, theoretical frameworks, contributing factors and measures of adjustment across chronic illnesses (Walker *et al.*, 2004; Martz and Livneh, 2007; Moos and Holahan, 2007; Stanton *et al.*, 2007; de Ridder *et al.*, 2008; Ramjeet *et al.*, 2008; Moss-Morris, 2013; Hurt *et al.*, 2014).

Some of the commonly used theories and models are described in Table 1-2. The most prominent model of adjusting to chronic disease is the stress and coping model (de Ridder *et al.*, 2008; Hoyt and Stanton, 2012; Moss-Morris, 2013). The stress and coping model of adjustment states that adjustment is influenced by the appraisal of stressors and the efficacies of coping strategies (Lazarus and Folkman, 1984). The authors outlined two types of coping: problem-focused strategies, which are directed towards finding a solution to the stressor, and emotion-based strategies, which include alleviating emotions and could involve avoidance, self-blame or wishing problems away. However, this model has been criticised; for example a single coping measure, such as social support, could include both strategies simultaneously and does not take into account changes in circumstances or progression of chronic illnesses (Klepac *et al.*, 2008; Ramjeet *et al.*, 2008; Moss-Morris, 2013).

Table 1-2: Theories of coping and adjustment

Model	Summary of model
Cognitive adaptation model[a]	Adjustment is centred around: i. the search for meaning and experience ii. regaining mastery over the event iii. restore self-esteem Successful adaptation relies on the perception of self-control, where the illusion of self-control acts as a buffer against threats
Crisis theory[b]	Chronic illness disrupts an individual's equilibrium as habitual coping processes are inadequate, causing a 'crisis' (psychological distress). Three factors contribute to the coping process: i. illness related factors (e.g. extent illness intrudes on life) ii. personal and background factors (e.g. age, ethnicity) iii. physical and social environment factors (e.g. social support) Coping processes contribute to outcome (cognitive appraisal, adaptive skills, coping skills). The outcome is successful adaptation and adjustment.
Self-regulation model[c]	Individuals with chronic illness regulate or minimise health risks in ways that are consistent with their perception of the illness. According to the model, an individual is an active problem solver who attempts to reconcile current health and ideal health (goals) using three adaptive features: i. representation of illness experience ii. action planning or 'coping' responses iii. 'appraisal' or monitoring of success/failure of coping response
Stress and coping model[d]	Chronic illness introduces stressors which the individual appraises as taxing and outside their control. Coping requires cognitive and behavioural efforts to manage these stressors using two strategies: i. problem focused strategies ii. emotion focused strategies

a Taylor (1983); b Moos and Schaefer (1984); c Leventhal et al. (1998); d Lazarus and Folkman (1984)

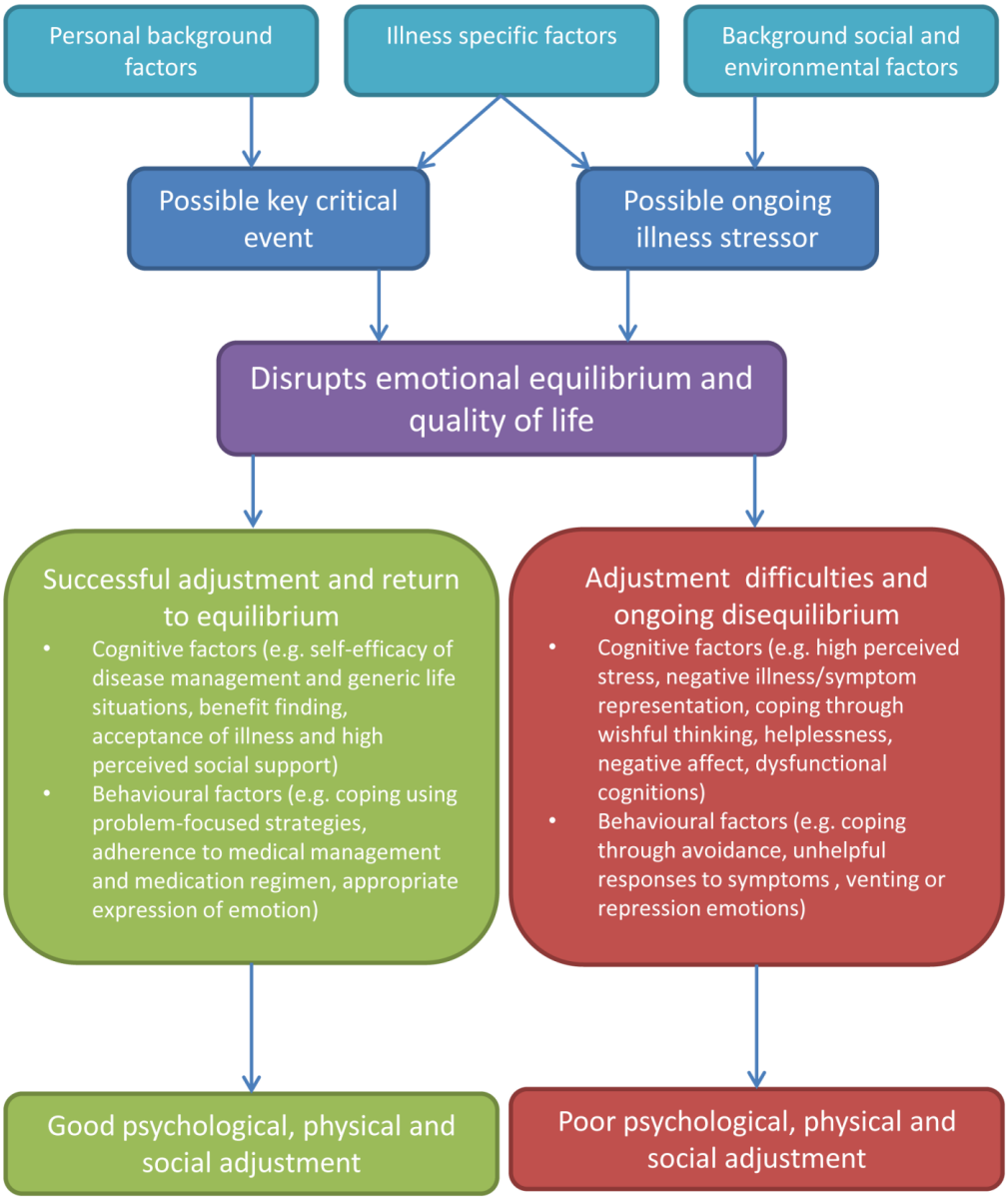
In a large literature review by Stanton *et al.* (2007), the authors gave three broad conclusions regarding what it means to adjust to a chronic health condition. First, chronic diseases require adjustment across life domains. Second, adjustment is not instantaneous and develops over time; and finally, how individuals adjust to chronic diseases is heterogeneous, where individual differences are central to how a person adjusts.

The effect of personality on successful coping and adjustment is important to consider. Personality affects QoL by influencing how individuals approach and react to life events, in this context chronic disease (Wrosch and Scheier, 2003). This was also suggested by Whitworth *et al.* (2013) who found that neuroticism and extroversion were significant predictors of the use of psychological coping strategies in PD. They also found that coping choice and the effectiveness of the coping strategies were influenced by personality. Optimism has been theorised to promote subjective

wellbeing and good health by facilitating the coping process (Wrosch and Scheier, 2003). According to the self-regulation model (Leventhal *et al.*, 1998), individuals with positive expectations will strive to achieve their goals compared to those without optimism (de Ridder *et al.*, 2000). As part of the PROMS-PD study, Hurt *et al.* (2014) found that optimism provided protection against negative illness perceptions in PD. Furthermore, they found that positive perceptions of PD predicted better QoL and psychological wellbeing. However, de Ridder *et al.* (2000) stated that unrealistic optimism was not helpful or beneficial in chronic illness as it could lead to mismanagement of health, such as neglecting medication regimen or underestimating illness.

Other individual differences that contribute to successful adjustment include: cognitive processing and appraisal, emotional regulation, socioeconomic status (SES), ethnicity and culture, gender, interpersonal support (including social support) and coping skills (Moos and Holahan, 2007; Stanton *et al.*, 2007; de Ridder *et al.*, 2008; Moss-Morris, 2013). These are not always accounted for in existing models of adjustment and coping, and some coping models are not specific to chronic illness. Moss-Morris (2013) proposed an overarching paradigm in the form of a new working model for adjustment of chronic illness, which is summarised in Figure 1-2. The author tries to address the shortcomings of existing models and to produce a model that can be used in progressive illnesses. The model suggests that background factors, such as personality and life experiences, social and environmental factors, such as age and culture, affect how people adapt to stressors. Illness specific stressors then have the potential to influence the nature of the event that disrupts equilibrium and QoL. According to the model, successful adjustment through psychological and social adjustment is regained through cognitive and behavioural factors (examples given in Figure 1-2). Those who poorly adjust have low positive affect and disproportional distress (Moss-Morris, 2013). However, this model is theoretical, although based on empirical evidence, and has not yet been tested.

Figure 1-2: A working model of adjustment to chronic disease as described by Moss-Morris (2013)



Moss-Morris (2013)

Adjustment and coping heavily rely on individuals having the cognitive reserve necessary to implement successful strategies outlined in the models and frameworks in Table 1-2 (Hindle *et al.*, 2014). Hurt *et al.* (2012) found that even mild to moderate cognitive impairment in subjects with PD can contribute to reduced task-oriented coping strategies. Similarly, Kudlicka *et al.* (2014) suggested that executive dysfunction could contribute to ineffective strategies to overcome limitations of PD or ineffective coping strategies relating to psychological distress. They further suggested that this could affect QoL due to poor adjustment and the difficulties of positive reappraisal, goal setting and adjusting expectation.

1.3 Cognitive Impairment in Parkinson's Disease

Cognitive impairment is common in PD. Studies estimate a point prevalence of 25-30% of people with PD have a diagnosis of dementia (PDD), which is six times higher than an aged-matched general population (Kulisevsky and Pagonabarraga, 2009). Cumulatively, however, the life-time prevalence of PDD is up to 80% (Hely *et al.*, 2008), although few studies have directly assessed this. The Sydney Multicentre Study followed up newly diagnosed PD patients over 20 years and assessed the cognition and prevalence of dementia, among other clinical and neuropsychological assessments (Hely *et al.*, 1999; Hely *et al.*, 2008). At 3 and 5 year follow up, 26% and 28%, respectively, were diagnosed with PDD. After 15 years, 48% of living participants were demented, with 36% displaying mild cognitive impairment (MCI). Twenty years from baseline, 100 out of 136 participants had died. Of the remaining participants 83% were demented. In another study, a cohort of incident PD patients found that 10 years from PD diagnosis, 46% had a diagnosis of PDD (Williams-Gray *et al.*, 2013). With such a high frequency of PD patients developing PDD, further research is necessary to understand risk factors of PDD, disease progression and treatment options.

1.3.1 Diagnostic criteria for Parkinson's disease dementia

Guidelines for the clinical diagnostic criteria for PDD (Table 1-3) have been outlined by Emre *et al.* (2007). The core features of PDD include, first having a diagnosis of PD, and second a dementia syndrome with insidious onset and slow progression within the context of established PD. It should be diagnosed through extensive testing, including a complete medical history and clinical and mental examinations.

Table 1-3: Diagnostic criteria for Parkinson's disease dementia

I. Core features
Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
• Impairment in more than one cognitive domain
• Representing a decline from premorbid level
• Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms
II. Associated clinical features
1. Cognitive features:
• Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
• Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
• Visuospatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
• Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
• Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioural features:
• Apathy: decreased spontaneity; loss of motivation, interest, and effortful behaviour
• Changes in personality and mood including depressive features and anxiety
• Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
• Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
• Excessive daytime sleepiness
III. Features which do not exclude PD-D, but make the diagnosis uncertain
• Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
• Time interval between the development of motor and cognitive symptoms not known
IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D
• Cognitive and behavioural symptoms appearing solely in the context of other conditions such as:
Acute confusion due to motor or autonomic symptoms
a. Systemic diseases or abnormalities
b. Drug intoxication
Major Depression according to DSM IV
• Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Emre et al. (2007)

Patients should also demonstrate impairment in more than one cognitive domain; the authors recommend using the five domains defined in Table 1-4. For a PDD diagnosis there should also be a decline from a pre-morbid level and the deficits should be such

that they are severe enough to impair activities of daily living (ADL). This impairment could be at a basic ADL level, which includes personal care such as bathing, dressing, eating and personal hygiene; at an instrumental ADL level, such as housework, food shopping, taking medications correctly and socialising. However, for a diagnosis of PDD, impairment in ADL must be independent from other PD symptoms, either motor or autonomic.

Table 1-4: Cognitive domains and their definitions

Domain	Impairment
Attention	To focus on a certain object or stimuli, to maintain concentration or vigilance for an extended period of time, to concentrate on more than one task or to resist distractions
Executive function	Higher order function including: planning, decision making, initiation, conceptualizing, organising and evaluating
Visuospatial function	To make sense of the visual world— to receive, interpret, and apply meaning to shapes, angles and images—to be able to make sense of orientation or location of an object or image in space
Memory	To assimilate knowledge or information, store this information and retrieve it at another point in time
Language	To both comprehend and express verbal and written means of communication

Lezak (2004) Neuropsychological assessment

1.3.2 Risk factors for Parkinson's disease dementia

Being able to predict the occurrence of PDD and its development is important in disease management and planning. Being able to identify people with PD who are likely to develop PDD could allow suitable interventions to be implemented with the aim of delaying or even preventing the development of dementia (Leroi *et al.*, 2012b). This could then prevent admittance to nursing homes, institutionalisation, alleviate costs and improve QoL (Galvin *et al.*, 2006; Leroi *et al.*, 2012b). Several risk factors have been identified for PDD, including both demographic and clinical features.

Age is one of the more prominent risk factors (Emre *et al.*, 2007). The Sydney Multicentre Study followed 149 PD patients over 20 years and found that the average age of dementia onset was 70 years (Reid *et al.*, 2011). This was regardless of PD duration or age of onset. However, patients with early onset PD seemed to have preserved language skills compared to the older adults. Aarsland *et al.* (2007b) also

found that the age of PD onset was not associated with the development of PDD, but age on its own was a risk factor.

The motor phenotype of PD may also be a risk factor for dementia. Burn *et al.* (2006) found that the PD subtype of postural instability gait difficulty (PIGD) was associated with a more rapid cognitive decline compared to tremor dominant or indeterminate subtypes. Cognitive decline is also associated with increased Hoehn and Yahr score, rigidity and bradykinesia (Aarsland *et al.*, 2004).

Non-motor symptoms have also associated with cognitive decline. In a large, multi-centre study Barone *et al.* (2009) found higher prevalence of apathy and psychiatric symptoms in participants with cognitive impairment. Depression, anxiety and sleep disturbances, particularly RBD are also common in dementia, and thus may also be independent risk factors (Naismith and Lewis, 2011). In particular, RBD has been identified as a risk factor for cognitive impairment in PD patients in other studies (Boeve *et al.*, 2004; Erro *et al.*, 2012), and more broadly with DLB (Ferman *et al.*, 2011), with insomnia and acting out dreams (i.e. presumed RBD) being strong predictors of mild cognitive impairment in PD (PD-MCI) (Erro *et al.*, 2012; Gunn *et al.*, 2013).

Hallucinations in non-demented PD patients have been shown to be a key predictor of subsequent dementia (Emre *et al.*, 2007; Naismith and Lewis, 2011). In an eight year prospective study, 75% PD participants who reported hallucinations before baseline developed dementia (Aarsland *et al.*, 2003). PD patients reporting visual hallucinations have also been reported to have more rapid cognitive decline (Aarsland *et al.*, 2004), but Emre *et al.* (2007) found that there are inconsistencies across studies identifying this as a risk factor. Hallucinations may instead be a concomitant of dementia, as in dementia with Lewy bodies (DLB) (Aarsland *et al.*, 2001).

Discrepancies in other reported risk factors include gender, education and the presence of depression (Emre *et al.*, 2007). Starkstein and Brockman (2011) also suggest that apathy is a risk factor for dementia and is significantly associated with cognitive decline, while other studies have shown a relationship between apathy and poorer scores for executive function (Pluck and Brown, 2002).

1.4 Mild Cognitive Impairment in Parkinson's Disease

More recently, there has been a focus on mild cognitive impairment in PD (PD-MCI). PD-MCI has been identified as a potential early marker or prodromal state for the development of PDD (Janvin *et al.*, 2005; Aarsland *et al.*, 2011; Barone *et al.*, 2011; Dalrymple-Alford *et al.*, 2011; Leroi *et al.*, 2012b; Litvan *et al.*, 2012; Broeders *et al.*, 2013). However, it is difficult to judge whether PD-MCI is a transitional stage as few prospective studies have investigated this, leaving open the possibility that, as in the general population, some people may have a stable MCI (Roberts *et al.*, 2014).

Most studies are cross-sectional or retrospective, which are unable to show any change in cognitive decline from PD-MCI to PDD. Janvin *et al.* (2006) is one of few studies that investigated this link. At baseline 53% of 72 non-demented patients were classified as having PD-MCI, with 18 (62%) developing dementia at four year follow up compared to six (20%) cognitively intact PD participants at baseline. However, the sample size was very small with high dropout and mortality rates, which could underestimate the development of dementia, since dementia is associated with increased mortality. As there were no interim measures over the four year follow up period, it is difficult to attribute a causal link.

More recently, Broeders *et al.* (2013) studied cognitive change over a five year period. At baseline, 35% of 123 PD patients were classified as PD-MCI. At the 3 year follow up, 53% participants were classified as having PD-MCI; six participants with baseline PD-MCI developed PDD and three who showed normal cognition at baseline also developed PDD. After five years, 37% of the remaining participants had a classification of PD-MCI and 26% had developed PDD (17% cumulatively), and all but three were classified as PD-MCI prior to PDD diagnosis. It was also observed that some participants who were classified as PD-MCI were subsequently classified as cognitively normal, which could suggest that PD-MCI is a fluid concept where patients can fluctuate between cognitively normal and MCI. Currently, there is an on-going incidence study of newly diagnosed people with PD with longitudinal follow up, which includes a large schedule of neuropsychological tests (Yarnall *et al.*, 2013a). This study found that in newly diagnosed patients, PD-MCI was present in 43% of the cohort.

The prevalence of PD-MCI is estimated to be between 15-50% at time of diagnosis (Foltynie *et al.*, 2004; Muslimovic *et al.*, 2005; Dalrymple-Alford *et al.*, 2011; Mason and Barker, 2012; Poletti *et al.*, 2012; Yarnall *et al.*, 2013a), with a study in a Chinese PD population finding 60% newly diagnosed PD patients with MCI (Wu *et al.*, 2012). This variance may be due to lack of census as to the definition of PD-MCI, which did not previously exist.

1.4.1 Diagnostic criteria for PD-MCI

Previous studies that have classified PD-MCI have varied in several key ways: i) the definition of PD-MCI and the operational cut-offs used; ii) the cognitive domains assessed; iii) the diverse range of neuropsychological tests used; iv) the number of tests per domain; v) the number of abnormal tests per domain; vi) the normative data used; and vii) the definition of PDD (Goldman *et al.*, 2013; Yarnall *et al.*, 2013b).

The range of these diagnostic criteria can be seen in Table 1-5. The cut-off of 1.5 standard deviations (SD) below normative data from age-matched controls was the most common criterion used, with 1.0 SD and 2.0 SD also being used. However, some studies used combined z-scores, with variable correction for age and level of education. Nonetheless, the variability in criteria is reflected by the reported prevalence, stability and rate of progression from PD-MCI to PDD.

Table 1-5: Differences of PD-MCI criteria between studies

Study	PD-MCI definition	Domains assessed	Definition of PDD	Prevalence of PD-MCI
Muslimovic et al. (2005)	Scored <2 SD below mean control score, controlling for age and education, in ≥3 neuropsychological tests	Psychomotor speed, attention, language, memory, executive and visuospatial functions	N/R	23.5%
Janvin et al. (2006)	Scored ≤1.5 SD below mean control score on ≥1 neuropsychological tests *Subtypes*: amnestic, single-domain non-amnestic, multi-domain non-amnestic	Memory, visuospatial function and attention/executive function; MMSE for global cognition	DSM-III-R Criteria	52.8% of non-demented participant, 28.3% cohort; PDD = 43.3%
Caviness et al. (2007)	Subjective cognitive complaint but no functional impairment plus scored ≤1.5 SD below age corrected mean score in ≥1 cognitive domains *Subtypes*: multi vs single domain, amnestic vs non-amnestic	Frontal/executive, amnestic, visuospatial, attention and language	DSM-IV Criteria	21%; PDD = 17%
Williams-Gray et al. (2007)	Scored <1 SD below normative data, either age and IQ matched healthy controls or normative data where available, on ≥1 neuropsychological test	Frontal, temporal and parietal function	MMSE score <24 and DSM-IV Criteria	67% at baseline; 57% PD-MCI at follow and 10% PDD at follow up (mean 3.5 years)
Aarsland *et al.* (2009)	Scored <1.5 SD below mean for age and education corrected z-score for ≥1 cognitive domain *Subtypes*: single-domain amnestic, multi-domain amnestic, single-domain non-amnestic, multi-domain non-amnestic	Verbal memory, visuospatial and attentional/executive function	Diagnostic criteria for PDD as defined by Emre *et al.* (2007)	18.9%
Elgh *et al.* (2009)	Scored <1.5 SD below means (where possible standardised for age, sex and education) in ≥1 domain; domain impaired when >50% tests in a domain were below cut off	Episodic memory, working memory, visuospatial function, verbal fluency, naming and executive function	MMSE score <24	30%
Kim *et al.* (2009)	Scored <1.5 SD below mean score of age and education matched control group in one or more cognitive domains *Subtypes*: multi vs single domain plus domain impaired	Attention, language, visuospatial, memory and executive function	Diagnostic criteria for PDD as defined by Emre *et al.* (2007)	40.4%

Study	PD-MCI definition	Domains assessed	Definition of PDD	Prevalence of PD-MCI
Aarsland et al. (2010)	Scored <1.5 SD below mean for age and education corrected z-scores (where possible) for ≥1 cognitive domain *Subtypes*: single-domain amnestic, multi-domain amnestic, single-domain non-amnestic, multi-domain non-amnestic	Memory, visuospatial and attention/executive function	Multi-centred study, definition differed between centres including DSM-III-R, DSM-IV, MDS criteria for PDD as defined by Dubois *et al.* (2007)	25.8%
Petrova et al. (2010)	Subjective cognitive complaint, plus MMSE >26, plus scored ≤1.5 SD below age and education matched norms, plus preserved functional capacity and ADL *Subtypes*: amnestic, single domain non-memory, multiple domain	Attention, initiation and perseveration, conceptualization, construction and memory	CDR and DSM-IV Criteria	47.9%
Sollinger et al. (2010)	Scored below standardised published normative scores in ≥2 tests in a domain, plus subjective cognitive complaint and clinical diagnosis by neuropsychologists	Visuospatial, language, attention, executive function and memory	N/R	52.8%
Costello et al. (2011)	Scored ≤2 SD below normative mean score on ≥1 test *Subtypes*: single-domain amnestic, multi-domain amnestic, single-domain non-amnestic, multi-domain non-amnestic	Intellectual, memory, language, perception and executive	N/R	63.7%
Dalrymple-Alford et al. (2011)	Evaluated various criteria using cut offs of 1, 1.5 and 2 SD with impairment in ≥1 or ≥2 tests Main data reported using scores of ≤1.5 SD in ≥2 tests	Executive function, attention and working memory, learning and memory, visuo-perception	Diagnostic criteria for PDD as defined by Emre *et al.* (2007)	14-89% depending on criteria used
Liepelt-Scarfone et al. (2011)	Evaluated various criteria using standardised z-scores for tests with cut offs of z= 1, 1.5 and 2 for either ≥1 test per domain or ≥2 tests per domain *Subtypes*: single-domain amnestic, multi-domain amnestic, single-domain non-amnestic, multi-domain non-amnestic	Executive function, attention, praxis and visual function, psychomotor speed and naming ability, list learning and memory recall, logical memory	MMSE <26 and diagnostic criteria for PDD as defined by Dubois *et al.* (2007)	9.9%–92.1% depending on criteria used

Study	PD-MCI definition	Domains assessed	Definition of PDD	Prevalence of PD-MCI
Goldman et al. (2012)	Z-score ≤1.5 for ≥1 cognitive domain; z-score calculated by taking the mean z-score for each test per domain *Subtypes*: single-domain amnestic, multi-domain amnestic, single-domain non-amnestic, multi-domain non-amnestic	Attentional/executive function, language, memory and visuospatial	N/R	47.7% single-domain non-amnestic; 24.2% multi-domain amnestic; 18.8% single-domain amnestic; 9.5% multi-domain non-amnestic
Poletti et al. (2012)	Scored ≤2 SD below normative mean score on ≥2 tests	Memory, language, executive function, praxis and visuospatial function; MMSE for global cognition	DSM-IV-TR Criteria	14.9%
Leroi et al. (2012c)	Scored ≤1.5 SD below mean scores of age-education matched control scores on ≥1 test as per MDS Level I PD-MCI Criteria (outlined in Table 1-6)	Attention and working memory, executive dysfunction, memory and one test of visuospatial function.	Diagnostic criteria for PDD as defined by Dubois *et al.* (2007)	37.8%; PDD 19.7%
Broeders et al. (2013)	Scored ≤1.5 SD below demographic adjusted control scores on ≥1 test as per MDS Level II PD-MCI Criteria (outlined in Table 1-6)	Memory, language, executive function, visuospatial and attention	Diagnostic criteria for PDD as defined by Emre *et al.* (2007)	35.0% baseline; 3 years 53.4%; 5 years 36.8%, PDD 26.3%

PD-MCI = Mild cognitive impairment in Parkinson's disease; PDD = Parkinson's disease dementia; SD = standard deviation; MMSE = Mini mental state examination; DSM-III-R= Diagnostic and Statistical Manual of Mental Disorders 3rd Edition, revised; DMS-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition; DMS-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision; ADL = Activities of daily living; CDR = Clinical Dementia Rating scale; N/R = not recorded

The Movement Disorder Society (MDS) recently set up a task force to outline the diagnostic criteria for PD-MCI (Litvan *et al.*, 2012) which is outlined in Table 1-6. To be classified as having PD-MCI, a person with PD must exhibit gradual cognitive decline that is not severe enough to impair functional independence or activities of daily living (ADL). They should show deficits in scores on batteries of neuropsychological tests or global tests. Litvan *et al.* (2012) classified PD-MCI criteria into Level I and Level II (Table 1-6); Level I utilises a less comprehensive battery of tests to classify *possible* PD-MCI, while Level II consists multiple assessments across cognitive domains to classify *probable* PD-MCI.

Table 1-6: Criteria for diagnosis of PD-MCI

I. Inclusion criteria	
Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria	
Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician	
Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III)	
Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present	
II. Exclusion criteria	
Diagnosis of PD dementia based on MDS Task Force proposed criteria	
Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)	
Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing	
III. Specific guidelines for PD-MCI level I and level II categories	
Level I (abbreviated assessment)	**Level II (comprehensive assessment)**
Impairment on a scale of global cognitive abilities validated for use in PD	Neuropsychological testing that includes two tests within each of the five cognitive domains (Table 1-4)
or	Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)	Impairment on neuropsychological tests may be demonstrated by: Performance approximately 1 to 2 SDs below appropriate norms or Significant decline demonstrated on serial cognitive testing or Significant decline from estimated premorbid levels
IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)	
PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or	
PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)	

Litvan et al. (2012); SD = Standard deviation

1.4.2 Subtypes of mild cognitive impairment

Several studies have assessed PD-MCI in specific cognitive domains. As discussed previously, studies have used a range of methods to assess cognitive impairment, including the number of domains assessed, the types of tests and the number of tests per domains (Litvan *et al.*, 2011; Goldman *et al.*, 2013); therefore, there is variability in the reported domains that have been impaired. There is some debate which is the most commonly impaired domain; executive function, attention, memory and

visuospatial function have been reported highly in various studies but language is rarely impaired (Janvin *et al.*, 2006; Caviness *et al.*, 2007; Aarsland *et al.*, 2010; Goldman *et al.*, 2012; Goldman *et al.*, 2013; Yarnall *et al.*, 2013a; Pfeiffer *et al.*, 2014).

Some studies have gone further than specific domains and looked at subtypes of PD-MCI, where patients have been grouped according to a pattern of cognitive impairment. As seen in Table 1-5, subtypes have typically been classified as single-domain vs. multi-domain and amnestic vs. non-amnestic. Some studies found non-amnestic subtypes and multi-domain subtypes to be most common in PD-MCI (Janvin *et al.*, 2006; Marras *et al.*, 2013).

The Norwegian ParkWest study categorised PD-MCI into four subtypes: single-domain amnestic (24%), multi-domain amnestic (11%), single-domain non-amnestic (3%) or multi-domain non-amnestic (62%) (Aarsland *et al.*, 2009). Multi-domain impairments were more common than single domain impairment, with multi-domain non-amnestic PD-MCI being the most frequently reported subtype. Three other studies have also found the most commonly reported subtype to be non-amnestic single domain PD-MCI, with impairments most common in executive and visuospatial function (Caviness *et al.*, 2007; Sollinger *et al.*, 2010; Goldman *et al.*, 2012).

A large, pooled, multi-centred study classified 26% of 1345 people with PD as PD-MCI (Aarsland *et al.*, 2010). Using three domains, attention and executive function (counted as one domain), memory and visuospatial function, participants were then categorised by subtype as described above by (Aarsland *et al.*, 2009). Memory was the most commonly impaired domain (14%), but single domain non-amnestic was the most common subtype. The various centres used different neuropsychological tests and used z-scores for comparison purposes, and the tests had different sensitivities. Furthermore, different criteria for PDD were used in each centre, which has implications for classifying PD-MCI.

The MDS PD-MCI guidelines recommend discontinuing use of the terms amnestic and non-amnestic for subtype categorisation (Litvan *et al.*, 2012). Instead, they suggest describing the domains impaired to increase specificity and understanding between subtypes (Table 1-6). For example, a participant with impairments in executive function and attention would have a subtype classification of multi-domain PD-MCI

executive function plus (+) attention, rather than being labelled as multi-domain non-amnestic.

Since the publication of the MDS PD-MCI guidelines, only two studies have used these new recommendations for subtyping. Goldman *et al.* (2013) used the five cognitive domains proposed by the MDS, attention, memory, executive function, visuospatial function and language, to classify participants into subtypes. They identified 22 subtypes of PD-MCI, with only 9% participants having a single domain classification. The subtypes with multiple-domains impaired ranged from two to five domains being impaired, with subtypes including three impaired domains being the most common (35%). Of those with multi-domain classification, the most common subtype was attention + executive function + memory + visuospatial function (17%). Overall, executive function was the most commonly impaired domain (78%) followed by memory (70%). Similarly, Cholerton *et al.* (2014) identified 21 sub-types using the MDS PD-MCI guidelines, 95% participants were multi-domain PD-MCI. The authors used principal component analysis (PCA) to identify seven cognitive factors using neuropsychological tests, however they were unable to characterise distinct cognitive groups.

Understanding PD-MCI subtypes would be valuable. Impairments in multiple domains may have prognostic significance in determining which participants are more likely to develop PDD (Leroi *et al.*, 2012b; Goldman *et al.*, 2013). This is important as earlier identification of those who are at risk to PDD and thus use appropriate therapies, to slow or even halt progression (Aarsland *et al.*, 2009; Goldman *et al.*, 2012). Furthermore, knowledge of which particular cognitive domains are impaired could help guide clinicians as to what pharmacological and non-pharmacological interventions might be particularly effective (Hindle *et al.*, 2013). However, as detailed above, the number of PD-MCI subtypes produced by the MDS criteria may be too numerous, be unstable over time and only one impaired test in one or more domain may lead to false classification (Cholerton *et al.*, 2014).

1.4.3 Treating mild cognitive impairment in Parkinson's disease

As illustrated, if PD-MCI is an early marker or prodromal state for the development of PDD, early diagnosis and treatment could be important to long-term outcomes for the

individual. Currently, there is little evidence into the efficacy of treatment of PD-MCI, either by pharmacological or non-pharmacological means (Hindle *et al.*, 2013). However, some interventions have been proposed as being potentially beneficial. For example, pharmacological therapies such as cholinesterase inhibitors and their effects on attention and memory (Bronnick *et al.*, 2006; Kehagia *et al.*, 2010), or cognitive training strategies focused on executive function (Calleo *et al.*, 2012).

Cholinesterase inhibitors have been used successfully in Alzheimer's disease (AD) and have been reported to improve cognitive symptoms in PDD (van Laar *et al.*, 2011; Weintraub *et al.*, 2011). There have been a greater number of studies investigating the effects of Rivastigmine compared to other cholinesterase inhibitors (van Laar *et al.*, 2011). Rivastigmine has been shown to significantly improve cognition, including memory and language (Weintraub *et al.*, 2011; Emre *et al.*, 2014). A large, multi-centred randomised and placebo controlled study found that subjects with PDD who were taking rivastigmine had improved ADL, compared to the placebo group (Olin *et al.*, 2010). More recently, a trend effect was observed in global cognition in PD-MCI participants prescribed the rivastigmine transdermal patch compared to a placebo group (Mamikonyan *et al.*, 2015). However, no statistically significant treatment effect was found in cognitive measures, although this could be due to the small sample size (n=26). Donepezil has also been shown to improve cognition, although most studies seem to be small (van Laar *et al.*, 2011). However, a large, randomised double-blind study by Dubois *et al.* (2012) found that Donepezil improved global cognition in subjects with PDD, with significant improvements in executive function. However, there were no significant differences in ADL. Goldman and Holden (2014) suggested that further research into donepezil is needed as it has yet to be proven as an effective treatment option for PDD.

Conversely, non-pharmacological interventions have been proposed as potentially useful to improve cognition or to prevent cognitive decline (Hindle *et al.*, 2013). Naismith *et al.* (2013) used a sample of 35 PD participants in a cognitive training intervention group to improve memory, with 15 participants with PD as a waitlist control group, which received standard treatment for seven weeks before also beginning the intervention. They found a moderate but significant improvement in learning and memory retention in the intervention group compared to controls.

However, follow up assessments were conducted within two weeks of completing the intervention but no later assessments were performed, so the long term effects of the intervention are not known.

A randomised controlled intervention for cognitive training to improve cognitive performance found improved attention, information processing speed, memory, visuospatial and visuoconstructive abilities, semantic verbal fluency and executive function (París *et al.*, 2011). However the study was small, with only 16 in the intervention group compared to 12 controls, which received speech therapy, with 50% of subjects in each group being classified as PD-MCI. Furthermore, participants were excluded if they had significant cognitive impairment, as determined by MMSE score <23. This limited the conclusions drawn as to suitability of the intervention to participants with dementia or more severe cognitive impairment that would potentially benefit from the intervention. Finally, there was no improvement in QoL, ADL or mood in subjects in either group.

Exercise has also been suggested as a suitable intervention for cognition in PD. A systematic review on the effects of exercise-based interventions on cognition found that exercise improved cognition (Murray *et al.*, 2014). However, there was only weak evidence supporting an improvement in global cognition. Nonetheless, the authors found moderate evidence across four studies that executive function significantly improved. Despite the limited evidence, it has been suggested that exercise could have a neuroprotective effect on cognition, in PD and in other cognitive disorders, that is novel and potentially cost effective (Hindle *et al.*, 2013).

1.5 Cognition and quality of life

In the dementia literature, there are a number of studies exploring the effects of dementia on QoL. Banerjee *et al.* (2006) found that in 101 people with dementia, poorer QoL was predicted by behavioural and psychological symptoms, as measured by the Neuropsychiatric Inventory (NPI), and age of the person with dementia. Several studies have found that behavioural and psychological symptoms in dementia are associated with poorer QoL (Ballard *et al.*, 2001a; Hurt *et al.*, 2008; Conde-Sala *et al.*, 2009).

Hurt *et al.* (2010) found that lack of insight, or the inability to understand their condition, in people with moderate dementia was associated with better QoL. Awareness of memory function in people with dementia has been shown to be detrimental to QoL (Trigg *et al.*, 2011). Furthermore, the authors suggested that awareness of memory function could mask functional ADL.

1.5.1 Cognition and quality of life in Parkinson's disease

Few studies have explored the relationship between cognition and QoL in PD. Although there are many studies that use QoL as an outcome measure that also include cognition as a variable, to a greater or lesser degree, few studies have investigated the link between the two. For example, in a study of non-motor symptoms and QoL in nursing home residents with PDD, where 77% participants had a diagnosis of PDD and measures of cognition were part of the assessment, cognition was not considered a possible factor of QoL (Weerkamp *et al.*, 2013).

Schrag *et al.* (2000) found that MMSE score was an independent predictor of QoL, in addition to depression, disease severity and postural instability. Barone *et al.* (2009) reported that attention and memory problems were associated with reduced QoL. A cross sectional study of 124 PD patients without PDD used a battery of neuropsychological tests across cognitive domains to determine the impact of cognition on QoL (Klepac *et al.*, 2008). Better cognitive performance was independently associated with better QoL, particularly in PD participants without dysfunction in visuospatial, executive function and attention. Rahman *et al.* (2008) noted that cognitive impairment was a predictor of poorer QoL, but only used self-reported measures (Peto *et al.*, 1995) as an indicator of impairment rather than neuropsychological tests. Conversely, Herman *et al.* (2015) did not find an association between cognition, using selected neuropsychological tests, and QoL scores. However participants were excluded if they had a diagnosis of dementia or low MMSE score (≤24) and so this may not have been a representative sample of participants with cognitive impairment.

In a longitudinal study with a two year follow up period, it was found that cognitive dysfunction at baseline was a predictor of reduced QoL; patients who exhibited cognitive decline had poorer QoL (Visser *et al.*, 2009). However, only the Scales for

Outcomes of Parkinson's disease- Cognition (SCOPA-COG) was used, which may not be suitable for longitudinal changes (Kulisevsky and Pagonabarraga, 2009).

Furthermore, impairment in specific cognitive domains can have a direct and detrimental impact on QoL, although difference in QoL between cognitive subtypes has not been investigated previously. In a cross-sectional study of 65 people with PD, participants completed measures for QoL and executive function (Kudlicka *et al.*, 2014). The results suggested that behavioural related executive dysfunction could be detrimental to QoL in people with PD; however, neuropsychological measures of executive dysfunction was not significantly associated. Nonetheless, executive dysfunction can impair instrumental ADL through causing difficulties with social and occupational functioning (Cahn *et al.*, 1998; Kehagia *et al.*, 2010). Subjective memory complaints have been reported to impact negatively on PD QoL (Duncan *et al.*, 2014; Valkovic *et al.*, 2014). A study by Trigg *et al.* (2011) suggested that awareness of memory impairments PDD has been shown to negatively impact on QoL. One study found that prospective memory was a significant predictor of difficulties with instrumental ADLs (Pirogovsky *et al.*, 2012).

Impaired attention is common in PD and PDD, with people with PDD exhibiting fluctuating attention similar to DLB (Ballard *et al.*, 2002). This could be potentially detrimental to QoL in PD. A cross-sectional study of 124 non-demented people with PD completed a battery of neuropsychological tests and the PDQ-39 as measure of QoL (Klepac *et al.*, 2008). They found that poorer QoL scores were associated with poorer attention/memory scores, in addition to poorer visuospatial and executive function scores. A larger cross-sectional study of 1072 people with PD found that attention/memory problems were also associated with poorer QoL scores using the PDQ-39 (Barone *et al.*, 2009). However, attention/memory deficits were classified as 'present' or 'absent' through semi-structured interviews, although the MMSE and Frontal Assessment Battery (FAB) were used their relationship with QoL was not assessed. Furthermore, neither of these studies looked at attention in isolation. Attentional deficits in PDD have been shown to significantly impact on both basic and instrumental ADL, including physical functioning and social interactions (Bronnick *et al.*, 2006). One study of DLB participants found fluctuations in attention were associated with significantly impaired ADLs (Ballard *et al.*, 2001b). Thus, as DLB and

PDD have many similarities, and may even be part of the same spectrum of disease, there may be a similar impact of attention on QoL in PD.

1.5.2 PD-MCI and quality of life

A recent study used the Level II PD-MCI criteria (Litvan *et al.*, 2012) to assess QoL in participants with PD-MCI. Significant difference in QoL were found between PD-MCI and normal cognition (PD-NC) participants for PDQ-39 sub-scores of stigma, communication and social support (Reginold *et al.*, 2013), although no differences were found in the single index scores. However, they used eight cognitive domains instead of the five suggested by Litvan *et al.* (2012), which included significantly more tests of executive function. Other factors, such as neuropsychiatric symptoms, were not considered. Participants were not newly diagnosed and cognitive decline was estimated using the Wechsler Test of Adult Reading (WTAR). However, this may over estimate premorbid intelligence (Mathias *et al.*, 2007) and therefore the severity of cognitive decline.

Leroi *et al.* (2012b) also did not find significant differences in QoL between PD subjects with normal cognition and PD-MCI using MDS Level I criteria, but did note that subjects with PDD reported worse QoL. However, the use of a limited schedule of neuropsychological tests and use of the PDQ-8 rather than the PDQ-39 may have been insensitive to subtle between group differences.

A possible explanation for these negative findings derives from an alternative theory: cognitive impairment, particularly MCI, may not have much of an added effect on QoL. It has been suggested that as the number of health deficits accumulate in an individual, a maximum is reached where additional factors have no additional effect (Mitnitski *et al.*, 2006). In the context of more severe motor and non-motor symptoms, the addition of cognitive impairment may only have a small or even negligible effect on QoL. However, this theory has been proposed in the context of frailty, not QoL (Rockwood and Mitnitski, 2007), although frailty is common in PD (Ahmed *et al.*, 2008; Lauretani *et al.*, 2012) and there is an association between frailty and QoL (Bilotta *et al.*, 2010; Roland *et al.*, 2012). However, this has yet to be explored in the context of cognitive impairment in PD and QoL.

1.6 Wellbeing and Quality of Life of Caregivers

Caregivers are affected by the burden of caring for people with PD (Playfer, 1999; Rahman *et al.*, 2008). Caregivers who facilitate more complex health needs of the recipient are more likely to experience difficulties and poorer QoL (Lavela and Ather, 2010). Reduced social activities, financial strain, perceived strain, emotional health and physical health associated with PD were related to QoL in the carers (Aarsland *et al.*, 1999; Schrag *et al.*, 2006; Leiknes *et al.*, 2010). Most caregivers are informal carers, a spouse, partner or family member, and provide physical and emotional support, which alleviates costs of health services (Schrag *et al.*, 2006; Leroi *et al.*, 2012b). However, only recently has the effect of NMS on caregivers of PD, including cognitive decline, been studied. There has been a paucity of research into the effects of PD, PD-MCI and PDD on carers of people with PD.

1.6.1 Caregivers in dementia literature

The effect on caregivers is more established in other chronic illnesses and forms of dementia. Table 1-7 compares the diagnostic and clinical features of PDD against two other forms of dementia: Alzheimer's Disease (AD) (American Psychiatric Association, 2000) and DLB (McKeith *et al.*, 1996). AD is the most common form of dementia and research into the wider issues associated with dementia, including quality of life and caregiver burden, is much more established than in PDD (Morrissey *et al.*, 1990; Clyburn *et al.*, 2000; Sanders *et al.*, 2008; Vellone *et al.*, 2008; Banerjee *et al.*, 2009; Conde-Sala *et al.*, 2009; Conde-Sala *et al.*, 2010; Hurt *et al.*, 2010; Mohamed *et al.*, 2010; Duggleby *et al.*, 2011; Karttunen *et al.*, 2011; Naglie *et al.*, 2011; Bosboom *et al.*, 2012; Werner *et al.*, 2012; Camic *et al.*, 2013; Miller *et al.*, 2013). Thommessen *et al.* (2002) suggested that carers of patients with stroke, dementia and PD experience similar levels of burden. However, it may be that the carers of PD patients with MCI or dementia, in addition to physical symptoms, experience an increased burden.

Table 1-7 Comparison of the diagnostic features of Alzheimer's disease, Parkinson's disease with dementia and dementia with Lewy bodies

Features	Alzheimer's Disease (AD)[a]	PD with dementia (PDD)[b]	Dementia with Lewy Bodies (DLB)[c]
Motor symptoms	No motor symptoms	UK Parkinson's Disease Society Brain Bank diagnosis of PD Dementia with slow progression within the context of established PD	Dementia symptoms precede the development of motor symptoms, or coincide within one year of the development of motor symptoms
Core features	Memory impairment with the addition of impairments in at least one other cognitive domain Functional impairment to daily activities	Impairment in more than one cognitive domain Decline from a pre-morbid level Functional impairment to daily activities	Fluctuating cognition with marked changes in attention and alertness Recurrent visual hallucinations that are typically well formed and detailed Functional impairment to daily activities
Other clinical Features	Exclusion if other condition interferes with cognition E.g. depression, delirium, hypothyroid, substance induced	Apathy Changes in mood Hallucinations Excessive daytime sleepiness	Falls Excessive daytime sleepiness REM sleep behaviour disorder (RBD)

a American Psychiatric Association (2000); b Emre, Aarsland, Brown, et al (2007); c McKeith, Galasko, Kosaka, et al (1996).

Caring for another person, whether they have a chronic illness or a degenerative disease like dementia, can be a burden and put strain on an individual or family involved with that care (Chappell and Reid, 2002). Social roles may change, the loss of the ability to work or provide a sustainable income can create financial pressures, and changes in relationships can also be a cause of stress (Glozman, 2004). Spouses have been reportedly the most likely to take on caregiver responsibilities (Glozman, 2004; Schölzel-Dorenbos *et al.*, 2009), with some studies suggesting that female carers, particularly wives, report increased perceived burden, anxiety and depression compared to male carers (Lavela and Ather, 2010). Thus, there is a gender aspect to informal care. This may be also be the case in PD, particularly as studies generally report a higher prevalence in males (Foltynie *et al.*, 2004; Marras *et al.*, 2004; Wooten *et al.*, 2004; Heller *et al.*, 2014).

Qualitative aspects of the carer experience associated with dementia have been thoroughly evaluated (Wuest *et al.*, 1994; Parsons, 1997; Murray *et al.*, 1999; Bruce and Paterson, 2000; Hansebo and Kihlgren, 2002; Paton *et al.*, 2004; Derksen *et al.*, 2006; Gruffydd and Randle, 2006; Todres and Galvin, 2006; Todres and Galvin, 2008;

Robinson *et al.*, 2011; Bunn *et al.*, 2012). Spousal carers of people with dementia or MCI experience an increased burden; they report increased stress, anxiety and depression, with self-care becoming neglected (Davies *et al.*, 2010). Carers of people with dementia stated feeling that their relationship had changed from a marital relationship to that of a parent and child. Moreover, the relationships of spouses and partners of people with dementia have been negatively affected (Vikström *et al.*, 2008; Clare *et al.*, 2012). Other studies have interviewed people with AD and their carers separately. Burden was a common theme, where people with AD were worried about being a burden and the carers felt an increased burden and responsibility (Frank *et al.*, 2006).

Patients with DLB report a significantly worse QoL than patients with AD (Boström *et al.*, 2007). However, few studies have explored carer burden in DLB. Although Boström *et al.* (2007) used caregivers as a proxy measure for patient QoL, caregiver QoL was not itself measured. A web-based survey of 962 caregivers of people with DLB reported that cognitive and motor problems were associated with increased carer burden (Galvin *et al.*, 2010). Sleep disruption and mood problems were most strongly associated with carer burden. Activities of daily living (ADL) were also impaired and caregivers became responsible for these, such as managing medication, managing personal affairs, help with personal hygiene and housekeeping. Carers most often reported fear of the future and the uncertainty, along with the stress of caring, as stressors. Leggett *et al.* (2011) also used an on-line survey to study carer burden. Three dimensions of burden were identified: role strain, personal strain and worry about performance. Age, gender, ADL, behavioural and emotional problems were also predictors of carer burden in this study. However, both of these studies used online surveys which are subject to bias. The participants were more likely to be younger, better-educated and seeking information about DLB and support, as they were recruited from a DLB Association website. There was no confirmation of DLB diagnosis or objective measures, only self-report.

A small study by Ricci *et al.* (2009) compared the neuropsychological symptoms, functional ability and carer distress of DLB and AD participants. DLB participants outperformed AD participants on memory assessments, but were poorer on attention and executive function assessments, in keeping with clinical features of both diseases

(McKeith *et al.*, 1996; American Psychiatric Association, 2000). However, DLB participants scored higher on the Neuropsychiatric Inventory (NPI-D) (Cummings *et al.*, 1994) than AD participants. Carer distress was also higher for participants with DLB, with delusions, hallucinations, anxiety and apathy being the symptoms that caused the most distress. This difference between DLB and AD was also found in another study by Walker *et al.* (2012), where there were no cognitive differences between the two groups at either baseline or follow up. Therefore, as there are similarities between DLB and PDD, which may be part of the same disease spectrum, it is reasonable to expect that cognitive impairment in PD would have a similar impact on carer QoL and wellbeing, and they would experience greater distress and burden compared to AD carers.

1.6.2 Parkinson's caregivers and quality of life

As PD is a progressive disease, caring for people with PD can be an increasing burden. Factors reported to affect PD caregiver QoL include: age of carer, disease progression, and physical dependency of the recipient (Aarsland *et al.*, 1999; Goldsworthy and Knowles, 2008; Carter *et al.*, 2010; Naismith *et al.*, 2011). Similarly to carers of people with dementia, carers of PD patients also tend to be female, and generally spouses, as shown in Table 1-8, and reported worse QoL than the general population (Martinez-Martin *et al.*, 2008; Lyons *et al.*, 2009; Greenwell *et al.*, 2015). This may be because many carers are spouses, who are themselves elderly and may have their own health problems (Berry and Murphy, 1995). Neuropsychiatric symptoms are also associated with carer burden, particularly depression (Aarsland *et al.*, 1999; Caap-Ahlgren and Dehlin, 2002; D'Amelio *et al.*, 2009).

Sleep disturbances such as: sleep fragmentation; cramps, pain, restless legs; impaired motor function and nightmares in patients with PD, can affect the partner's sleep (Happe *et al.*, 2002; Whitehead *et al.*, 2008). Sleep disturbance and RBD are associated with cognitive decline and dementia (Boeve *et al.*, 2004). Those with RBD often experience dreams that are vivid, and sometimes frightening, which they may "act out". Partners who share the same bed have reported injuries including: lacerations, bruises and fractures (Boeve *et al.*, 2004). Some spouses resort to sleeping in separate beds, which also affected marital relations (Habermann, 2000). Therefore, those with MCI are more likely to have RBD, which could lead to reduced QoL for their carer.

Table 1-8: Table of studies of carers of people with Parkinson's disease

Study	Design	Participants	Outcome/Findings
Aarsland *et al.* (1999)	Cross sectional, self-reported questionnaires	94 carers of people with PD; controls: carers of diabetes and healthy other adults	Higher depression scores and psychological distress in PD spousal carers Stress associated with motor, functional and mental disturbances, but mental disturbances was the most significant factor
Schrag *et al.* (2006)	Cross-sectional study using postal surveys	123 carers of people with PD, 66% female	40% indicated worse health due to caregiving Carer burden increased with presence of depression, hallucinations, confusion and falls Carer burden associated with PD QoL and carer perception of the marital relationship
Goldsworthy and Knowles (2008)	Cross-sectional study using online surveys	136 carers of people with PD	Behavioural problems of person with PD adversely effected burden Frequency of break and perceived social support ameliorate carer burden Carer-care recipient relationship may be a protective factor The authors associated carer burden as a factor of QoL
Martinez-Martin *et al.* (2008)	Cross-sectional self-assessments	289 PDs and their carers	Mood disorders were higher for carers than in the general population Mood status (HADS score) was a significant predictor of carer burden and perceived health status PD related variables influenced carer mood and carer burden
D'Amelio *et al.* (2009)	Cross-sectional study	40 PDs and their carers	Hoehn and Yahr stage as a measure of disease severity and neuropsychiatric symptoms were associated with carer distress
Lyons *et al.* (2009)	Longitudinal study, time points at baseline, 2 years and 10 years	255 spousal PD carers at baseline, 157 at 10 years	Female spousal gender predicted role strain at 10 years and faster increase in role strain over 10 years Higher mutuality, optimisms and low pessimism were protective against carer strain
Leiknes *et al.* (2010)	Cross-sectional study, primary measure NPI-D	198 PD carers, 168 healthy controls	50% PD carer reported distress, significantly higher than in health controls Most distressing neuropsychiatric symptom was apathy followed by depression, anxiety and irritability.
Roland *et al.* (2010)	Repertory grid method, using interviews and factor analysis	5 PD carers	Carers found greater burden from mental stress (e.g. worry) compared to physical stress Safety of their spouse was a source of worry Carers reported "little deaths" each time the person with PD showed disease progression, e.g. loss of independence or social network diminishing
Morley *et al.* (2012)	Cross-sectional study, used self-reported PDQ-39 and PDQ-Carer	238 PDs and their carers	Carer QoL was affected by carer age, gender, health status and duration on caring Higher mobility and cognitive impairment sub-scores of the PDQ-39 were associated with poorer carer QoL

Study	Design	Participants	Outcome/Findings
Abendroth *et al.* (2012)	Qualitative, semi-structured interviews using Grounded Theory	20 PD carers, 17 female and 3 male	Carer strain was a risk factor for instutionalisation Carer strain resulted from an increased caregiving load and increased severity of PD over time Factors of strain included diminished formal and informal support, poor sense of self-preservation, pre-PD life circumstances and the diminished ability to manage life events Planning, seeking knowledge, adjusting to the environment, social support and self-care reduced carer strain
Carod-Artal *et al.* (2013)	Cross-sectional study	50 PDs and their carers; 88% female, 78% spouses	Carer burden associated with PD sleep disorders, behavioural and psychotic symptoms, mood disturbances of carer and time spent caregiving Mood status as measured by the HADS was a significant predictor of QoL of caregiving
Oguh *et al.* (2013)	Cross sectional study	2476 PD carers	PD QoL measured using the PDQ-39 single index was the most significant predictor of carer strain PD severity as measured by Hoehn and Yahr stage, the use of anti-depressant medication, anti-psychotic medication, male gender and decreased verbal fluency scores in the person with PD significantly predicted carer strain
Tew *et al.* (2013)	Cross sectional study	274 PDs and their carers	Depression and anxiety were the strongest predictors of QoL in carers The personality trait conscientiousness was associated with better psychological QoL in carer; neuroticism was associated with poorer psychological QoL Openness positively predicted benefits in environmental QoL (e.g. finances, home environment, health and social care)
Drutyte *et al.* (2014)	Cross sectional study of Parkinson's UK members, self-assessments	1881 PD carers	Increased number of stress related symptoms in carers was associated with the number of caring tasks carried out by the caregiver, higher numbers of comorbidities in the carer and worse financial status Carers of male gender were predicted to have fewer stress related symptoms
Viwattanakulvanid *et al.* (2014)	Cross sectional study	89 PD carers, predominantly female, 49% spousal	Carer burden significantly increased with disability and dependence of person with PD Carer burden increased with occurrence of anxiety, nocturnal akinesia and sleepiness in the morning in the person with PD Spousal carers reported significantly higher burden than offspring carers
Martinez-Martin *et al.* (2015)	Cross-sectional study	584 PDs and their carers	Strongest predictors of carer burden were mood/apathy, psychosis, PD duration and PD-related disability PDD carer burden was predicted by mood/apathy and psychosis
Santos-Garcia and de la Fuente-Fernandez (2015)	Cross sectional study	121 PD carers; 72% female	High correlation between carer strain and burden Schwab and England activities of daily living score for person with PD was the strongest predictor of carer strain and burden, followed by depression scores in person with PD

PD = Parkinson's disease, PDD = Parkinson's disease dementia, QoL = Quality of life, PDQ-39 = Parkinson's Disease Questionnaire

Through the development of the Parkinson's Disease Questionnaire for Carers (PDQ-Carer) (Jenkinson *et al.*, 2012), in-depth qualitative interviews were conducted with 21 carers. The main themes that affected carers of people with PD were: personal and social activities; anxiety and depression and self-care and strain, although there is no report yet available on the analysis of the qualitative interviews. The few studies that have used qualitative interviews to investigate carer experiences of caring for a person with PD also found similar themes (Hounsgaard *et al.*, 2011; McLaughlin *et al.*, 2011). Caregivers reported prioritising the care of the person with PD over their own care (Hounsgaard *et al.*, 2011). The increased responsibility and adapting to living with a chronically ill person, such taking over finances and providing emotional support to the person with PD, also reportedly made the carers feel more stressed (Hounsgaard *et al.*, 2011; McLaughlin *et al.*, 2011).

As shown in Table 1-8, studies have generally explored the negative impact of caring on QoL but a few studies look at the positive impact. Some studies have investigated factors that may lessen carer burden. Goldsworthy and Knowles (2008) found that perceived social support, frequency of breaks and a positive relationship with the carer recipient decreased burden and improved QoL. In a qualitative study by Abendroth *et al.* (2012), nursing home placement was delayed when carers felt less under strain. Decreased carer strain occurred when carers felt supported, had a strong sense of self-preservation and that they were able to cope with significant life events, such as serious illness or financial trouble. Similarly, Lyons *et al.* (2009) found high mutuality in the relationship with the care recipient to be protective of carer strain, as was optimism and low pessimism.

The gains of caregiving has been observed in some dementia studies (Netto *et al.*, 2009). Carers reported improved understanding and patience, better communication with family members and closer relationships. One study in carers and people with PD found that benefit finding, the experience of personal growth and other positive changes in the face of stressors were related to improved marital quality (Mavandadi *et al.*, 2014). A qualitative study by Chiong-Rivero *et al.* (2011) found that both carers and people with PD found a new appreciation for life and that meaningful relationships with loved ones were strengthened. However, finding benefits or meaning has not

been explored thoroughly in PD literature, but may be an important aspect of the carer experience of PDD and PD-MCI.

1.6.3 Cognitive impairment in Parkinson's, quality of life and caregivers

There is little research into this area and measures of cognitive impairment have been varied. D'Amelio *et al.* (2009) found that lower MMSE scores were associated with higher psychosocial burden of spousal PD caregivers. Poorer cognition in PD patients was associated with poorer physical health of their carer and increased stress (Aarsland *et al.*, 1999). A more recent study found that carer QoL was significantly affected by cognitive impairment, in addition to age, gender, health status, duration of caregiving and mobility of the person with PD (Morley *et al.*, 2012). Carer burden was predicted by disease severity and executive function-related behavioural problems in a regression model by Kudlicka *et al.* (2014).

Oh *et al.* (2015) found neuropsychiatric symptoms were significantly associated with carer burden in people with PDD. Delusions, hallucinations, agitation and aggression, anxiety, irritability and aberrant motor behaviour were associated with caregiver stress. Neuropsychiatric symptoms were found to be associated with, and predictors of, carer burden in PD carers, with PDD carers finding neuropsychiatric symptoms in the care recipient more prevalent and reported greater burden (Martinez-Martin *et al.*, 2015). Neuropsychiatric problems in people with PDD were also reported to be the greatest contributors of carer burden by Shin *et al.* (2012b). Furthermore, the authors suggested that carer burden was higher in carers of people with PDD compared to Alzheimer's disease. Another study found that cognitive decline, depression and hallucinations predicted increased carer burden, but not carer QoL (Martinez-Martin *et al.*, 2008). Other studies did not find a significant relationship (Goldsworthy and Knowles, 2008). However, they used brief, global measures such as the MMSE which are insensitive to several cognitive changes, particularly in PD (for example, executive dysfunction) (Burdick *et al.*, 2014).

Carer grief, where carers felt they had "lost" their spouse or family member, was higher in participants who cared for people with PD with severe cognitive impairment, depression, anxiety and hallucinations (Carter *et al.*, 2012). Although there is a paucity of research into pre-death grief in PDD, this has been explored in dementia studies

(Sweeting and Gilhooly, 1997; Meuser and Marwit, 2001; Sanders *et al.*, 2008) and may be significant to the QoL and wellbeing in carers of PD-MCI and PDD.

Leroi *et al.* (2012b) used the MDS PD-MCI criteria (Litvan *et al.*, 2012) to evaluate QoL and carer burden in PD. Using Level I criteria of "possible" PD-MCI, PD patients were grouped as either cognitively normal (PD-CN), PD-MCI or PDD. QoL and disability were assessed among PD patients, and their caregivers were assessed for burden and distress. Leroi *et al.* (2012b) found that PDD patients reported reduced QoL and increased carer burden compared to PD-CN and PD-MCI. There were no significant differences between the three groups for neuropsychiatric symptoms or caregiver distress. However, there was a weak correlation between carer burden and PD severity. Overall, disability was greater as cognition declined across the groups. However, the study was cross-sectional, so no causal links could be made. Level I PD-MCI criteria were used, rather than the more comprehensive Level II criteria. Any possible relationship between PD-MCI subtypes, QoL and carer burden were not examined. Finally, PD specific measures for carer burden were not used and so may not be sensitive enough to detect changes in PD. Nonetheless, this is the only study so far that has attempted to explore the wider issues of PD-MCI and cognitive decline and the impact that this has on not only the PD patient, but those who care for them.

1.7 Summary

Longitudinal studies in incident cohorts are therefore needed, with PD participants completing a comprehensive battery of neuropsychological tests in addition to motor and non-motor symptoms. This would enable disease progression and changes in cognition to be observed and measured with minimum bias. Furthermore, these studies should include the QoL and wellbeing measures of the individual with PD and cognitive impairment, in addition to their family and social circle, as there are even fewer studies that investigate the wider effects on the person with PD. Future studies should assess the impact PD and cognition have on carers and family members, as well as the individual with PD. Doing so would help to identify factors that might be targeted by suitable interventions to improve QoL, for either the individual, their carer or both, which is important in the management of a complex disease like PD.

Chapter 2 Objectives and Hypotheses

2.1 Objectives

There is currently a paucity of longitudinal studies tracking disease progression and cognitive decline in Parkinson's disease (PD) from diagnosis. Furthermore, many studies fail to account for the wider effects of PD and cognition, including the impact on quality of life (QoL) and wellbeing of the individual living with PD and on their family and carers.

This study aimed to use a mixed methods approach to explore the impact of cognitive impairment on QoL in PD over a three-year period. To achieve this, both quantitative and qualitative methodologies were used to investigate and evaluate the impact of disease progression and cognitive impairment on both people with PD and their carers, and also the relationship between subject and carer. The use of quantitative and qualitative methods offered complimentary perspectives, with the aim of producing a more comprehensive understanding of PD, cognitive impairment and dementia (PDD), and their impact upon QoL.

2.2 Hypotheses

My overarching hypothesis was that PD participants with more severe cognitive impairment would experience poorer QoL over and above the impact of motor and other non-motor symptoms. I hypothesised that participants with declining cognition would exhibit a decline in QoL compared to those with stable cognition; participants who developed PDD would be affected to a greater extent than those with mild cognitive impairment in PD (PD-MCI). Furthermore, I expected that carers of participants with PD-MCI or PD and PDD would experience greater levels of burden and strain than those with normal cognition, as they would have to cope with cognitive symptoms in addition to motor and non-motor symptoms. This would also impact on the QoL of carers. Furthermore, I anticipated that there would be a relationship between PD and carer QoL and wellbeing, where the degree of QoL in one would directly impact on the QoL of the other.

2.2.1 Specific hypotheses

In Chapter 4 I explored the impact that different operational cut offs for diagnosing PD-MCI had on QoL and whether QoL differed between subtypes of PD-MCI. I hypothesised that those with PD-MCI would have a poorer QoL compared to those with normal cognition and that the effect across the different PD-MCI subtypes would not be equal, with executive dysfunction and attention having a greater impact.

In Chapter 5 I explored the changes in cognition and QoL at baseline, 18 months and 36 months. I hypothesised that, first, that at each time point the presence of PD-MCI would negatively impact on QoL and that more severe cognitive impairment would be associated with poorer QoL. Second, I hypothesised that participants who exhibited cognitive decline over time between baseline and 36 months would present with declining QoL over that same time interval. Furthermore, participants without cognitive impairment at each time point would report negligible changes in QoL compared to those with cognitive impairment. I also expected that a small proportion of participants would develop PDD by 36 months, and that this group would report the poorest QoL.

In Chapter 6 I explored QoL in carers of people with PD at 36 months and whether cognitive impairment was an additional stressor. I hypothesised that, first, carers would be predominantly spousal and female. Secondly, there would a relationship between carer QoL and PD QoL, such that as the QoL of the person with PD deteriorated, the QoL of the carer would decline. Thirdly, there would be a significant relationship between carer QoL and cognitive impairment of the care recipient, where carers of people with PD and cognitive impairment would have poorer QoL and those who care for people with PDD would report the poorest QoL.

In Chapter 7 I used qualitative methods to explore the impact of cognitive impairment on people with PD and their carers using three groups: normal cognition, PD-MCI and PDD. I expected to find differences between these three groups, for both people with PD and their carers. I anticipated that those with cognitive impairment would have different experiences to those with normal cognition, due to having to contend with both the physical illness associated with PD with the added stressor of cognitive impairment.

Chapter 3 Methods

This study was approved by the NHS Local Research Ethics Committee, Newcastle and North Tyneside 1, and all participants gave written informed consent prior to study inclusion. All participants in this study had the capacity to give informed consent.

3.1 The ICICLE-PD Study

This study is part of the Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's Disease (ICICLE-PD) study from Newcastle and Cambridge, UK. ICICLE-PD is a longitudinal study that aims to understand the anatomical, biochemical and genotypic mechanisms determining the transition from PD to PD with dementia (PDD). This will establish which clinical features are risk factors for incident PDD and the biomarkers that could help predict which patients will develop PDD.

Participants with newly diagnosed PD were assessed at 18 month intervals and completed a wide range of assessments, including clinical and neuropsychological. Additional assessments were also undertaken by participants who gave consent to do so. These comprised: blood tests including genetic tests, structural and functional magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, lumbar puncture for cerebrospinal fluid analysis, short latency afferent inhibition (SAI), sleep assessment and gait assessment. Carers of participants were also asked to complete questionnaires. A sample of PD participants and their carers were asked to complete semi-structured interviews.

3.2 Mixed Methods

This study utilises a mixed methods approach, which is the use of both quantitative and qualitative methods. Qualitative methods seek to explore phenomena, generally through language and verbal responses, often using interviews or written accounts, and interpreting what they mean (Bryman, 2008; Smith, 2008). Whereas quantitative methods are concerned with reducing phenomenon into numerical data for statistical analysis, often using questionnaires or objective measures.

3.2.1 The quantitative approach

Quantitative methods use numerical data and have a deductive approach, where the researcher has a theory to test and has specific findings or hypotheses they expect to find (Bryman, 2008). It is often described as the natural science approach (Smith, 2008). It stems from the positivist approach, where empirically examining the relationship between variables is central to testing hypotheses (Creswell, 2009). The emphasis on quantitative research is being able to produce results or a theory that are generalizable and replicable (Bryman, 1988).

From the initial theory, a research design is devised to test the theory. The researcher must chose appropriate measures or variables to produce numerical data (Creswell, 2009). This could be objective data like age or gender which are easily measured (Bryman, 2008). However, some abstract concepts, also referred to as theoretical constructs, such as mood, medication adherence or quality of life (QoL) are difficult to measure (Kimberlin and Winterstein, 2008). For these theoretical constructs, an instrument has to be designed to measure this phenomenon. However, these instruments should be rigorously tested for reliability and validity before use (Creswell, 2009). These instruments provide a means of empirically testing data by converting concepts into numerical and measureable items by statistical analysis (Bryman, 2008). The statistical method for analysis depends on the data collected, this could be due to the distribution of the data, which could affect which tests you are able to perform, or the type of hypothesis being tested (Field, 2013). The results from the analysis is then interpreted by the researcher, which could either refute or support their hypothesis, resulting in new theories to be tested and further research (Bryman, 2008).

3.2.1.1 Reliability and validity

Measuring an abstract concept or theoretical construct objectively can be difficult. Instruments designed to measure a theoretical construct can be subjective or open to bias, such as recall or social desirability bias, or may not measure what the researcher wants to measure (Bryman, 2008). Therefore, it is important to assess the reliability and validity of an instrument before it is used in empirical research (Kimberlin and Winterstein, 2008; Creswell, 2009).

Reliability is the consistency of an instrument (Kimberlin and Winterstein, 2008). There are three main points to consider when assessing reliability: stability, internal consistency and inter-observer consistency (Bryman, 2008). Stability refers to whether a measure is stable over time and can be easily tested using test-retest methods (Kimberlin and Winterstein, 2008). This is the administration of a measure to the same individuals at two different time points; the scores should be highly correlated with each other. Internal consistency refers to whether the individual items of an instrument are consistent and equivalent (Bryman, 2008). Items measuring the same construct should correlate. This is typically measured using Cronbach's alpha, which is an average of the inter-correlations of each item of an instrument (Kimberlin and Winterstein, 2008). Therefore, having multiple items in a construct is more reliable than single item constructs. Inter-observer consistency refers to the scores of an instrument being equivalent when recorded by different observers or researchers (Bryman, 2008). This is measured by more than one observer independently rating or scoring the same phenomenon independently and correlating the scores (Kimberlin and Winterstein, 2008). This attempts to limit bias and subjectivity that can arise from relying on the judgement of an individual to measure theoretical constructs.

Validity refers to whether the instrument in reality measures the concept it is designed to measure (Plano Clark and Creswell, 2008). For an instrument to be valid it has to be reliable, but a reliable instrument is not necessarily a validated one (Kimberlin and Winterstein, 2008). There are several forms of validity to consider: face validity is whether the instrument reflects the content of questions it is measuring; concurrent validity is whether an instrument correlates well with a previously validated instrument; predictive validity is whether an instrument correctly predicts a certain criterion; construct validity is whether the instrument actually measures the construct being measured and no other variables; and convergent reliability, which is the degree to which two different instruments measuring the same thing are well correlated (Bryman, 2008; Plano Clark and Creswell, 2008).

Therefore, in order to make firm conclusions based on quantitative methods, the instruments used to measure the theoretical constructs must be sound (Kimberlin and Winterstein, 2008). Using a well validated and reliable instrument as a measure is preferable to a newer measure that has not been widely tested. Using measures that

have been widely used also increases claims of generalizability and reliability (Bryman, 1988).

3.2.2 The qualitative approach

Qualitative methods have a different aim to quantitative methods. Qualitative research is concerned with examining behaviour and interactions, as well as how people perceive the world (Silverman, 2011). They seek to explore phenomena by asking 'what', 'why' and 'how' about the world, people and behaviour (Green and Thorogood, 2009). It is often described as inductive, where theory is the outcome of research, unlike quantitative methods where theory guides the research (deductive) (Bryman, 2008). The epistemological position of qualitative research, the theory of knowledge, is described as interpretivist (Green and Thorogood, 2009). Unlike the positivist approach, which is rooted in the philosophy that reality is stable and the application of empirical, natural scientific methods, the interpretivist approach requires the researcher to understand and interpret phenomena through subjective meaning (Bryman, 2008; Plano Clark and Creswell, 2008). The positivist approach adopts the view that only theories and hypotheses that are observable and testable are real (Smith, 2008). Qualitative methods are also based on the ontological approach of constructivism, where there are multiple truths of our world that are based on our constructions of reality (Plano Clark and Creswell, 2008). As reality is a social construct, it is constantly changing.

There are several types of qualitative research designs including: ethnography, phenomenology, grounded theory (GT), narrative research and case studies (Smith, 2008; Green and Thorogood, 2009). This study will use thematic analysis to analyse the raw data, but will use the constant comparative method outlined in GT (described below) to aid iterative sampling and interpretation.

3.2.2.1 Grounded theory

Grounded theory is an approach for developing theory that is *"grounded in data systematically gathered and analysed"* (Strauss and Corbin, 1994). It is an iterative interview and analysis process that is grounded by the views and experiences of the participant (Creswell, 2009). It uses theoretical sampling, a form of purposeful sampling, to select participants with key characteristics relevant to the phenomenon

being studied (Green and Thorogood, 2009). Thus, the main principal of GT is to use systematic techniques to explore phenomenon qualitatively (Smith, 2008); for this reason it has been described as both positivist and interpretivist.

A key component of GT is the constant comparative method; data is iteratively collected and analysed in parallel (Bryman, 2008). Researchers continually compare phenomenon being studied; each new set of data is repeatedly compared to previous extracts and referred back to each other to see how well the coding frame fits. (Smith, 2008). New codes and categories are then added, categories are grouped together and organised to form a coherent understanding or theory of the phenomenon being studied (Green and Thorogood, 2009). The process is repeated until data saturation, the point when no new categories or themes emerge, is reached (Strauss and Corbin, 1994).

However, providing a definitive account is difficult. Notably, the developers of GT, Strauss and Glaser, differed in their opinions of the approach of GT (Strauss and Corbin, 1994). They each developed different approaches to their analysis, which has led to some controversy over definition and which approach to follow (Smith, 2008). GT has also been criticised for being unrealistic and vague. It requires the researcher to suspend their preconceived beliefs and theories, which generally arise from previous research and literature reviews, to allow theories to emerge from the data (Bryman, 2008). The term “grounded theory” has also been widely used in qualitative research without actually being followed (Green and Thorogood, 2009). Some researchers claiming to use GT actually use a rudimentary thematic analysis and do not explore the data in rich detail, but simply describe themes. GT is also time consuming and can be costly; if data collection and analysis continues until saturation point, the lack of a definitive end point can be limited by time constraints (Bryman, 2008).

3.2.2.2 Thematic analysis

The most basic thematic analysis is of the content of the data to identify reoccurring themes (Green and Thorogood, 2009). There is much debate regarding analytical methods, as finding meaningful themes is common across qualitative methods (Braun and Clarke, 2006). Thus, thematic analysis could be seen as a skill to acquire within a specific research design, such as GT or critical discourse analysis (Bryman, 2008).

However, Braun and Clarke (2006) argue thematic analysis is an analytical method in its own right. It also has the advantage of being more flexible than other forms of qualitative analysis. However, thematic analysis has also been criticised for lacking structure; for example not having clear, set guidelines as to conducting the research or subsequent analysis (Silverman, 2011).

The key phases of thematic analysis as outlined by Braun and Clarke (2006) are shown in Table 3:1. Thematic analysis begins with the researcher; interviews are transcribed and read over several times along with any interview notes to familiarise themselves with the data before coding begins. Data coding is an important part of thematic analysis (Green and Thorogood, 2009). Phrases or expressions from the transcripts are coded to identify interesting features. These are then grouped together into categories to generate early themes, organising participants' thoughts, opinions and experiences. These early themes are reviewed by comparing them to other transcripts to refine and develop recurrent themes (Braun and Clarke, 2006). From this, the themes are defined and a thematic map or coding frame is produced which includes sub-themes. The thematic map or coding frame with final themes is used in the final analysis and report of results. The codes help to identify key data extracts to use as evidence of themes and sub-themes.

Table 3:1 Phases of thematic analysis

Phase	Description
Getting familiar with the data	Transcribing data, researcher reads several times to familiarise themselves with the data
Generating codes	Interesting features of the data are systematically identified and given a code Data is divided into similar groups and forms preliminary categories of information
Searching for themes	Categories are grouped together, early themes emerge
Reviewing themes	Early themes are organised and integrated Themes are checked and refined, thematic map coding frame is developed
Defining themes	Continual analysis to refine specifics of each theme, including definitions and identifying sub-themes
Producing the report	Final analysis and write up of themes using examples from the data

Braun and Clarke, (2006)

3.2.3 The mixed methods approach

The use of one research method, i.e. quantitative or qualitative, might not adequately explain a phenomenon or relationship. Applying both methodologies allows meaning

and experiences to be explored, as well as gauging the degree of change and predictive values of the variables (Bryman, 2008; Silverman, 2011). Looking at a phenomenon from only one point, i.e. only a quantitative perspective or only a qualitative perspective, can constrain our understanding (Hesse-Biber and Leavy, 2008). For example, using only quantitative methods to explore a phenomenon could build a predictive model that could be tested, but would mean the rich detail and individual experiences were lost (Smith, 2008; Green and Thorogood, 2009). Conversely, only using qualitative methods could give in depth detail about meaning and experiences, but may not be testable or generalised to others.

There are three commonly used approaches to mixed methods research: sequential mixed methods, where the researcher aims to expand or expound the outcomes of one method with the other method; concurrent mixed methods, where the researcher collects both quantitative and qualitative data simultaneously to provide a comprehensive analysis of a phenomenon; and transformative mixed methods, where the researcher has a theoretical perspective in the design of the study, including methods of collecting data and outcomes (Creswell, 2009). This study used a concurrent approach, where quantitative and qualitative data were collected at the same time to address the same overarching aims and hypotheses.

This design has been described as complementary, where the use of the quantitative and qualitative data offsets the weakness of the other method, as well as utilising the complementary strengths of both (Greene, 2007; Bryman, 2008). Table 3:2 shows some of the main strengths and limitations, as well as some criticisms, of both research methods. The complementary approach seeks to gain a deeper, richer and more complete understanding of a phenomenon by utilising the different methods to investigate either overlapping phenomena or different aspects of a single phenomenon (Plano Clark and Creswell, 2008). Interpretation of the results is helped by collecting the data concurrently. Complementary designs can also elaborate or expound on the results or interpretation of results of the other method (Greene, 2007; Plano Clark and Creswell, 2008).

Table 3:2: Features of quantitative and qualitative research

	Quantitative methods	Qualitative methods
Strengths	• Useful for testing theories • More objective • Can distinguish subtle differences between variables and groups of people • Measurement give a consistent benchmark to gauge differences • Able to estimate the degree of relationships, predictors or causes • Able to generalise results to populations of people	• Answers questions that cannot be answered by quantitative methods e.g. meaning and experience • Able to collect data for small sample sizes, useful for small populations • Explores understanding and different perspectives • Is flexible • Can provide a rich and detailed understanding of phenomena
Limitations and criticisms	• Failure to distinguish people and social interactions, ignoring the capacity for self-reflection • Measuring collective experiences may be artificial or conducted in an artificial setting • Statistics can be misleading or manipulated • Need large samples for statistical tests to have sufficient power	• Lacks structure, many analysis models exist • Unscientific, is not deductive and so cannot be used to test theories • Difficult to replicate • Subjective and not generalizable, can only produce the views of a small number of cases • Lacks transparency, both in what the researcher actually did and what methods of analysis was used

(Bryman, 2008; Green and Thorogood, 2009; Silverman, 2011)

Thus, in this study, a mixed methods approach enabled a more in-depth exploration of relationships between PD, cognitive impairment, QoL and their effect on carers, as well as being able to measure change in cognition, QoL and to build predictive models to test theories or concepts that emerged from the qualitative data. The use of both research methods was intended to give a more complete overall understanding of the phenomenon than using one method in isolation.

3.3 Participants

As shown in Figure 3:1, 682 people who had newly diagnosed PD were invited to take part in the ICICLE-PD study; 226 consented to take part, 312 declined to take part and the remaining was excluded on the basis of predefined criteria, outlined below. Participants were recruited through outpatient clinics in Newcastle upon Tyne, Gateshead, and Cambridgeshire. All patients had newly diagnosed idiopathic PD, confirmed by a movement disorder specialist and fulfilled Queen's Square Brain Bank criteria (Hughes *et al.*, 1992).

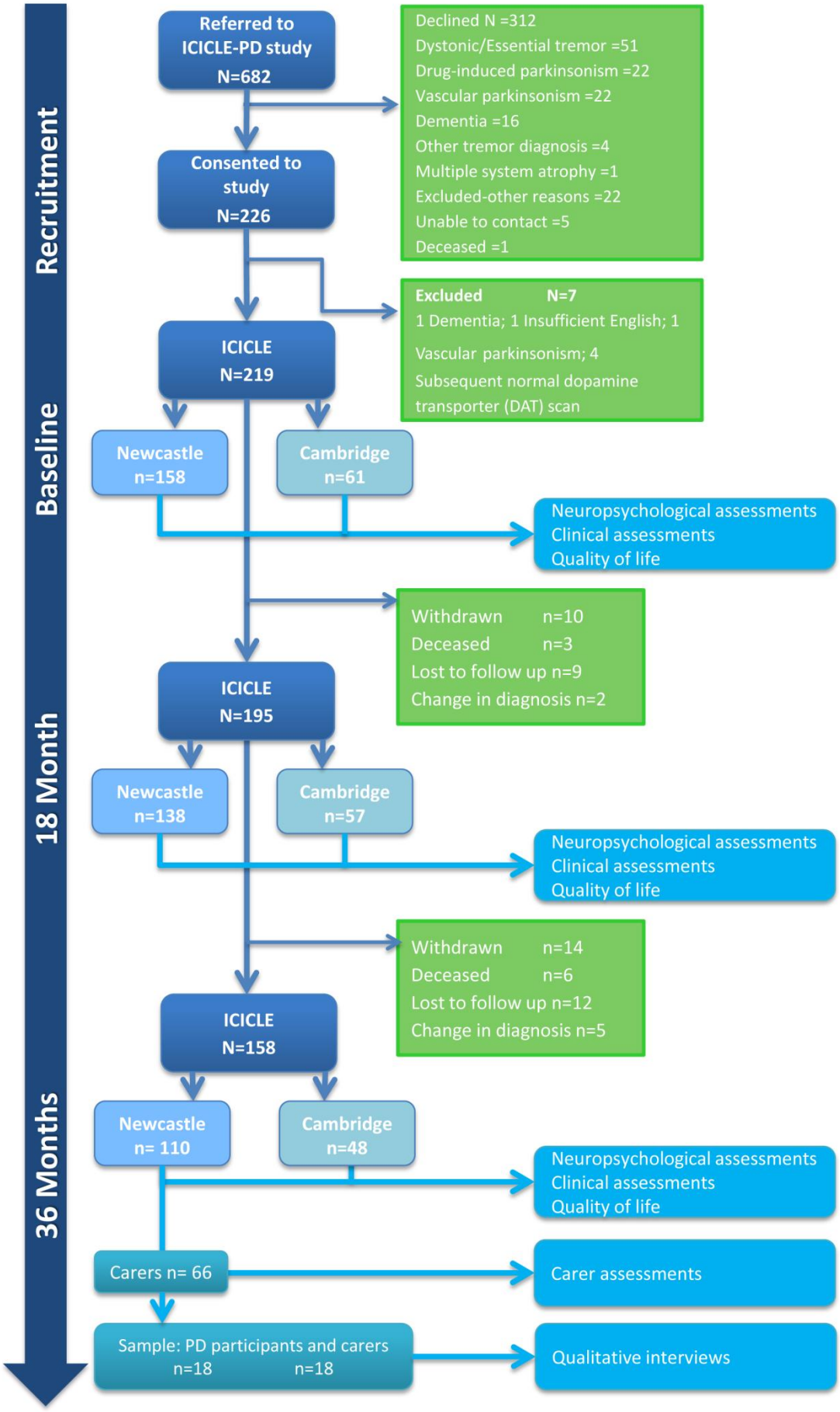
Participants were excluded if they had significant cognitive impairment at presentation (Mini Mental State Examination (MMSE) <24), met the DSM-IV criteria for dementia

(American Psychiatric Association, 2000) criteria or the Movement Disorder Society (MDS) criteria for dementia (Emre *et al.*, 2007). Other exclusion criteria included: a diagnosis of PD before onset of the study, insufficient knowledge and understanding of the English language to perform assessments, insufficient capacity to provide informed consent, parkinsonian disorder other than idiopathic PD, which included dementia with Lewy bodies (DLB), drug induced parkinsonism, vascular parkinsonism, supranuclear palsy, multiple system atrophy, or corticobasal degeneration.

Age-sex matched healthy controls (n=99) were recruited through word of mouth and local advertising to provide normative data. Controls were not spouses, relatives or carers of PD participants to limit potential responder bias. The inclusion of a control group provided comparative age-matched data. Controls were over the age of 45; English was their first language or had fluent command of English; able to walk independently without the use of an aid; and had no history of dementia, significant cognitive impairment, movement disorder or current significant mood disorder. Controls were excluded if they scored <24 on MMSE, met DSM-IV criteria for dementia (American Psychiatric Association, 2000) or had insufficient capacity to provide informed consent.

Carers of participants with PD were also invited to take part. In this study, a carer was defined as a spouse/partner, adult family member or friend who was the primary caregiver of the participant with PD and spent a significant amount of time with them each week (a minimum of 4 hours). This is consistent with previously applied definitions (Martinez-Martin *et al.*, 2008; Leroi *et al.*, 2012b; Peters *et al.*, 2013).

Figure 3:1: Assessment Schedule



3.4 Scales and Assessments

Selected assessments from the main ICICLE-PD study were used: neuropsychological, clinical, QoL, carer questionnaires and qualitative interviews, as shown in Figure 3:1.

3.4.1 Neuropsychological assessment

Global cognitive function was assessed using the MMSE (Folstein *et al.*, 1975) and Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005). Both tests have been widely used in research and are used in clinical practice; they are quick and simple to administer. Both have a maximum score of 30, and scoring less than 26 is indicative of cognitive impairment (Zadikoff *et al.*, 2008). However, the MMSE may not be an appropriate test for people with PD and may be insensitive to mild cognitive impairment (MCI) (Hoops *et al.*, 2009; Nazem *et al.*, 2009). The MMSE primarily assesses memory and language, whereas the MoCA tests a wider range of domains, including executive function, and has more demanding components for memory, attention and visuospatial function (Zadikoff *et al.*, 2008). Nazem *et al.* (2009) found that 52% people with PD who were classified as having normal cognition using MMSE score ($\geq$26) had cognitive impairment according to MoCA scores (<26). Therefore, the MoCA may be more sensitive to cognitive impairment in PD and a more appropriate test for screening MCI in PD (PD-MCI) (Hoops *et al.*, 2009; Litvan *et al.*, 2012).

Lessig *et al.* (2012) evaluated longitudinal change in MMSE and MoCA scores in PD over three years. They found that while the MoCA was more sensitive to cognitive impairment, scores did not significantly change over time, whereas MMSE scores did. This may be due to the increased number of components assessing attention and executive function in the MoCA, which are influenced by dopaminergic medication. Thus the MMSE may be a more appropriate test for tracking cognitive change over time (Lessig *et al.*, 2012). Consequently, we opted to include both the MMSE and the MoCA as global measures of cognition.

Five cognitive domains were assessed using a schedule of neuropsychological tests: attention, executive function, visuospatial function, memory and language (Table 3:3). Selective tests from the computerised Cognitive Drug Research (CDR) battery (Nicholl *et al.*, 1995) and Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins *et al.*, 1994) were used as described in Table 3:4. As CANTAB relies on visual,

motor and comprehensive abilities, the Motor Screening Test (MOT) was used to screen for any impairment that might compromise the validity of the tests.

Table 3:3 Neuropsychological tests

Domain	Test
Attention	CDR:
	Power of Attention (PoA)
	Digit Vigilance (Accuracy)
Executive function	CANTAB:
	One Touch Tower of London (OTS)
	Phonemic Fluency (FAS)
	Semantic Fluency (Animals)
Visuospatial function	Pentagons
Memory	CANTAB:
	Pattern Recognition Memory (PRM)
	Spatial Recognition Memory (SRM)
	Paired Associate Learning (PAL)
Language	MoCA:
	Naming
	Language

CDR = *Cognitive Drug Research Battery, CANTAB = Cambridge Neuropsychological Test Automated Battery, MoCA = Montreal Cognitive Assessment*

Power of Attention (PoA) is a composite measure from the CDR and was calculated using the mean time in milliseconds (msec) for Simple Reaction Time (SRT), Choice Reaction Time (CRT) and Digit Vigilance (Table 3:4). A higher score indicates greater impairment. Accuracy of Digit Vigilance was also a measure of attention, which is the percentage of accurate responses by participants. A lower score indicates greater impairment.

Three tests from the CANTAB were used to assess memory. Pattern Recognition Memory (PRM) and Spatial Recognition Memory (SRM) were measured by the number of correct answers given by participants. PRM and SRM have maximum possible scores of 24 and 20, respectively, with lower scores indicating increased impairment. Paired Associate Learning (PAL) was measured by the mean number of trials until the participant correctly identifies which patterns belong in which box out of a possible eight stages. The PAL score of mean trials to success was calculated using the total

number of trials completed by the participant divided by the total number of stages completed (0-8). A higher score indicated greater impairment.

Table 3:4 Descriptions of tests in computerised batteries

Computer battery	Cognitive test	Description
CDR	*Simple Reaction Time (SRT)*	The word "Yes" appears on the screen at random intervals Subjects are required to press the "Yes" button on their controller every time the word "Yes" appears
	Choice Reaction Time (CRT)	The word "Yes" or "No" appears at random on the screen Subjects are required to press the "Yes" button on their controller every time the word "Yes" appears, and "No" when the word "No" appears
	Digit Vigilance	Subjects are randomly assigned a number between 0 and 9 The numbers 0 to 9 appear rapidly one by one in the centre of the screen Subjects are required to press the "Yes" button as quickly as they can every time their assigned number appears
CANTAB	*Motor Screening Test (MOT)*	Screening test for visual, motor and comprehensive deficits Subjects are presented with a series of flashing crosses appearing one by one in different areas on the screen Subjects are asked to press the centre of the crosses
	One Touch Stockings of Cambridge (OTS)	Spatial planning test Subjects are shown two displays of three coloured balls in "stockings" Subjects are asked to work out the number of moves it takes to make one display match the other by moving the balls
	Pattern Recognition Memory (PRM)	Forced choice pattern recognition memory test Subjects are presented with a series of patterns to remember Subjects are required to choose between two patterns, one they have seen before and a new pattern
	Spatial Recognition Memory (SRM)	Forced choice spatial recognition memory test Subjects are presented with a white square in five locations on the screen Subjects are required to choose between a square in a previous location and a distractor square in a new location
	Paired Associate Learning (PAL)	Visual memory and new learning test Boxes are displayed on the screen and open in a random order, one or more contains a pattern The patterns shown previously in the boxes are shown one at a time in the centre of the screen; subjects are asked to touch the box the pattern was in

CDR = Cognitive Drug Research; CANTB = Cambridge Neuropsychological Test Automated Battery

Executive function was assessed using the One Touch Stockings of Cambridge (OTS) from the CANTAB and verbal fluency assessments. The OTS (Table 3:4) was measured using the number of problems solved on the choice, which had a maximum possible score of 20. A lower score indicated greater impairment. In the Phonemic Fluency test participants were asked to generate as many words as possible in 60 seconds beginning with the letters F, A and S (Benton, 1968). Similarly, for Semantic Fluency

participants were asked to list as many animals as they could in 90 seconds (Tombaugh *et al.*, 1999). Lower scores for both fluency tests indicated greater impairment.

Visuospatial function was evaluated using the pentagon copying item of the MMSE (Folstein *et al.*, 1975) and was graded using a modified 0-2 rating scale (Ala *et al.*, 2001). Language was assessed using naming, identifying animals from an illustration with a possible score of 0-3, and language, repeating sentences with a possible score of 0-2, drawn from the MoCA.

Consistent with the MDS Task Force Level II criteria, participants were classified as having PD-MCI using cut offs of 1 standard deviation (SD), 1.5 SD and 2 SD below the means of appropriate norms (controls) on at least two neuropsychological tests across five cognitive domains: attention, executive function, visuospatial function, memory and language. For non-normally distributed data, percentiles derived from a normal distribution were used to calculate cut-offs. Additionally, subjective cognitive decline and functional independence of participants were determined through semi-structured interviews with participants and/or their carers, which are also necessary for classification of PD-MCI (Litvan *et al.*, 2012). At 18 and 36 month follow up, participants were classified as PDD using MDS criteria (Emre *et al.*, 2007).

3.4.2 Quality of life

Quality of life was measured using the Parkinson's Disease Questionnaire (PDQ-39) (Jenkinson *et al.*, 1997b), which is widely used in PD research and clinical service (Martinez-Martin *et al.*, 2011a). It includes a 39 item Likert scale covering eight domains: mobility, activities of daily living (ADL), emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort (Appendix B). The single index of this scale was used as a global measure of QoL in PD. The single index scores range from 0 (best possible QoL), to 100 (worst possible QoL). Using the single index score provides a measure of overall QoL and may reduce the role of chance, which may arise from multiple statistical tests on the individual domains (Jenkinson *et al.*, 1997b). In a review evaluating scales used to assess QoL in people with PD, the PDQ-39 was a "recommended" scale (Martinez-Martin *et al.*, 2011a).

3.4.3 Clinical assessments

Demographic information, including age, sex and education was collected. Participants also completed the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II and III (Goetz *et al.*, 2008). Premorbid intelligence was measured using the National Adult Reading Test (NART) (Mathias *et al.*, 2007). Depression was assessed using the Geriatric Depression Score (GDS-15) (Yesavage *et al.*, 1982); a cut-off of ≥5 suggested possible depression (Schrag *et al.*, 2007). Pittsburgh Sleep Quality Index (PSQI) measured sleep disturbance, with a score of ≥ 5 indicating significant sleep disturbance (Buysse *et al.*, 1989). Daytime somnolence was measured by the Epworth Sleepiness Scale (ESS); scores ≥ 10 suggest excessive daytime somnolence (Johns, 1991). Neuropsychiatric symptoms were measured by the Neuropsychiatric Inventory (NPI-D) (Cummings *et al.*, 1994). Participants were assessed when "on." Levodopa equivalent dose was calculated for all dopaminergic medications using methods described by Tomlinson *et al.* (2010).

3.4.4 Carer assessments

Additional measures were added to the main study at 36 month evaluation to capture the wellbeing and QoL of carers of the PD participants. Demographic information of caregivers/informants was also collected, including: age, sex, level of education and current or previous occupation (Appendix C). Caregiving information was also collected; including the relationship to the person with PD and how many hours they spent caregiving per week. Carers were also asked to rate their current sleep quality using a visual analogue scale on a 100mm line (Appendix C); a score of 0 indicated worst possible night's sleep and a score of 100 indicated best possible night's sleep. Physical health was assessed using the Duke OARS (Older Americans Resources and Services) Physical Health Checklist (Whitelaw and Liang, 1991); this included a list of common physical health problems and, if present, impact on activities (not at all, a little, a great deal) and medication use was recorded (Appendix C). Comorbidities in mental health were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). There are two subscales of anxiety (HADS-A) and depression (HADS-D) where higher scores more severe symptoms. The authors suggest the following cut offs: 0-7 for normal, 8-10 mild symptoms, 11-15 moderate symptoms and 16 or above indicates severe symptoms.

Quality of life in carers was measured by the Scale of Quality of Life of Care-Givers (SQLC) (Glozman *et al.*, 1998) and the Parkinson Disease Questionnaire for Carers (PDQ-Carer) (Jenkinson *et al.*, 2012). Both scales are PD specific measures of QoL in carers (Appendix C). The SQLC incorporates the professional activity of the carer, social and leisure activities and responsibilities of the carer to help the person with PD in activities of daily living. The scale gives a total score where lower scores indicate poorer QoL and higher scores indicate better QoL. The PDQ-Carer has a single index score to measure global QoL in PD carers, ranging from 0 (best possible QoL), to 100 (worst possible QoL). There are also four dimensions measures by the PDQ-Carer: Social and Personal Activities, Anxiety and Depression, Self-care, and Strain. These can also be used to give sub-scores for each carer QoL domain. The strengths and limitations of the SQLC and PDQ-Carer are compared in Table 3:5.

Table 3:5 Comparisons of Scale of Quality of Life of Care-Givers and the Parkinson's Disease Questionnaire for Carers

	SQLC	PDQ-Carer
Strengths	• Specifically designed for carers of PD • Evaluates occupation activity, social and leisure activities and caregiving responsibilities • Evaluates changes since before PD diagnosis • Sensitive to carer strain in relation to PD • Short questionnaire that is quick to administer • Good internal consistency and validity	• Specifically designed for carers of PD • Short self-reported questionnaire that is easy to administer • The scale can be used as a global single index, or as subscales: social and personal activities; anxiety and depression; self-care and stress • High internal consistency and validity
Limitations	• Complex marking system • No validated English version, original version in Russian • Not widely used • Subject to recall bias	• New questionnaire that has yet to be used in other studies • No information available for test-retest reliability • Does not take into account changes before PD diagnosis • Subject to recall bias

SQLC = Scale of Quality of Life of Care-Givers (Glozman et al., 1998), PDQ-Carer = Parkinson Disease Questionnaire for Carers (Jenkinson et al., 2012)

3.5 Qualitative Methods

A sample of participants from the main ICICLE-PD cohort and their informal carers were invited to take part in qualitative interviews. Informal carers were spouses, partners, adult family members or friends who were the primary caregiver of the participant with PD.

3.5.1 Sampling method

Participants were selected based on theoretical sampling (Green and Thorogood, 2009): whether they had a carer, attended the 36 month follow up visits with their carer, their cognition level and gender. Three classes of cognition level were identified: normal cognition (PD-NC), PD-MCI and PDD. Participants were classified as "possible PD-MCI" if they had a MoCA score of <26 and there was evidence of cognitive impairment throughout assessments as part of ICICLE-PD follow up visits. They were then given a formal Level II PD-MCI classification based on their results on the neuropsychological tests (Litvan *et al.*, 2012). Participants were classified as PDD if they had been given a formal DSM-IV diagnosis of dementia (American Psychiatric Association, 2000) by a psychiatrist or neuropsychologist since enrolling in the study.

The three groups (PD-NC, PD-MCI and PDD) were chosen to explore the supposition that participants with cognitive impairment would have different experiences and general wellbeing to participants who were cognitively intact, as they have to contend with cognitive difficulties in addition to PD symptoms. Carer experiences were also expected to be different, as they would have to deal with more demanding tasks, taking on more responsibility as people with PD experience memory problems, and challenges in organising and decision making (Klepac *et al.*, 2008). They may also have had to deal with the emotional impact of watching their partner or relative decline both physically and cognitively (Carter *et al.*, 2012).

Sampling continued until there were approximately equal proportions of participants in each cognition level and a gender ratio which was representative of people with PD. This was to ensure that each group was adequately represented in the sample, both for people with PD and their carers, to explore the impact of cognitive impairment and dementia on QoL and carer burden. Participants were iteratively sampled until saturation was reached.

3.5.2 Procedure

Participants meeting sampling criteria and their carers who consented to the interviews being recorded were interviewed separately using a digital voice recorder. Interviews were conducted separately so that both participant and their carer might speak more freely about their experiences without the presence of their

partner/relative affecting their responses. The interviews lasted approximately 30-60 minutes, depending on how much the interviewee wished to disclose.

Semi-structured interviews were used. Semi-structured interviews involve the researcher having a predetermined list of questions or specific topics to cover, usually referred to as an interview schedule or guide (Bryman, 2008). However, unlike structured interviews, which have specific questions in a specific order and are typically used for quantitative studies, semi-structured interviews are more flexible (Green and Thorogood, 2009). Semi-structured interviews have a wider range of possible responses, as the questions are predominantly open ended (Smith, 2008), and can be adapted to the individual being interviewed (Bryman, 2008). For example, the interviewer does not have to ask the questions in the same order that they are written in the interview schedule, or they may ask additional questions to expand on interesting or novel points raised by the interviewee (Smith, 2008). Thus, the schedule is more of a guide than a rigid itinerary. This flexible approach to interviewing allows the researcher to cover the issues or topics of their research questions while enabling them to also explore novel subjects or themes, which provides a richer and in depth data set (Bryman, 2008; Smith, 2008). This method was applied to this study. An interview schedule first developed.

3.5.3 Developing an interview schedule

An initial list of questions was compiled, based on a literature review of previous qualitative and quantitative studies investigating the effects of chronic disease, PD, QoL and carer experiences (Appendix D) (Habermann, 2000; Thommessen *et al.*, 2002; Carter *et al.*, 2010). These questions formed the initial interview schedule, with the intention of refining the questions using the data collected in the pilot interviews for subsequent interviews.

Two participants in the ICICLE-PD study and their caregivers were approached to take part in a pilot study at their 36 month follow up assessment. Participants were purposively sampled, based on whether they attended with a carer and whether they scored less than 26 on the MoCA. Based on previous research, it was felt that these subjects would give the richest source of information with respect to their experiences of PD and cognitive decline. Participants were given instructions before the start of the

interview, such as what to expect from the interview, and given the opportunity to ask any further questions. Participants were then asked the questions from the interview schedule. Following the interviews, the interviews were transcribed verbatim.

The pilot interviews were then appraised. The interview schedule was altered to include more open ended questions to facilitate more in depth discussion of topics. Some potentially useful follow up questions were also added to the interview schedule to ensure interesting and important points could be explored in detail. Additional questions were also added to explore in more depth the changes to the interviewees' lives since PD diagnosis, their relationship to the other person, their experiences with cognitive impairment, what coping mechanisms they have used and their impressions of dementia and cognitive impairment compared to the motor symptoms of PD. For example, in the initial interview schedule, interviewees where asked, 'Has your life changed since you/your spouse/relative was diagnosed with PD?' This was amended to first asking the interviewee how long they had known the other person (carer or care recipient as appropriate), to sum up their relationship, how they spent their time, and then asking whether their lives had changed since PD was diagnosed and in what way. This was to give a context to the experiences of the individual and helped to make comparisons regarding how PD and cognitive impairment had affected the interviewee. More in depth questions were also added to encapsulate the impact on carers and to explore the ways they have been affected, for example, 'How have these changes in your spouse/relative affected you?' The final interview schedule was refined for use in subsequent interviews (Appendix D).

3.6 Data Analysis

3.6.1 Quantitative analysis

Statistical analyses were performed using SPSS software (Version 19.0; SPSS, Inc., Chicago, IL) and R software (R Core Team, 2013). Data were examined for normality of distribution with visual histograms and Kolmogorov-Smirnov's test. Comparisons of means between two groups were performed using independent t-tests or Mann-Whitney U test as appropriate. For more than two group comparison, one way ANOVAs or Kruskal-Wallis tests were used as appropriate. Multiple comparisons were corrected using Bonferroni's correction; the cut off for significance was calculated

using α/n where α is the significance level (0.05) and n is the number of tests. Pearson or Spearman correlations were used as appropriate to test for associations between variables. Regression models were used to build predictive models of QoL. Specific methods of statistical analysis are detailed in each chapter as appropriate.

3.6.2 Qualitative analysis

The interviews were transcribed verbatim. Any identifiable information was removed, such as first names or surnames mentioned during interviews, to ensure the anonymity of interviewee. Upon discussion, “erms,” “ahhs” and “mmhmms” were removed from the transcripts so the dialogues were less broken and more fluid when read. Within the interview transcripts, commas indicated a short pause by the speaker; full stops indicated a longer pause by the speaker; ellipsis (…) represented the omission of one or more words; square brackets ([]) indicated an insertion by the researcher to indicate a change, such as the deletion of a name, or additional information relevant to the conversation; and speech marks (“”) to indicate when the speaker was recounting a conversation.

The transcriptions formed the formal text that was used for analysis. The interview content was analysed using thematic analysis, as described by Braun and Clarke (2006) (Table 3:1). Open coding was at first used in great detail, which allowed the early formation of themes and concepts. The constant comparative method, as detailed in GT (Strauss and Corbin, 1994), was also used (see Section 3.2.2.1). Each new set of data was compared to previous extracts to see how well the coding frame fitted; new codes and themes were then added as necessary (Appendix E). Interviews continued until saturation was reached, the point when no new themes emerge (Green and Thorogood, 2009). NVivo 9 software (QSR International, 2010) was used to aid analysis.

Chapter 4 Does severity of mild cognitive impairment in early Parkinson's disease contribute to poorer quality of life?

4.1 Background

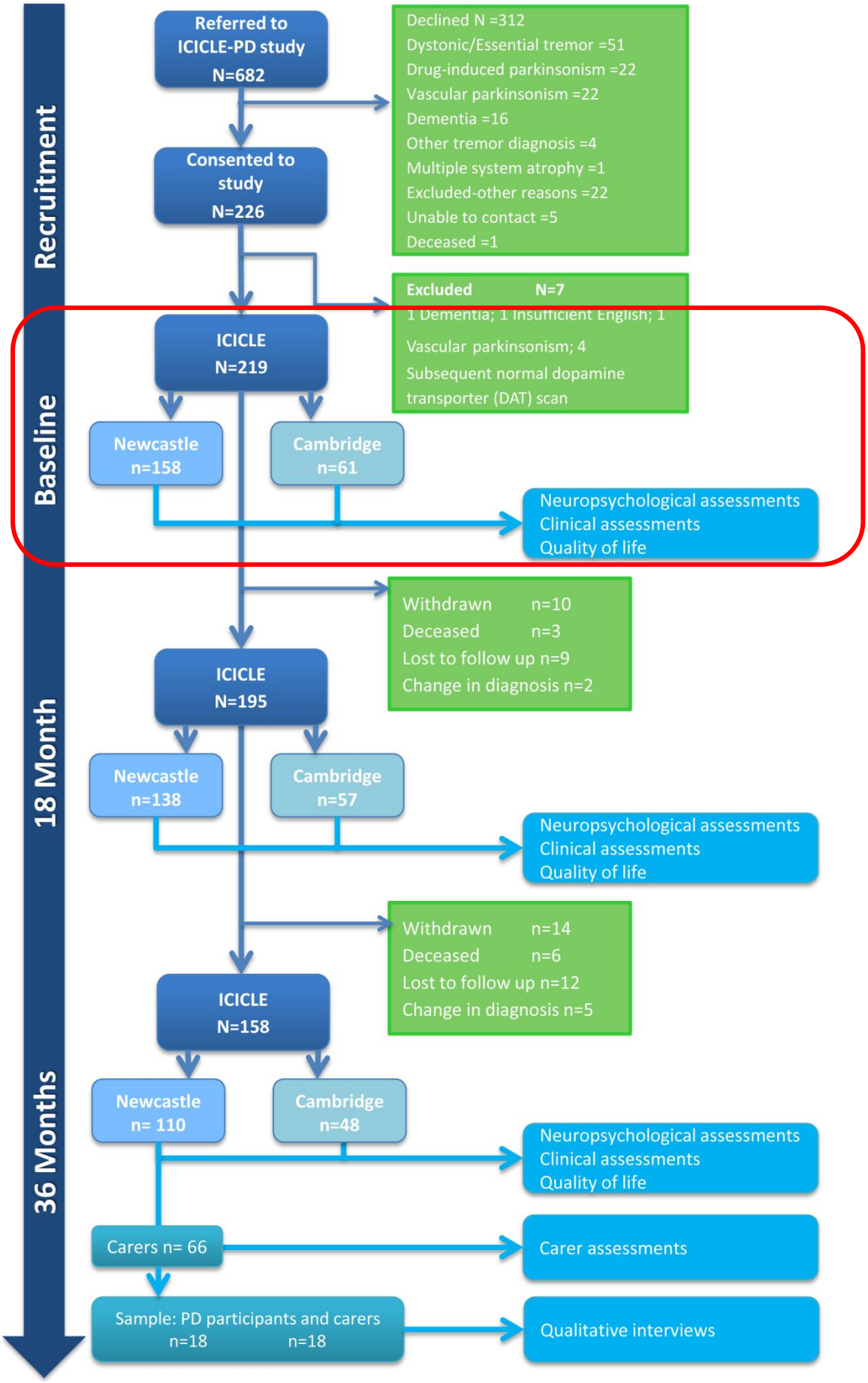
As shown in Chapter 1, for the individual living with Parkinson's disease (PD), the development of dementia (PDD) has a significant impact upon quality of life (QoL) (Leroi *et al.*, 2012b). Mild cognitive impairment in PD (PD-MCI) is a potential early marker for the development of PDD (Janvin *et al.*, 2006; Williams-Gray *et al.*, 2009; Broeders *et al.*, 2013) so may also be associated with poorer QoL (Reginold *et al.*, 2013).

The Movement Disorder Society (MDS) Task Force defines PD-MCI as performing 1 to 2 standard deviations (SD) below appropriate normative values in neuropsychological tests with no impairments of activities of daily living (ADL) (Litvan *et al.*, 2012). However, the use of potential cut-offs between 1 to 2 SD leaves much room for variation.

Furthermore, QoL may be affected by particular subtypes of MCI (Leroi *et al.*, 2012b). Combined impairments in multiple domains may have greater cognitive burden and thus may cause greater difficulties in activities of daily living (ADL) and poorer QoL (Klepac *et al.*, 2008; Goldman *et al.*, 2012). Additionally, specific impairments, e.g. the deficits in attention and executive function which are common in PD, may be more detrimental to ADL and QoL (Bronnick *et al.*, 2006; Klepac *et al.*, 2008; Kudlicka *et al.*, 2014).

As outlined in Chapter 2, this chapter aimed to investigate the impact that different operational cut offs for diagnosing PD-MCI had on QoL and whether QoL was different between subtypes of PD-MCI. I hypothesised that those with PD-MCI would have poorer QoL compared to those with normal cognition (PD-NC) and that the effect across the different MCI subtypes would not be equal, with executive dysfunction and attention having a greater impact.

Figure 4-1: Assessment schedule



4.2 Specific Methods

As shown in Figure 4-1, the methods and results in this chapter relate to the analysis of baseline measures in the ICICLE-PD study. The details of the assessments used in this study are described in Chapter 3.

4.2.1 Classifying mild cognitive impairment

Implementation of our schedule of neuropsychological tests preceded the establishment of the MDS Task Force Level II criteria for PD-MCI, as described in Chapter 1 (Litvan *et al.*, 2012). However, broadly we were able to meet Level II criteria with our testing, despite having only one test specific for visuospatial impairment. Consistent with the MDS criteria, participants were classified as having PD-MCI using cut offs between 1 to 2 SD below the means of appropriate norms (controls) on at least two neuropsychological tests across five cognitive domains: attention, executive function, visuospatial function, memory and language. Additionally, subjective cognitive decline and functional independence of participants were determined through semi-structured interviews with participants and/or their carers.

To explore the impact of different operational cut offs for PD-MCI within the 1 to 2 SD range, we used cut offs of 1 SD, 1.5 SD and 2 SD as defined in Table 4-1. These three cut offs have been used in other studies, although 1.5 SD is the most common (Yarnall *et al.*, 2013b).

Table 4-1: Criteria for PD-MCI cut off classification

PD-MCI cut off classification	Classification criteria
PD-NC	PD participants scored <1 SD below normative data
PD-MCI 1 SD	PD participants scored ≥1 SD but <1.5 SD below normative data in at least two tests
PD-MCI 1.5 SD	PD participants scored ≥1.5 SD but < 2 SD below normative data in at least two tests
PD-MCI 2 SD	PD participants scored ≥2 SD below normative data in at least two tests

PD = Parkinson's disease; NC = normal cognition; MCI = mild cognitive impairment; SD = standard deviation

For data that was not normally distributed and could not be transformed appropriately, percentiles derived from a normal distribution were used to estimate cut-offs of 1 SD (16th percentile), 1.5 SD (7th percentile) and 2 SD (2nd percentile), therefore the cut-offs give approximately the correct percentage of people impaired. For example, the pentagon score was assessed as: 2 (shape includes 10 angles and

clear intersection), 1 (two intersecting figures, one with five angles) or 0 (less acceptable copy); using corresponding percentiles from the control group, participants scoring 1 were classified as having impairment at the 1 SD and 1.5 SD level, and participants scoring 0 were classified as having impairment at the 2 SD level.

The MDS Task Force suggest using single or multi-domain PD-MCI and specifying the impaired domains (Litvan *et al.*, 2012), rather than the previous classification of amnestic or non-amnestic (Goldman *et al.*, 2012). Single-domain PD-MCI was defined as impairment in two tests in the same domain; multi-domain classification required at least one impaired test in more than one domain (Litvan *et al.*, 2012). Participants were then classified according to impairments in specific domains. For example, a participant impaired in only attention would be classified as single-domain attention PD-MCI; a participant impaired in attention and executive function would be classified as multi-domain attention plus (+) executive function PD-MCI.

4.2.2 Specific statistical analysis

Statistical analyses were performed using SPSS software (Version 19.0; SPSS, Inc., Chicago, IL). Data were examined for normality of distribution with visual histograms and Kolmogorov-Smirnov's test. Comparisons of means between two groups were performed using independent t-tests or Mann-Whitney U test as appropriate. For more than two group comparisons one way ANOVAs or Kruskal-Wallis tests were used as appropriate. Multiple comparisons were corrected using Bonferroni's correction; the cut off for significance was calculated using α/n where α is the significance level (0.05) and n is the number of tests. Logistic regression was used to build a model to predict QoL; data was dichotomised using the median, such that scores below the median were low and scores above the median were high.

4.3 Results

Participants with PD (n=219) were aged between 35 and 87 years (mean of 65.9±9.7); 63.9% were male (n=140). Mean time since diagnosis was 5.5±5.0 months, 83% were rated as Hoehn and Yahr stage 1 or 2 and 16% were drug naïve. The ages of the control subjects (n=99) ranged from 48 to 88 years (mean of 67.9±8.2) and 55% were male (n=54). There was no significant difference between age ($p>0.05$) and sex ($p>0.05$) of PD participants and controls. Neither was there a significant difference between PD

participants and controls in terms of number of years of education (mean of 13.1±3.4 and 12.8±3.6, respectively; p>0.05) and NART scores (mean of 115.8±8.7 and 114.3±10.3, respectively; p>0.05).

4.3.1 Severity of mild cognitive impairment and quality of life

Table 4-2: Mean and standard deviation of neuropsychological test results used for control group

Neuropsychological test	Controls (n=99)	
	Mean	**SD**
MoCA	27.0	2.5
MMSE	29.0	1.2
Phonemic fluency	13.0	4.7
Semantic fluency	23.9	6.1
Power of attention (msec)	1277.9	136.0
Digit vigilance accuracy (%)	96.0	5.8
Pattern recognition memory	20.7	2.5
Spatial recognition memory	16.1	1.8
Paired associates learning	1.8	0.6
One touch stockings	16.4	2.5
Pentagon copying	1.9	0.2
Naming	2.8	0.4
Sentence	1.7	0.6

MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination

The PD-MCI cut-offs were calculated using the test results from the neuropsychological assessments completed by control participants (Table 4-2). The clinical characteristics of the cohort classified by PD-MCI severity, as defined in Table 4-1, are shown in Table 4-3. 34.2% of PD participants were classified as normal cognition (PD-NC). Using the previously described operational cut offs, participants were classified as PD-MCI 1 SD (23.2%), PD-MCI 1.5 SD (21.1%) and PD-MCI 2 SD (22.4%). In each group, participants scored below the means of appropriate norms (controls) on at least two neuropsychological tests for that standard deviation.

As a group, participants with PD-MCI (≥1 SD below normative data) were significantly older, had spent fewer years in education and had a lower premorbid IQ (NART) than PD-NC (all p<0.01). They also had a higher MDS-UPDRS III score (p<0.01) and Hoehn and Yahr stage (p<0.01), but there was no significant difference in levodopa equivalent dose (LED). Mean depression scores were significantly higher for the PD-MCI group

compared to the PD-NC, although this is below the suggested cut-off for possible depression (GDS-15 >5) (Yesavage and Sheikh, 1986). Post hoc comparisons between PD-MCI groups (Table 4-3) showed an overlap in scores for PDQ-39, seen clearly in Figure 4-2, highlighting the variation of QoL scores by severity of cognitive impairment. Figure 4-2 is the density curve or probability distribution of PDQ-39 scores for each cognitive group. The density curve is the relative frequency of PDQ-39 scores, thus the area under the curve is proportional to the number of subjects. Only the 2 SD group significantly differed from the other groups, hence only more marked cognitive impairment at 2 SDs had a greater impact on QoL. Because of this, we focused our subsequent analyses using 2 SD as a cut off for PD-MCI.

Table 4-3: Mean and standard deviation of clinical data across cognitive groups

	Normal Cognition (n=75)		PD-MCI 1SD (n=51)		PD-MC 1.5SD (n=44)		PD-MCI 2SD (n=49)		F/χ^2	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age (years)	61.2	10.0	67.3	8.4	68.9	8.8	69.0	8.7	10.6**	
Education (years)	14.4	3.7	13.1	3.3	11.2	2.4	11.4	3.7	42.6**	a,b
NART	118.4	7.2	115.2	10.5	112.1	10.2	108.9	11.6	26.5**	b
PD Duration (Months)	5.3	4.9	6.1	4.8	5.8	6.9	4.8	3.3	2.7	
Time since symptom onset (Months)	18.7	13.5	26.1	20.6	28.7	37.6	26.7	25.1	6.7	
UPDRS III Total	23.0	9.4	27.2	10.4	31.7	11.9	31.6	13.9	8.6**	
Hoehn and Yahr†	2.0	1.0	2.0	0.0	2.0	0.0	2.0	1.0	19.1**	
LED (mg/d)†	100.0	220.0	120.0	224.0	130.0	200.0	150.0	200.0	3.2	
MoCA	27.4	1.8	26.1	2.4	24.5	3.2	22.3	3.9	55.5**	a,b,c
MMSE	29.3	0.9	28.8	0.9	28.5	1.3	27.9	1.6	31.7**	b
Phonemic fluency	14.3	4.4	11.8	4.4	9.7	4.0	9.8	4.5	15.0**	
Semantic fluency	25.0	5.8	21.5	5.3	19.1	5.6	16.7	6.8	21.6**	b
GDS-15	2.3	1.9	2.8	2.9	2.9	2.6	4.0	4.0	10.4*	b
NPI Total	6.2	3.9	7.3	4.3	5.6	5.7	7.5	5.4	1.1	
NPI Distress	2.9	9.1	3.5	9.7	3.4	10.1	3.3	10.4	1.0	
PDQ-39	24.3	19.4	26.6	21.9	28.8	21.1	38.2	25.2	11.7**	b

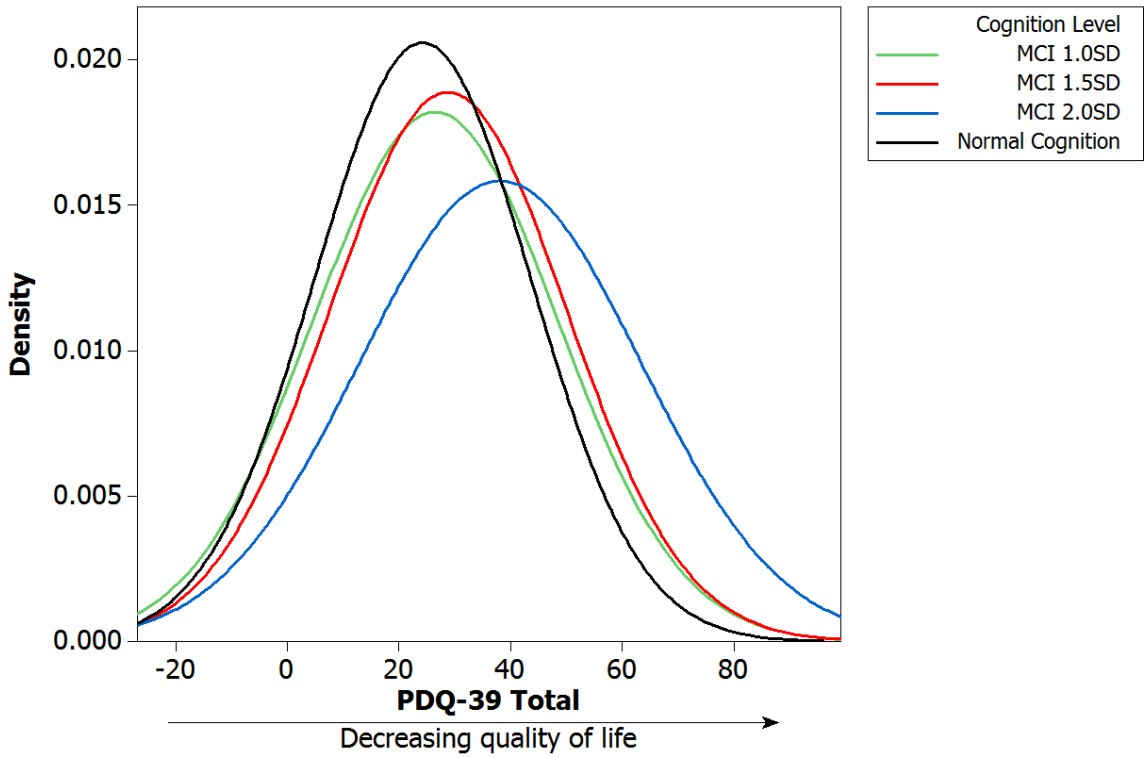
** p<0.05, ** p<0.01*

† Figures are median and interquartile range

Post hoc Bonferroni correction for 3 group comparison at p<0.017, a PD-MCI 1SD vs. PD-MCI 1.5SD; b PD-MCI 1SD vs. PD-MCI 2SD; c PD-MCI 1.5SD vs. PD-MCI 2SD

NART = National Adult Reading Test, UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LED = Levodopa equivalent dose, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, GDS-15 = Geriatric Depression Score, NPI = Neuropsychiatric Inventory, PDQ-39 = Parkinson's Disease Questionnaire.

Figure 4-2: Distribution of quality of life between cognitive groups



Graph of probability density function of PDQ-39 scores for the discreet groups of normal cognition, PD-MCI 1 SD, PD-MCI 1.5 SD and PD-MCI 2 SD.

4.3.2 Predicting quality of life

Stepwise logistic regression was used to determine predictors of QoL and to remove potential confounders. The final model (Table 4-4) correctly predicted 72.0% of QoL scores compared to observed values. Goodness of fit tests yielded a Nagelkerke R^2 of 0.346. The model shows that higher scores of motor severity, depression and neuropsychiatric symptoms predicted worse QoL (Table 4-4). The presence of MCI was an independent predictor of poorer QoL. Younger participants were predicted to have lower QoL.

Table 4-4: Regression model predicting quality of life

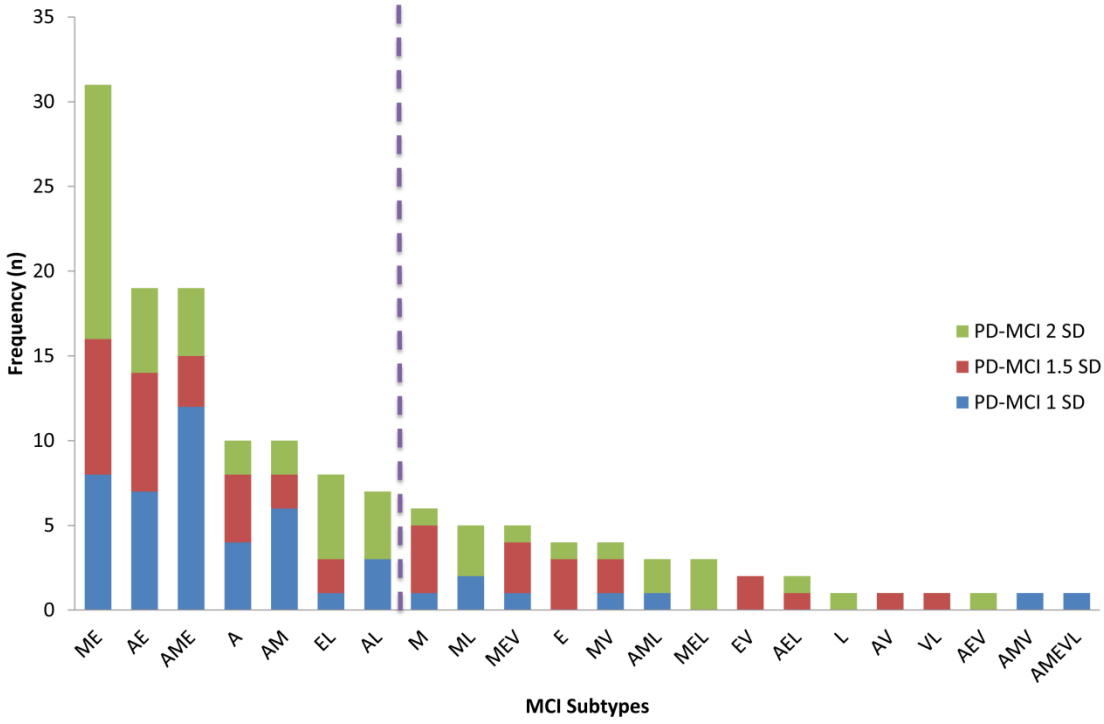
	β	SE	p	Exp(β)
Age	1.1	0.4	0.007	2.9
UPDRS III	-0.8	0.4	0.033	0.5
GDS-15	-2.5	0.8	0.002	0.1
PD-MCI	-1.5	0.5	0.003	0.2
NPI Total	-1.0	0.4	0.016	0.4

SE = Standard error, UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, GDS-15 = Geriatric Depression Score, PD-MCI = Mild Cognitive Impairment using 2 stand deviation cut off, NPI-D = Neuropsychiatric Inventory.

4.3.3 *Quality of life and mild cognitive impairment in early Parkinson's disease: does subtype matter?*

Implementation of the MDS PD-MCI criteria identified 22 subtypes (Figure 4-3). Significantly more subjects were classified as having multi-domain than single-domain PD-MCI (85% vs 15%; p<0.01). Executive function (67%), memory (61%) and attention (51%) were most frequently impaired. The most common subtypes were memory + executive function (22%), attention + executive function (13%) and attention + memory + executive function (13%). Figure 4-3 also shows that the number of participants in each subtype was relatively small; the first seven subtypes accounted for the majority of participants, with those after the divide making up less than 5% of participants in each subgroup.

Figure 4-3: Subtypes of mild cognitive impairment in participants with newly diagnosed Parkinson's disease

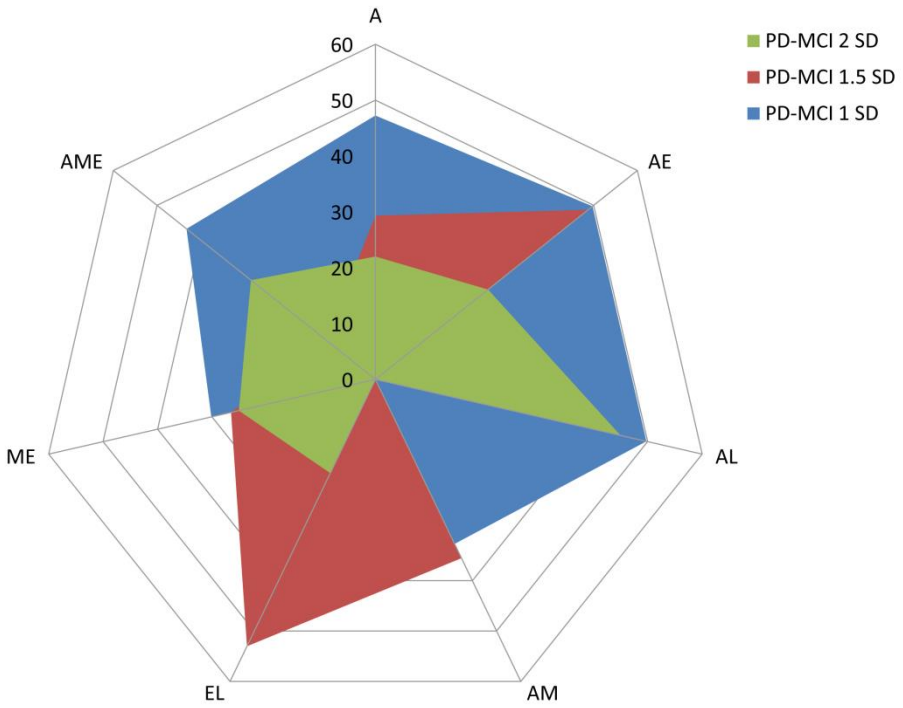


Subtypes of mild cognitive impairment (MCI): A = Attention; E = Executive function; L = Language; M = Memory; V = Visuospatial function.

Figure 4-4 shows a radar plot of the seven most frequent subtypes and PDQ-39 score by PD-MCI cut off; values extending from the centre of plot indicate worse QoL. In most subtypes, QoL decreased as cognitive impairment increased. Single-domain attention and multi-domain attention + memory + executive function tended to be associated with poorer QoL at the 2 SD cognitive cut off compared to other cut offs,

but overall there were no significant differences in QoL between MCI subtypes (p>0.10).

Figure 4-4: Subtypes of mild cognitive impairment and PDQ-39 scores



Radar plot of mean PDQ-39 scores of each PD-MCI cut-off, (1 SD, 1.5 SD and 2 SD below normative values) for the most frequent subtypes of PD-MCI. Scale on graph is PDQ-39 score, where higher values indicate worse quality of life. A = Attention; E = Executive function; L = Language; M = Memory; V = Visuospatial function; PDQ-39 = Parkinson's Disease Questionnaire.

Due to the prevalence of multiple-domain PD-MCI a secondary analysis was conducted using classifications outlined by Marras *et al.* (2013) to increase statistical power. This required two tests impaired in at least one domain for classification as PD-MCI. As expected, this identified fewer PD-MCI participants (≥1 SD below normative data; n=104) with significantly more single-domain impairments (76%; p<0.01). The most common subtypes were single-domain executive function (25%) and memory (19%); memory + executive function remained the most common multiple-domain subtype (5%). There were no significant differences in QoL between subtypes (p>0.10).

4.4 Discussion

We have shown that PD-MCI at 2 SDs below normative values is an independent, significant predictor of QoL in patients with newly diagnosed PD. QoL declined with increasing cognitive impairment in patients with PD, even when other contributory factors were taken into account. The greatest decline was seen in those who scored

more than 2 SD below normal on cognitive measures. This cut-off identified 22% of our cohort as having PD-MCI, which is consistent with other estimates of prevalence (Yarnall *et al.*, 2013b). We identified a number of PD-MCI subtypes and found more multi-domain impairments than single-domain, although there were no significant differences in QoL between subtypes. This may suggest that in PD-MCI, it is the severity of cognitive impairment, rather than the nature of impairment, that impacts on QoL.

We have shown that increasing cognitive impairment was associated with a number of factors, including QoL, depression and PD severity. Therefore, the operational definition of PD-MCI used has an influence on the association between MCI and QoL; while QoL scores were statistically different in patients with "milder" PD-MCI, i.e. at 1 SD or 1.5 SD, the effect of cognitive impairment on QoL was strongest if PD-MCI was defined by cognitive performance 2 SD or more below the control mean. Thus, there is a transition effect at a 2 SD threshold at which cognitive difficulties have a noticeable impact on peoples' lives. From this perspective we would suggest that 2 SD may be an appropriate operational cut off for defining PD-MCI.

This transition effect supports the conclusions of Leroi, et al. (Leroi *et al.*, 2012b), which is one of only two recent studies investigating QoL in PD-MCI using the newly outlined PD-MCI criteria by from MDS Task Force (Leroi *et al.*, 2012b; Reginold *et al.*, 2013). Leroi *et al.* assessed QoL and caregiver burden in participants classified as PD-NC, PD-MCI and PDD. As cognitive impairment increased, QoL became more impaired across the three groups, although only PDD was significantly higher (Leroi *et al.*, 2012b). This could be due to the use of Level I criteria of "possible" PD-MCI, which offers less diagnostic certainty than Level II criteria (Litvan *et al.*, 2012). Our study showed declining QoL with increasing cognitive impairment, with more severe PD-MCI having the greatest decline in QoL. This transition effect could indicate that these participants are likely to develop PDD (Williams-Gray *et al.*, 2009).

Applying the MDS Task Force Level II criteria, Reginold *et al.* (2013) found changes from premorbid cognition and PD-MCI were associated with reduced QoL in the PDQ-39 sub-scores of Stigma, Communication and Social support, but not in overall QoL (PDQ-39 single index score). However, cognitive decline was estimated using the

Wechsler Test of Adult Reading (WTAR), which may over estimate premorbid intelligence and cognitive decline (Mathias *et al.*, 2007). Our study, however, found significant differences in the PDQ-39 single index score, and was independently predicted by the presence of PD-MCI.

Impairment was most common in executive function, memory and attention. Two thirds of PD-MCI participants had executive dysfunction. A recent study has also observed high frequencies of executive dysfunction in PD-MCI (Goldman *et al.*, 2013), which can impair ADL (Kehagia *et al.*, 2010). Memory was the second most common impaired domain, which was also reported by Goldman *et al.* (2013), and has been shown to negatively impact on QoL (Barone *et al.*, 2009; Trigg *et al.*, 2011; Valkovic *et al.*, 2014). Half of PD-MCI participants had attentional dysfunction, which was also the most common single-domain subtype. This has also been observed in a previous study (Dalrymple-Alford *et al.*, 2011) and has been shown to significantly impact physical functioning and social interaction (Bronnick *et al.*, 2006). Significantly, only 15% of PD-MCI subjects had single-domain impairment. The high proportion of multi-domain impairments has also been found in other studies (Janvin *et al.*, 2006; Aarsland *et al.*, 2009; Goldman *et al.*, 2013; Marras *et al.*, 2013; Cholerton *et al.*, 2014).

To our knowledge, this is the first study to explore the relationship between QoL and PD-MCI subtypes. Although we did not find any significant differences in QoL score between subtypes, subtypes with attentional deficits seemed to have slightly poorer PDQ-39 scores. However, impairment in specific domains may become more important once a full dementia syndrome develops (Dubois *et al.*, 2007).

Previous studies have variable findings between cognitive domains. Attention and memory problems have been associated with worse QoL (Barone *et al.*, 2009), whilst another study found visuospatial function, executive function and attention/memory in PD participants affected QoL (Klepac *et al.*, 2008). Impairment in specific domains can inhibit everyday functioning and ADL (Bronnick *et al.*, 2006), or results in less effective coping strategies (Kudlicka *et al.*, 2014). Attentional deficits can impact on instrumental and functional ADL including bathing, eating and leisure activities, such as reading or watching television (Bronnick *et al.*, 2006). Trigg *et al.* (2011) have suggested that awareness of impairment may impact on QoL. Speculatively,

participants with PD-MCI may have perceived poorer QoL in that they are aware of cognitive changes and the impact they are having on their ADLs, and may draw comparisons to how they are performing now in comparison to their premorbid levels of function. Therefore, there may be an interaction between PD-MCI and other lifestyle variables; those with higher premorbid functioning may find the challenge of having PD-MCI greater (Trigg *et al.*, 2011).

Interestingly, our model showed that younger PD participants were predicted to have poorer QoL. This could reflect that younger participants with PD have higher expectations of QoL than older PD participants or find it harder to adjust, and therefore have perceived poorer QoL (Kudlicka *et al.*, 2014). Indeed previous studies have found that older subjects with PD are more accepting of disability and impairment as they are perceived as being appropriate to their age (Schrag *et al.*, 2003). Younger participants may also perceive having PD as "unfair" and are less able to deal with stigma and experience more severe psychosocial consequences (Schrag *et al.*, 2003; Knipe *et al.*, 2011; Murphy *et al.*, 2013).

The main strengths of this study are the large cohort of newly diagnosed PD patients and the range of validated instruments used to assess motor and non-motor symptoms, including a detailed schedule of neuropsychological tests. We used the PDQ-39 single index score to measure QoL, which is validated for PD and is widely used (Martinez-Martin *et al.*, 2011a; Reginold *et al.*, 2013). The MDS guidelines state that normative values should be age, education, gender, and culturally appropriate (Litvan *et al.*, 2012). As demonstrated in the results section, there were no significant differences between controls and PD participants in terms of age, gender, education and premorbid intelligence (NART score). Furthermore, control participants were not spouses or relatives of PD participants to limit potential bias, and were recruited locally through word of mouth and advertising to reflect the community and cultural population. We also examined the scores and cut offs for cognitive tests using age and education as covariates. However, remodelling our data did not have a significant impact either on PD-MCI classification or on QoL.

There are several limitations. The challenging nature of accurately assessing MCI raises the possibility of falsely identifying some participants as having PD-MCI (Litvan *et al.*,

2012). However, the use of Level II criteria and the 2 SD as a cut off for PD-MCI, in addition to semi-structured interviews with participants and/or their carers, increases diagnostic certainty. We used modified MDS criteria since the study design predated the recent PD-MCI guidelines. While the assessments for executive function, attention and memory were suitably covered, we had limited assessments for language and particularly visuospatial function, which included only one domain-specific test, which has implications for classification. This also has implications for subtyping and may increase the frequency of impairments in these domains. However, language has been shown to be relatively preserved in previous studies (Yarnall *et al.*, 2013b; Pfeiffer *et al.*, 2014) and impaired ability to copy pentagons has been shown to predict dementia (Williams-Gray *et al.*, 2009). Moreover, the small number of participants in each subtype reduced statistical power, decreasing the sensitivity of our study to detect subtle differences between subtypes.

Furthermore, MoCA scores in patients with PD-MCI at 2 SD (mean score of 22.3) were low in our study and below the cut off that suggests possible dementia. This mean is nonetheless comparable with MoCA scores for PD-MCI from previous studies (Reginold *et al.*, 2013), and ultimately dementia is not determined by MoCA score alone and all participants underwent rigorous clinical assessment to exclude dementia (including a carer interview). Participants were recruited from outpatient clinics and 84% were on anti-parkinsonian medication, which reflects current clinical practice.

In summary, cognitive impairment specifically contributes, independently, to poorer QoL even in early PD. More marked degrees of PD-MCI (2 SD below normal values) have a greater impact upon QoL, suggesting a transition effect. This could also be an early indication of an inflexion point in the progression of PD. Previous studies have suggested that the rate of decline is the same for all people with PD once they reach an advanced stage of disease (Kempster *et al.*, 2010; Johnson and Galvin, 2011). Thus PD-MCI is complex with severity of impairment, rather than subtype, affecting QoL. It could be inferred that the current MDS guidelines for subtyping PD-MCI may not be optimal; we identified 22 subtypes using the proposed guidelines. Numerous subtypes may be impractical in clinical settings; this could indicate that subtyping is of no real significance to patients and that their QoL is not affected by the specific nature of the impairment.

Increased awareness and understanding of the impact of PD-MCI would inform clinicians of which cognition focused interventions, such as cognitive training or cognitive stimulation interventions, are potentially beneficial (Calleo *et al.*, 2012; Yarnall *et al.*, 2013b). Previous studies have suggested targeting specific cognitive impairments to improve everyday function, ADL and coping strategies may also have a direct positive impact on QoL (Klepac *et al.*, 2008; Kudlicka *et al.*, 2014). However, our results suggest that perhaps improving global cognition would be more beneficial to patients at this stage of cognitive impairment, for example with donepezil (Dubois *et al.*, 2012), rivastigmine (Mamikonyan *et al.*, 2015) or physical exercise (Murray *et al.*, 2014). Nonetheless, people with PD who then develop PDD may need targeted interventions to specific domains in order to improve QoL (Dubois *et al.*, 2007; Leroi *et al.*, 2012b). Consequently, studies investigating cognitive or disease modifying interventions should include QoL measures.

Chapter 5 Changes in cognition and quality of life: from diagnosis to 36 month follow up

5.1 Background

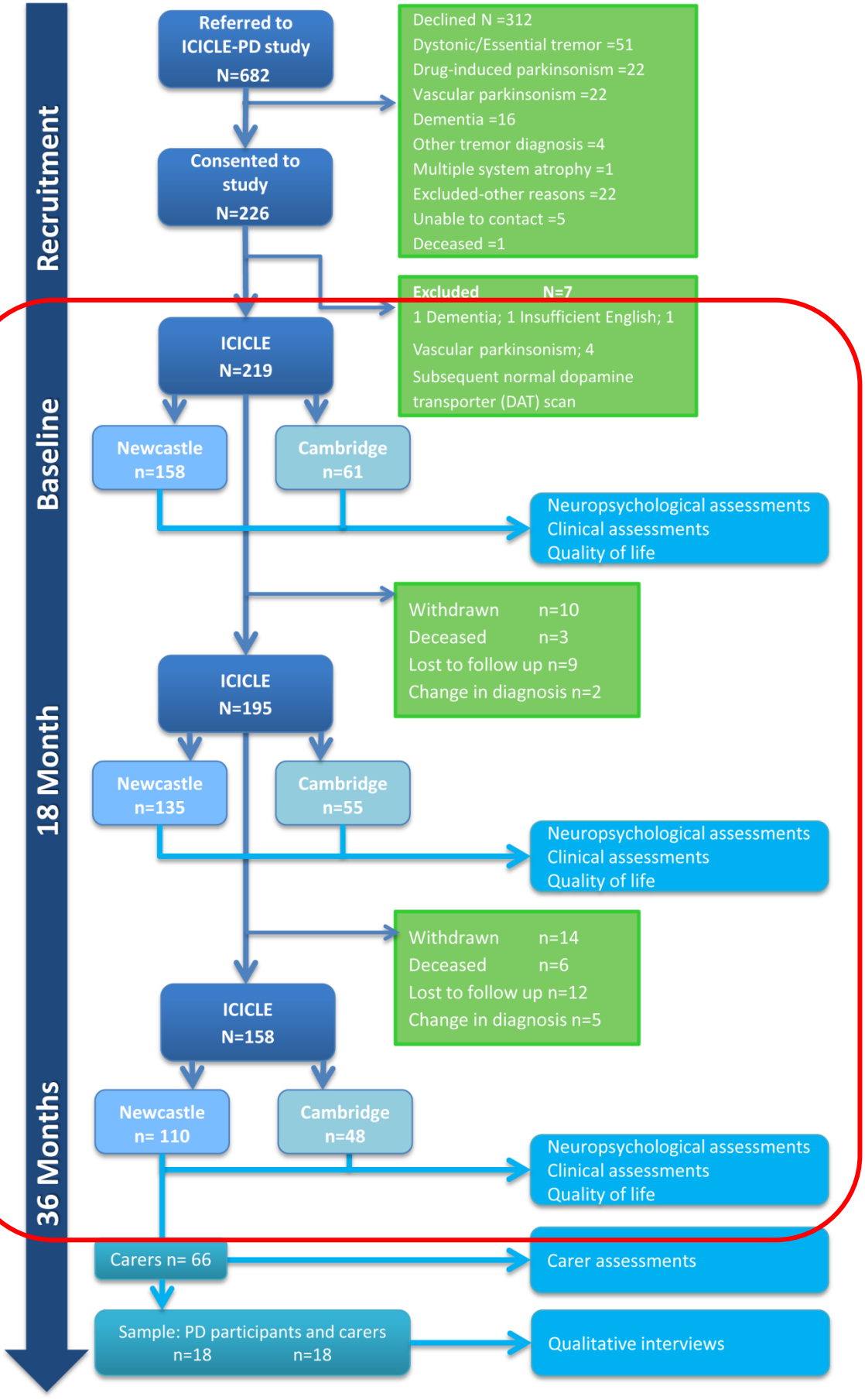
As discussed in Chapter 1, quality of life (QoL) is not fixed and is likely to change over time due to progression of disease and disease specific stressors that may disrupt emotional equilibrium and QoL (Moos and Schaefer, 1984; de Ridder *et al.*, 2000; Moss-Morris, 2013). Cognitive impairment is also not necessarily stable and may be subject to decline (Domellof *et al.*, 2015) or may improve in some cases (Koepsell *et al.*, 2013; Loftus *et al.*, 2015). Offsetting these changes in external factors may be changes in adaptation within patients and carers. Chapter 4 demonstrated an association between PD-MCI and poorer QoL in newly diagnosed PD, but this association may change over time.

As outlined in In Chapter 2, this chapter aims to investigate whether there is a relationship between changes in cognition and changes in QoL from baseline to 36 month follow up. I hypothesised that the presence of PD-MCI, whether present at baseline, 18 months or 36 months, would be associated with poorer QoL. Moreover, I expected that participants who demonstrated cognitive decline over 36 months would have significantly poorer QoL at the time of their final assessment compared to those who had maintained a stable or normal cognition during the follow-up period. I also predicted that the small proportion of participants would have developed PDD by 36 months would report the poorest QoL.

5.2 Specific Methods

As shown in Figure 5-1, the methods and results in this chapter relate to the analysis of baseline measures, 18 month follow up measures and 36 month follow up measures of PD participants in the ICICLE-PD study. The details of the assessments used in this study are described in Chapter 3.

Figure 5-1: Assessment Schedule



5.2.1 Specific statistical analysis

Statistical analyses were performed using SPSS software (Version 19.0; SPSS, Inc., Chicago, IL). Data were examined for normality of distribution with visual histograms and Kolmogorov-Smirnov's test. Transformations were applied to non-normal data in an attempt to normalise the data, however, this was not successful and so non-parametric methods were used as appropriate. Comparisons of means between two groups were performed using independent t-tests or Mann-Whitney U test as appropriate. For more than two group comparisons, one way ANOVAs or Kruskal-Wallis tests were used as appropriate. Multiple comparisons were corrected using Bonferroni's correction; the cut off for significance was calculated using α/n where α is the significance level (0.05) and n is the number of tests. Hierarchical regression was used to determine significant predictors of QoL.

In Chapter 4, the results showed that MDS PD-MCI guidelines for subtyping produced a large number of unstable categories which would be unreliable in further analyses. However, due to the number of cognitive measures used, using all the neuropsychological tests in a single regression analysis was also not possible. Thus, a principal component analysis (PCA) was used to reduce the high number of tests to a smaller number of cognitive dimensions, so allowing the determination of which domains or groups of tests predicted QoL scores. PCA is a multivariate method of analysing data which consists of several variables that are inter-correlated (Abdi and Williams, 2010). The main use of PCA is to understand the pattern or structure of variables and to extract information that explains the greatest variance in the constructs being measured i.e. the principal components (Abdi and Williams, 2010; Field, 2013). This information can then be used to reduce the number of variables to a combination of linear components or factors, which are fewer in number than the original data (Jolliffe, 2014). Oblique rotation was used, as theoretically the correlations between the resultant components of neuropsychological tests may be acceptable (Field, 2013). PCA with oblimin rotation, an oblique rotation, was used in this study to determine the underlying patterns of the cognitive data and to reduce the large number of highly correlated cognitive variables to a smaller number of variables that could be used in the final analysis. This also allowed an evaluation of whether

certain components (i.e. a particular group of cognitive tests) could be used to predict QoL.

R (R Core Team, 2013) and *lme4* (Bates *et al.*, 2014) were used to perform linear mixed effects analysis of the relationship between QoL and cognition from baseline to 36 months. This form of multilevel modelling is suitable for longitudinal data analysis because it accounts for random effects between individuals and does not assume independence between variables, making it a suitable analytical method for repeated measures (Laird and Ware, 1982; Field *et al.*, 2012). Mixed effects modelling can also include random intercepts (where the regression line crosses the y-axis) and random slopes (the gradient of the regression line), these are random effects (Faraway, 2005). For example, where the subjects may have individual variability and so do not all start at the same level, they can be given their own "personal" intercept which randomly differs from the mean intercept of the group (Field *et al.*, 2012). Similarly, if individuals are expected to change at different rates, a random slope can be introduced to give them their own "personal" slope that differs from the mean gradient of the group. This allows a more realistic model to be constructed because individual differences can be taken into account (Faraway, 2005). Another advantage is its ability to handle missing data (Verbeke *et al.*, 2009; Field *et al.*, 2012). Multilevel modelling does not require full data sets, and so the omission of individual variables at one time point does not result in all of the data for that subject being excluded from analysis. Thus, all data can be used, which is not possible with more commonly used regression models.

A random intercept model was used, where the intercept varied at the participant and time level. This allowed for by-subject and by-time variability to be taken into account (Field *et al.*, 2012). Gender, completed years of education, age, levodopa equivalent dose (LED), depression score (GDS-15), disease severity (MDS UPDRS III) and time were entered into the model as fixed effects, as well as interactions of time with depression (GDS-15 x Time), LED (Time x LED) and disease severity (Time x MDS UPDRS III). Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. Fit of the models was assessed by likelihood ratio tests between the initial model and models with measures of cognition.

5.3 Results

Between baseline and 36 month follow up, seven participants were re-diagnosed as not having idiopathic PD and were consequently excluded from further analysis (Figure 5-1). Of the remaining participants, 24 withdrew from the study, 21 participants were not contactable (lost to follow up) and nine participants died; thus a total of 158 participants (75%) returned for evaluation at 36 months. The baseline demographic and clinical data of participants who completed assessments at each time point are reported in Table 5-1; the baseline data of participants who did not return for further evaluation is also reported. Comparison of mean tests at baseline between completers and non-completers showed no significant difference in participants' age, number of years of education, premorbid IQ (NART), disease severity, LED, depression, global cognition or QoL ($p>0.05$ for all). The proportion of males and females was also insignificant between completers and non-completers ($\chi^2=0.55$, $p=0.46$).

Table 5-1: Comparison of baseline demographic and clinical characteristics of participants who returned for 36 month evaluation (completers) and non-completers of assessments

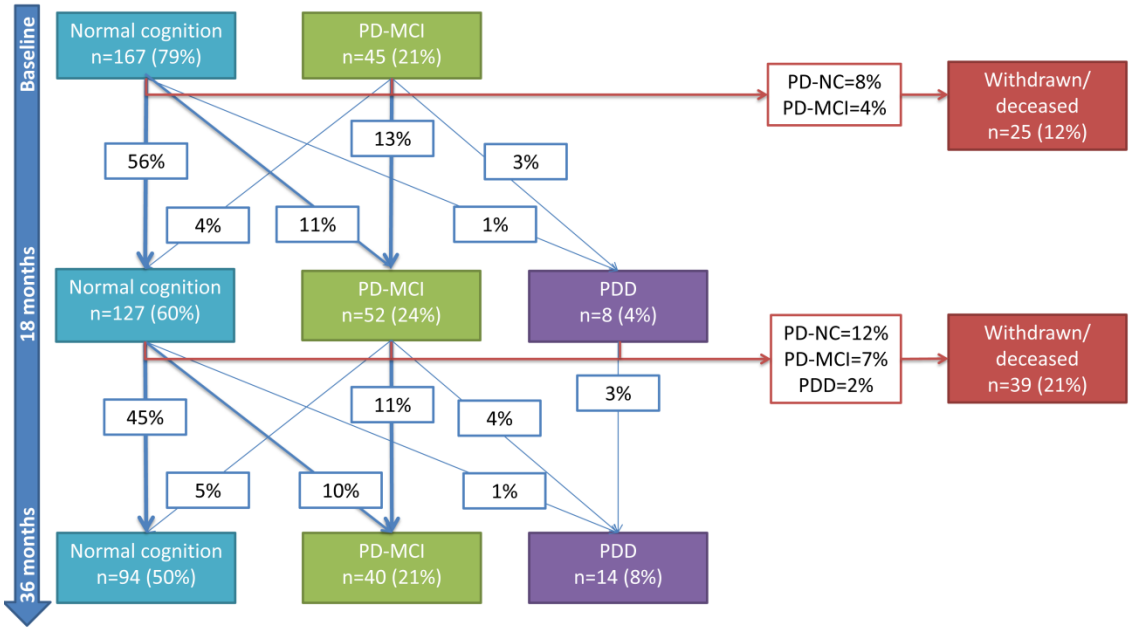
	Completers (n=158)		Non-completers (n=53)		$t/z/\chi^2$	p
	Mean	**SD**	**Mean**	**SD**		
Age (years)	65.5	9.4	66.8	10.9	-0.8	0.403
Education (years)	12.9	3.5	12.5	4.0	-0.9	0.38
NART	114.2	10.5	115.0	9.7	-0.4	0.66
UPDRS III Total	26.5	10.9	30.5	14.1	-1.5	0.12
Hoehn and Yahr stage	1.9	0.7	2.0	0.7	-0.5	0.60
LED (mg/d)	172.8	139.7	196.7	194.3	-0.1	0.95
GDS-15	2.7	2.5	3.3	2.8	-1.6	0.12
PDQ-39	18.2	13.8	19.2	15.7	-0.2	0.86
MoCA	25.4	3.5	25.2	3.3	-0.6	0.58
MMSE	28.8	1.2	28.6	1.5	-0.1	0.95
	n	**%**	**n**	**%**	**χ2**	**p**
Gender (male)	103	65	31	59	0.4	0.25

NART = National Adult Reading Test, UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LED = Levodopa equivalent dose, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, GDS-15 = Geriatric Depression Score, NPI = Neuropsychiatric Inventory, PDQ-39 = Parkinson's Disease Questionnaire.

5.3.1 Cross-sectional analysis at 18 months and 36 months

The cross-sectional analysis in Chapter 4 was repeated using the 18 month and 36 month follow-up data. The baseline data showed that MDS classification of PD-MCI using the 2 SD below normative values was the most appropriate operational cut-off; therefore, this cut-off was used in subsequent analyses. Participants were classified as PD-NC, PD-MCI or PDD at 18 months and 36 months. The changes in cognitive classification between assessments are shown in Figure 5-2. The percentages reported relate to each time point to show the relative change in proportions of cognitive classification. Comparisons of the main variables at these time points are shown in Table 5-2 and Table 5-3, respectively.

Figure 5-2: Changes in cognitive classification: from baseline to 36 months



PD-NC = Normal cognition, PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD = Parkinson's disease dementia.
Percentages reported are for the total number of participants at each time point.
This figure includes n=4 participants who completed PDQ-39 questionnaires at baseline and 8 months, but not at 18 months; all were PD-NC at baseline. Of these, two participants had stable normal cognition, one developed PD-MCI and one developed PDD at 36 months

At the 18 month evaluation, 183 (86%) of PD participants returned and completed assessments; seven participants did not complete the PDQ-39 questionnaire and were excluded from the 18 month cross-sectional analysis. There were no significant differences in demographic or clinical data for these participants ($p>0.05$). Figure 5-2 shows eight participants developed PDD 18 months from baseline. There were no significant differences between those with PD-NC, PD-MCI or PDD in terms of gender,

LED and depression score (p>0.05 for all). Other clinical, neuropsychological and QoL measures were significantly different between the three groups, as shown in Table 5-2.

Table 5-2: Comparison of demographics, clinical and neuropsychological characteristics between cognitive groups: 18 month follow-up

	PD-NC (n=124)		PD-MCI (n=51)		PDD (n=8)		F/χ^2	p	
	Mean	SD	Mean	SD	Mean	SD			
Age (years)	66.1	9.4	72.3	8.3	74.8	6.3	11.1	<0.001	a,b
Gender (male: n,%)	77	62	33	65	5	63	0.1	0.948	
Education (years)	13.4	3.5	11.2	2.9	12.1	4.4	20.2	<0.001	a
NART	116.8	9.6	110.3	10.0	107.3	11.7	22.3	<0.001	a,b
UPDRS III Total	30.1	11.1	40.7	12.0	48.1	8.9	37.8	<0.001	a,b
Hoehn and Yahr stage	2.1	0.5	2.4	0.6	2.6	0.7	10.9	0.004	a
LED (mg/d)	420.7	233.0	430.5	256.1	303.1	123.6	2.2	0.329	
GDS-15	2.5	2.5	3.5	3.2	3	1.3	5.2	0.074	
PDQ-39	17.9	14.3	26.6	18.9	28.3	13.9	10.3	0.006	a
MoCA	27.3	2.7	24.4	3.1	17.4	3.7	51.3	<0.001	a,b,c
MMSE	28.9	1.3	27.6	1.7	25	2.2	41.8	<0.001	a,b,c
Verbal fluency	14.0	4.6	10.9	3.9	7	2.6	28.9	<0.001	a,b,c
Semantic fluency	23.4	6.4	18.1	6.0	12.8	4.7	33.3	<0.001	a,b
PoA	1331.3	127.9	1573.2	214.1	1852.5	284	63.8	<0.001	a,b,c
Digit Vigilance	95.9	5.5	85.0	14.0	62.5	24.4	52.4	<0.001	a,b,c
PRM	20.9	2.2	17.8	2.8	15.9	3.3	50.3	<0.001	a,b
SRM	15.6	1.9	13.1	2.6	10.5	2.8	47.5	<0.001	a,b
PAL	1.7	0.8	3.0	1.1	4	2.2	48.2	<0.001	a,b
OTS	16.3	2.8	11.4	4.7	4.5	6.2	62.8	<0.001	a,b,c

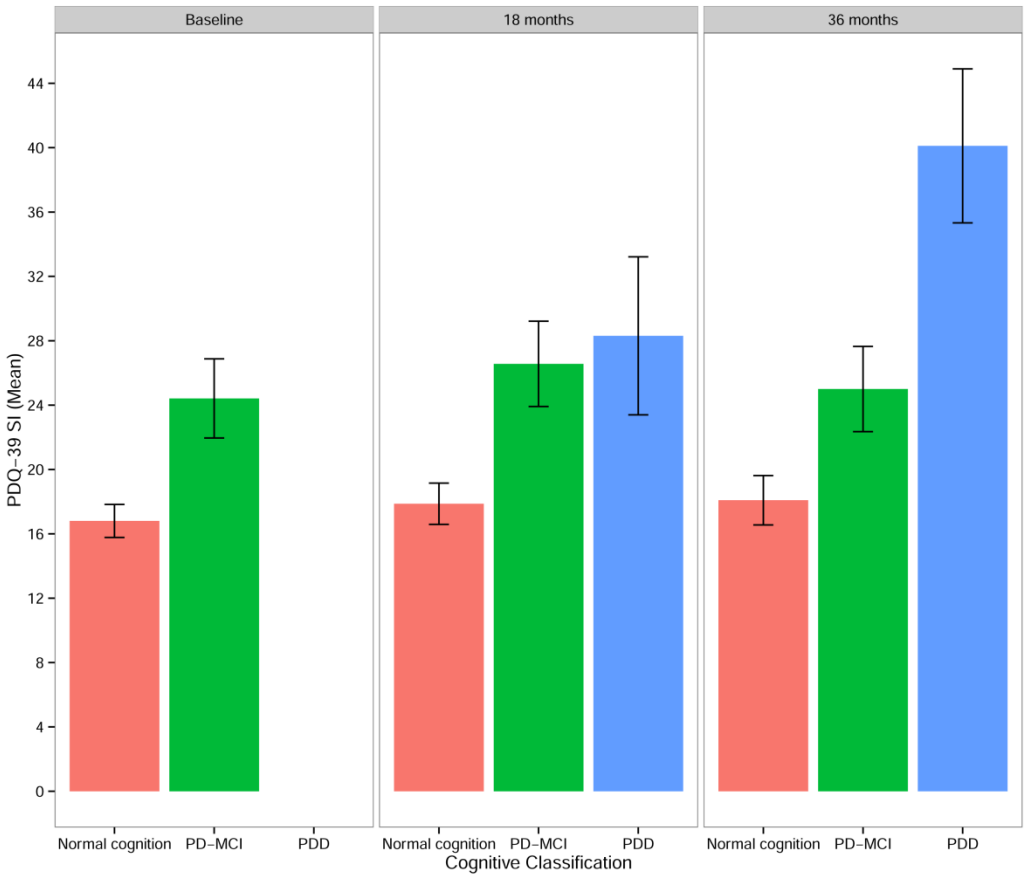
Post hoc Bonferroni p<0.0167; a = PD-NC vs. PD-MCI, b = PD-NC vs. PDD, c = PD-MCI vs. PDD
NART = National Adult Reading Test, UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LED = Levodopa equivalent dose, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, GDS-15 = Geriatric Depression Score, NPI = Neuropsychiatric Inventory, PDQ-39 = Parkinson's Disease Questionnaire, PoA = Power of attention, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, OTS = One Touch Stockings.

Post-hoc analysis showed that at 18 months participants with PD-MCI or PDD were significantly older than those with normal cognition, had lower premorbid IQ (NART), more severe disease and scored lower in all neuropsychological tests (p<0.001 for all) . Comparisons between neuropsychological tests between PD-MCI and PDD showed significant difference between tests of global cognition (MoCA and MMSE), attention (PoA and Digit Vigilance) and executive function (verbal fluency, OTS).

Mean PDQ-39 scores increased as cognitive impairment increased between PD-NC, PD-MCI and PDD (17.9±14.3, 26.6±18.9, 28.3±13.9) suggesting poorer QoL in those with

cognitive impairment. Between the groups there was a significant difference in QoL scores (p=0.006), which is illustrated in Figure 5-3. Post hoc analysis showed QoL was significantly poorer in those with PD-MCI compared to PD-NC (p<0.01), which was similar to the results reported in Chapter 4. However, there was no significant difference in the PDD group, quite possibly due to the small number of participants in this group (n=8).

Figure 5-3: Mean PDQ-39 scores with standard error between cognitive groups at baseline, 18 month and 36 month follow up



PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD= Parkinson's disease dementia, PDQ-39 = Parkinson's Disease Questionnaire Single Index.

At the 36 month evaluation, 158 (83%) PD participants returned and completed assessments; 10 participants did not complete the PDQ-39 questionnaire and were excluded from the 36 month cross-sectional analysis. Thus, the total number of evaluable participants at 36 months was 148. As indicated in Table 5-3, CDR data was unavailable for 27 participants due to data collection problems. Differences between participants with missing CDR data and those with data were examined graphically and analytically. Participants with missing CDR data were representative of the whole

sample, with no significant differences between groups at baseline for QoL, clinical data or neuropsychological tests. At 36 months, those with missing CDR data had less severe PD than those with CDR data (UPDRS III 27.4±14.6 vs 37.1±14.1, respectively, p<0.01) and scored better on PAL (1.5±0.5 vs 2.1±1.2, 0<0.05) but scored slightly higher for depression (GDS-15 4.1±2.0 vs 2.9±2.6, respectively, p<0.01). Power calculations determined that no significant power was lost as a result of missing CDR data (99.9% power for n= 158 vs 98.9% for n=121, α=0.05).

Table 5-3: Comparison of demographics, clinical and neuropsychological characteristics between cognitive groups: 36 month follow-up

	PD-NC (n=94)		PD-MCI (n=40)		PDD (n=14)		F/χ2	p	
	Mean	SD	Mean	SD	Mean	SD			
Age (years)	66.7	9.2	71.9	8.7	75.3	7.4	8.9	<0.001	a,b
Gender (male: n,%)	58	62	28	70	10	71	1.1	0.566	
Education (years)	13.5	3.5	11.9	2.9	12.1	3.9	11.6	0.003	a
NART	117.4	8.0	109.4	12.6	107.3	11.0	18.9	<0.001	a,b
UPDRS III Total	31.8	12.9	41.1	15.0	46.5	15.8	17.8	<0.001	a,b
Hoehn and Yahr stage	2.0	0.5	2.2	0.6	2.7	0.8	13.5	0.001	a,b
LED (mg/d)	511.2	290.5	588.4	297.5	493.1	239.9	1.1	0.585	
GDS-15	2.7	2.4	3.5	2.6	4.5	2.8	8.0	0.018	a,b
PDQ-39	18.1	14.9	25.0	16.8	40.1	17.9	21.2	<0.001	a,b,c
MoCA	27.3	2.4	23.8	3.2	19.6	4.3	55.7	<0.001	a,b,c
MMSE	28.8	1.4	27.4	2.4	24.4	3.4	33.4	<0.001	a,b,c
Verbal fluency	16.9	10.4	12.0	6.2	8.3	4.5	23.9	<0.001	a,b
Semantic fluency	24.4	7.6	18.9	6.3	12.6	5.8	33.8	<0.001	a,b,c
PoA†	1372.4	165.9	1654.9	491.8	1877.3	531.7	27.8	<0.001	a,b
Digit Vigilance†	96.5	5.9	85.8	10.8	65.9	18.7	47.6	<0.001	a,b,c
PRM	20.9	2.4	16.8	5.2	14.5	4.8	41.5	<0.001	a,b
SRM	15.4	1.8	11.8	3.9	11.8	2.1	47.6	<0.001	a,b
PAL	1.7	0.6	2.5	1.2	3.5	2.0	28.0	<0.001	a,b
OTS	16.0	2.6	9.2	5.8	3.7	4.1	58.9	<0.001	a,b,c

Post hoc Bonferroni p<0.0167; a = PD-NC vs. PD-MCI, b = PD-NC vs. PDD, c = PD-MCI vs. PDD
† For PoA and Digit Vigilance: PD-NC n=77, PD-MCI n=33, PDD n=11.
NART = National Adult Reading Test, UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LED = Levodopa equivalent dose, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, GDS-15 = Geriatric Depression Score, NPI = Neuropsychiatric Inventory, PDQ-39 = Parkinson's Disease Questionnaire, PoA = Power of attention, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, OTS = One Touch Stockings.

At the 36 month evaluation, a similar pattern was found to that of the 18 month results. Table 5-3 shows no significant difference between the three groups (PD-NC,

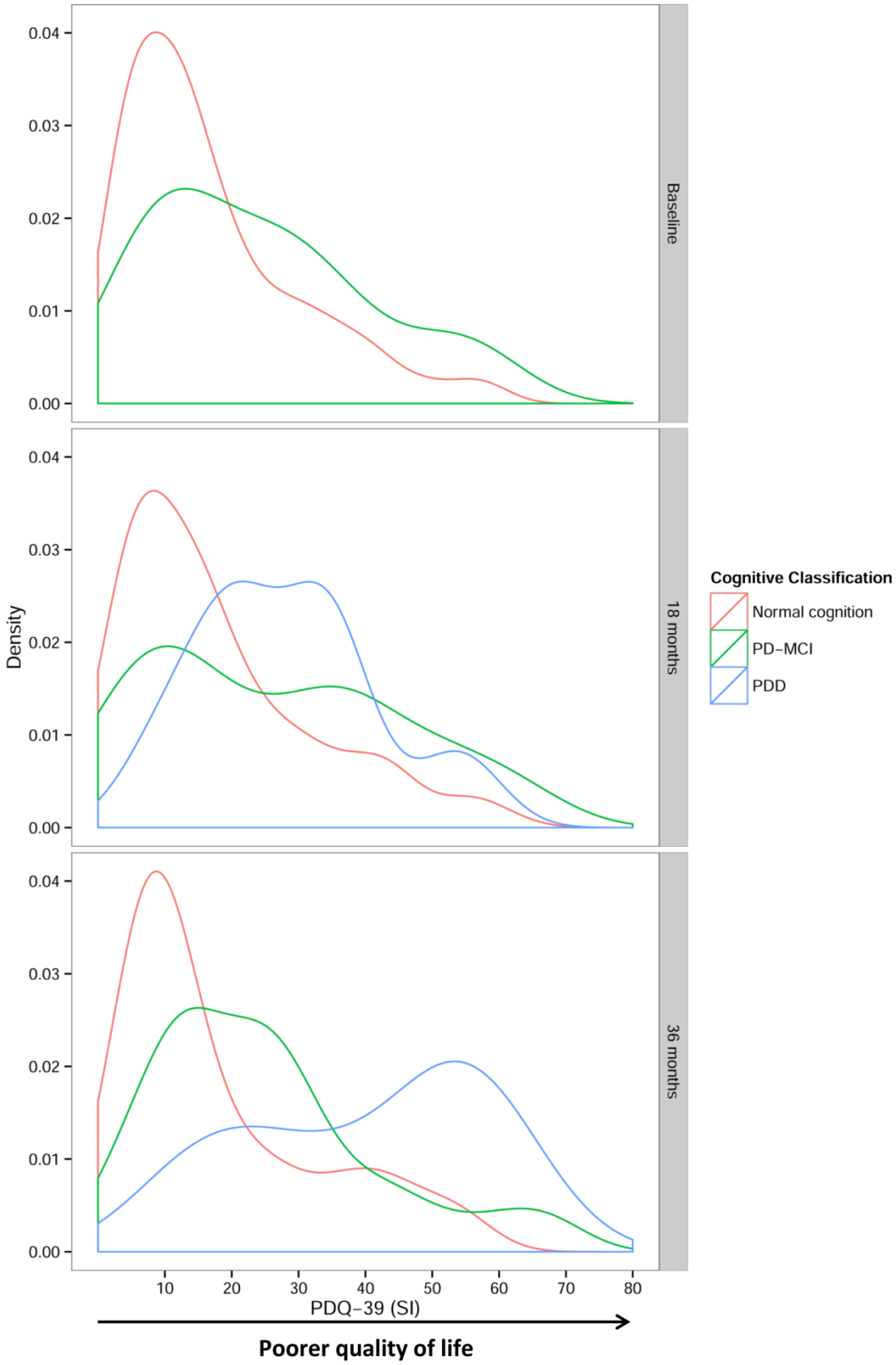
PD-MCI and PDD) in gender or LED score ($p>0.05$). The other clinical, neuropsychological and QoL measures were significantly different between the three groups ($p<0.05$ for all).

Post hoc analysis showed that at 36 months participants with PD-MCI or PDD were significantly older than those with normal cognition, had lower premorbid IQ (NART), more severe disease and scored lower in all neuropsychological tests ($p<0.001$ for all) . Comparisons between neuropsychological tests between PD-MCI and PDD showed significant difference between tests of global cognition (MoCA and MMSE), digit vigilance, semantic fluency and OTS ($p<0.01$ for all). This could suggest that these tests might be suitable to differentiate subtle differences between PD-MCI and PDD.

Again, PDQ-39 scores were significantly different between PD-NC, PD-MCI and PDD (18.1±14.9, 25.0±16.8, 40.1±17.9, respectively, $p<0.001$). Post-hoc analysis for three group comparisons showed that PDQ-39 scores significantly increased as cognitive impairment increased, as illustrated in Figure 5-3. Thus, both PD-MCI and PDD reported significantly poorer QoL compared to PD-NC ($\chi^2=2.7$, $p=0.007$; $\chi^2=-4.1$, $p<0.001$), with those with PDD reported poorer QoL compared to those with PD-MCI ($\chi^2=-2.5$, $p=0.012$).

The difference in the cross-sectional PDQ-39 between cognitive groups is more clearly illustrated by probability density distributions, which were plotted for PD-NC, PD-MCI and PDD at each time point (Figure 5-4). As highlighted in Chapter 4, the PDQ-39 score density curves, or probability density functions, of each cognitive group overlap. However, comparison of means tests determined that PDQ-39 scores were significantly higher in those with cognitive impairment. The density curves in Figure 5-4 show that at each time point a greater proportion of those with cognitive impairment were more likely to score highly on the PDQ-39, with those with PDD at 36 months reporting the poorest QoL. As time progressed, the graphs show that a greater proportion of people with PD and cognitive impairment were more likely to report poorer QoL compared to those with normal cognition, with a greater proportion of people with PDD reporting the poorest QoL.

Figure 5-4: Distribution of quality of life between cognitive groups at baseline, 18 months and 36 months



PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD= Parkinson's disease dementia, PDQ-39 = Parkinson's Disease Questionnaire Single Index.

Hierarchical regression was used to predict QoL at 18 month and 36 month follow up. Non-significant predictors were excluded using backward stepwise regression; age, sex, years of completed education, disease severity, LED, depression were included in the model. Significant predictors were then included; cognitive classification (PD-NC, PD-MCI, PDD) was then entered to produce a final model for that time point. MoCA score was added as it is a measure of global cognition that is frequently used in clinical settings.

Table 5-4: Regression models predicating quality of life: cross sectional analysis

	R	R2	Adj R2	Change Statistics			β	t	p
				ΔR2	ΔF	Sig. ΔF			
18 months									
Basic model	0.76	0.58	0.56	-	40.1	<0.001	-	-	-
Age	-	-	-	-	-	-	-0.3	-5.0	<0.001
Gender	-	-	-	-	-	-	0.1	2.8	0.006
UPDRS III	-	-	-	-	-	-	0.4	6.6	<0.001
GDS-15	-	-	-	-	-	-	0.5	9.0	<0.001
Education (years)	-	-	-	-	-	-	-0.1	-2.4	0.016
Cognitive classification	0.76	0.57	0.56	0.01	3.23	0.074	0.1	1.8	0.074
MoCA	0.76	0.58	0.56	0.02	7.48	0.007	-0.2	-2.7	0.007
36 months									
Basic model	0.78	0.61	0.59	-	43.9	<0.001	-	-	-
Age	-	-	-	-	-	-	-0.2	-3.0	0.004
Gender	-	-	-	-	-	-	0.1	2.4	0.020
UPDRS III	-	-	-	-	-	-	0.5	9.1	<0.001
GDS-15	-	-	-	-	-	-	0.4	7.4	<0.001
LED	-	-	-	-	-	-	0.1	2.3	0.022
Cognitive classification	0.80	0.64	0.62	0.03	11.2	0.001	0.2	3.3	0.001
MoCA	0.80	0.64	0.62	0.04	16.0	<0.001	-0.3	-4.0	<0.001

UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, GDS-15 = Geriatric Depression Score, LED = Levodopa equivalent dose, MoCA = Montreal Cognitive Assessment.

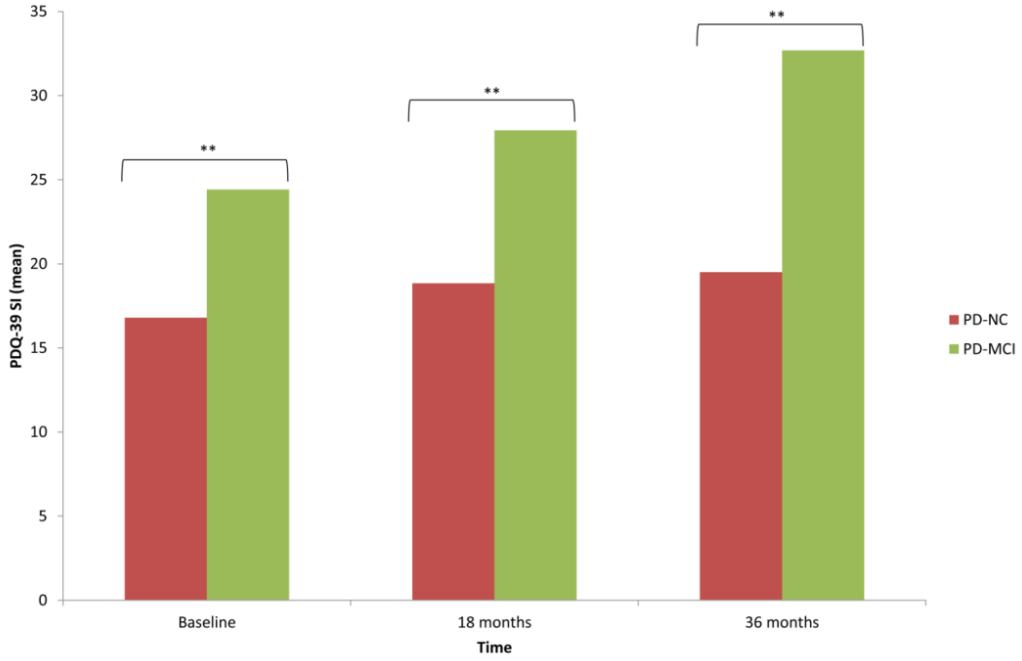
The model at 18 months showed that poorer QoL was predicted by younger age, being female, higher scores for motor severity, higher depression score and fewer years of education (Table 5-4). This model accounted for 56% of the variance in PDQ-39 scores (adjust R^2=056, p<0.001). Adding cognitive classification, using PD-MCI and PDD criteria, did not significantly improve the model (ΔR^2=0.01, p>0.05), whereas MoCA

score was a significant predictor although inputting this only improved the model by 2% (ΔR^2=0.02, p<0.01).

PDQ-39 scores at 36 months were predicted by age, gender, disease severity, depression and LED (Table 5-4), accounting for 59% of the variance (adjusted R^2=0.59, p=0.001). Both cognitive classification and MoCA scores were significant predictors of QoL at 36 months, accounting for 2.9% (ΔR^2=0.03, p<0.01) and 4.2% (ΔR^2=0.04, p<0.01) of the variance, respectively. This suggests that cognition has a small but significant additional effect on QoL that increases in strength as PD duration increases.

5.3.2 Longitudinal changes

Figure 5-5: Comparing quality of life from baseline to 18 month follow up using cognitive classification at baseline



*** p<0.01*
PDQ-39 = Parkinson's disease questionnaire, PD-NC = Normal cognition, PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off.

The longitudinal changes of the cohort were then examined. The mean paired score change for PDQ-39 SI scores between baseline and 36 months was 4.1±13.7 (Z=-4.1, p<0.001). This shows that as a single group of people with PD, QoL declined over time. Using baseline classification of cognition, PDQ-39 scores were compared over time as shown in Figure 5-5. Comparison between groups showed that baseline PD-MCI participants reported significantly poorer QoL scores than PD-NC participants at each time point (p<0.01) (Figure 5-5). Participants classified as PD-MCI at baseline reported

higher PDQ-39 scores over time (mean scores of 24.4±16.5 vs 27.9±18.2 vs 32.7±20.8, p<0.01), with a mean paired change of 9.1±15.0. This was compared to a mean paired change of 3.0±13.3 in PDQ-39 scores for those classified as PD-NC at baseline (χ^2=7.6, p<0.05). Thus, those with PD-MCI reported poorer QoL compared to those with normal cognition at baseline, and greater decline in QoL over time compared to PD-NC.

The effects of changes in cognitive classifications were then examined between the three time points. As shown above in Figure 5-2, the majority of participants were cognitively stable. Of the participants who showed change in cognition, the majority tended to decline cognitively, although some participants were classified as PD-NC after a previous classification of PD-MCI (4% at 18 months and 5% at 36 months), suggesting improvement in cognition. Changes in neuropsychological tests were then determined, as shown in Table 5-5. From baseline to 36 month evaluation, only MMSE, SRM, PoA and OTS demonstrated significant decline (p<0.01 for all), while verbal fluency significantly improved (p<0.01). All other scores showed no significant changes.

Table 5-5: Changes in neuropsychological tests: from baseline to 36 month follow up

	Baseline		18 months		36 months		Paired Differences (36 months - Baseline)					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	95% CI		Z	p
									Lower	Upper		
MoCA	25.5	3.5	26.1	3.6	25.7	3.8	0.2	2.9	-0.3	0.7	-0.6	0.524
MMSE	28.7	1.3	28.4	1.7	28.1	2.3	-0.7	1.9	-1.0	-0.3	-3.8	<0.001
Verbal fluency	11.8	4.7	12.9	4.8	14.4	9.3	2.6	7.8	1.3	3.8	-4.3	<0.001
Semantic fluency	21.2	6.6	21.5	6.9	21.5	8.1	-0.4	6.8	-1.5	0.6	-1.3	0.184
PoA†	1375.2	233.1	1426.4	226.6	1507.6	387.4	141.9	270.3	93.6	190.1	-6.9	<0.001
Digit Vigilance†	92.2	12.9	91.5	12.6	90.8	12.8	-2.1	11.9	-4.2	0.0	-1.6	0.104
PRM	19.6	3.2	19.8	2.8	19.4	4.2	-0.7	3.6	-1.3	-0.1	-1.8	0.069
SRM	15.3	2.2	14.7	2.6	14.2	3.0	-1.3	3.2	-1.8	-0.7	-4.6	<0.001
PAL	2.0	0.8	2.2	1.3	2.0	1.1	0.1	0.9	0.0	0.2	-1.7	0.085
OTS	14.6	4.1	14.4	4.8	13.3	5.6	-1.6	4.4	-2.3	-0.8	-3.6	<0.001

n=148, † n=121 for PoA and Digit Vigilance
CI = Confidence interval, SD = standard deviation, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination,, PoA = Power of attention, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, OTS = One Touch Stockings.

5.3.3 Principal component analysis

Table 5-6: Factor loadings based on principal component analysis with oblimin rotation

	Component		
	Memory/ Executive function factor	**Attention factor**	**Global cognition factor**
PAL	-0.81		
PRM	0.78		
SRM	0.72		
OTS	0.70		
PoA		0.87	
Digit Vigilance		-0.81	
Verbal fluency			0.83
MMSE			0.64
MoCA			0.63
Semantic fluency			0.55

MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, PoA = Power of attention, PRM = Paired Recognition Memory, SRM = Spatial Recognition Memory, PAL = Paired Associated Learning, OTS = One Touch Stockings.

The number of neuropsychological tests in the cognitive assessment battery and the change in cognitive classification of participants between time points posed a challenge in terms of how to best measure change and predict QoL. Thus, principal component analysis (PCA) was used to identify patterns or underlying structure of the data that explained the most variance; this was then used to reduce the data set into its principal components. Table 5-6 shows the factor loadings of the neuropsychological tests using an oblimin rotation after performing PCA using the baseline data. Three principal components or factors were identified: Memory/Executive function, Attention and Global cognition; these principal components accounted for 62% of the variance (40%, 12% and 10%, respectively, for each component) of baseline cognition. Factor scores were then calculated using the component score coefficient matrix at baseline, 18 months and 36 months. Attention scores were multiplied by minus 1 to aid interpretation with other factor scores; thus lower scores indicated poorer cognitive function in each factor score.

The change in PCA factor scores across time points was then examined. The mean and standard deviation for all participants is shown in Table 5-7. The results showed a small but significant difference between baseline and 36 months factor scores for

Memory/Executive function (χ^2=7.0, p=0.031). There was no significant change in Attention (χ^2=0.1, p=0.93) or Global cognition (χ^2=4.8, p=0.09) factor scores between baseline and 36 months. Paired change scores (between baseline and 36 months) showed that participants tended to decline over time (Memory/Executive function mean paired change = -0.18±0.66, Attention mean paired change = -0.01±0.65, and Global cognition mean paired change = -0.01±0.67).

Table 5-7: Mean and standard deviation of factor scores at baseline, 18 month and 36 months

	Baseline		18 months		36 months		χ^2	p
	Mean	SD	Mean	SD	Mean	SD		
Memory/Executive function	-0.01	0.99	0.01	1.02	-0.08	1.08	7.0	0.031
Attention	-0.02	1.04	0.03	0.95	0.02	1.06	0.1	0.929
Global cognition	0.06	0.97	0.05	1.01	0.02	1.01	4.8	0.090

SD = Standard deviation

Table 5-8: Correlations of PDQ-39 with cognitive factor scores at baseline, 18 months and 36 months

	Baseline (n=175)		18 months (n=175)		36 months (n=118)	
	ρ	p	*ρ*	p	*ρ*	p
Memory/Executive function	-0.11	0.157	**-0.27**	**<0.001**	**-0.50**	**<0.001**
Attention	**-0.21**	**0.006**	-0.20	0.010	-**0.42**	**<0.001**
Global cognition	-0.10	0.203	**-0.29**	**<0.001**	**-0.37**	**<0.001**

ρ = Spearman's Rho correlation coefficient
Bonferroni correction p<0.0056 for 9 comparisons highlighted in bold

To explore the relationship between QoL and cognition further, Spearman's correlations were performed between PDQ-39 scores and factor scores calculated from the PCA analysis at each time point (Table 5-8). The results show that at baseline there was a weak but significant association between PDQ-39 and the Attention factor score (ρ=-0.21, p<0.01) after Bonferroni corrections were applied. At 18 months, weak but significant correlations were observed between QoL and Memory/Executive function (ρ=-0.27, p<0.001) and Global cognition (ρ=-0.29, p<0.001); Attention was also significantly correlated but not after Bonferroni corrections were applied (ρ=-0.20, p<0.05). At 36 months, the correlation of PDQ-39 scores with Memory/Executive function (ρ=-0.50, p<0.001), Attention (ρ=-0.42, p<0.001) and Global cognition (ρ=-0.39, p<0.001) are stronger, with Memory/Executive function reaching moderate

correlations. Thus at 36 months, the correlation coefficients (ρ) increased across most factors. This could suggest that the relationship between QoL and cognition may strengthen over time, with poorer cognitive scores indicating poorer QoL.

5.3.4 Do baseline measures of cognition predict quality of life at 36 months?

Hierarchical regression was used to explore whether QoL at 36 months could be predicted using baseline data. Backwards stepwise regression was used to determine a basic model of predictors using: age, sex, years of completed education, disease severity, LED and depression. Non-significant predictors were excluded. Significant predictors were then included and measures of cognition entered to produce a final model. The characteristics of the basic model are shown in Table 5-9. The model showed that baseline characteristics accounted for 30% of the variance of PDQ-39 SI score at 36 months (adjusted R^2=0.30, F=21.9, p<0.001). The model showed that fewer years in education, higher disease severity and higher depression scores at baseline were significant predictors of poorer QoL 36 months later (p<0.05 for all).

Table 5-9: Baseline predictors of quality of life (PDQ-39) at 36 month follow up: basic model

	β	t	p	95% CI for β	
				Lower Bound	Upper Bound
Education (Years)	-0.17	-2.42	0.017	-1.50	-0.15
Baseline UPDRS III	0.32	4.26	0.000	0.27	0.75
Baseline GDS-15	0.32	4.30	0.000	1.12	3.02

R=0.56; R^2=0.32; Adjusted R^2=0.30; F=21.9, p<0.001
UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, GDS-15 = Geriatric Depression Score.

Measures of cognition were then added to determine whether baseline cognitive impairment could improve the prediction of QoL at 36 months. Three measures of cognition were used: baseline MoCA score as a measure of global cognition, commonly used in clinical settings; cognitive classification as PD-NC, PD-MCI defined as 2 SD below normative cut offs and PDD; and the factor scores from the PCA analysis for Memory/Executive function, Attention and Global cognition.

Table 5-10 shows that adding baseline MoCA scores to the basic model (as shown in Table 5-9) significantly improved the model by 3% (ΔR^2=0.03, p<0.05). Adding baseline

PD-MCI instead accounted for 4% of the total variance of PDQ-39 scores at 36 months (ΔR^2=0.04, p<0.01), which was also significant.

In contrast, adding the baseline factor scores accounted for the largest percentage change, accounting for 13% of the variance of QoL at 36 months (ΔR^2=0.13, p<0.001). As shown in Table 5-10, only the Attention factor was significant (t=2.27, p<0.001). Thus, baseline factors for Memory/Executive function and Global cognition were not significant predictors of future QoL. The regression model with only the Attention factor added to the basic model increased the explained variance by 11% (ΔR^2=0.11, p<0.001). These results suggest that cognitive impairment at baseline, assessed using MoCA scores or the presence of PD-MCI, is a significant predictor of poorer QoL 36 months from diagnosis and can be identified; however, baseline attentional deficits may be the strongest predictor of long term QoL.

Table 5-10: Regression coefficients and model fit of baseline cognitive predictors of quality of life at 36 months

Predictors in model	β	t	p	95% CI for β		R	R^2	Adj R2	Std. Error	Δ R^2
				Lower Bound	Upper Bound					
Baseline MoCA	-0.17	-2.27	0.025	-1.6	-0.11	0.58	0.33	0.31	14.11	0.03
Baseline PD-MCI 2 SD	0.2	2.91	0.004	2.86	14.95	0.6	0.35	0.34	13.7	0.04
Baseline factor scores	-	-	-	-	-	0.64	0.41	0.38	13.36	0.13
Baseline Memory/Executive function factor score	-0.11	-1.28	0.203	-5.4	1.16	-	-	-	-	-
Baseline Attention factor score	-0.3	3.64	<0.001	2.27	7.68	-	-	-	-	-
Baseline Global cognition factor score	-0.09	-1.03	0.305	-4.8	1.52	-	-	-	-	-
Baseline Attention factor score	-0.35	4.48	<0.001	3.26	8.42	0.63	0.39	0.37	13.5	0.11

MoCA = Montreal Cognitive Assessment, PD-MCI 2 SD = PD-MCI classified using the Movement Disorder Society with 2 standard deviation (SD) cut off

5.3.5 Predicting quality of life: longitudinal analysis

To investigate whether cognition was related to changes in QoL over 36 months, linear mixed effects modelling was used. All 212 participants were included in the model. A reduced basic model was determined by including: age, gender, years of completed

education, LED, UPDRS III score, GDS-15 score, NPI-D total, time, time x UPDRS, time x GDS-15, time x LED and time x UPDRS III; non-significant predictors were excluded from the final model. Significant predictors of longitudinal QoL (PDQ-39 SI scores) across the three time points are shown in Table 5-11. The model shows that being female, having spent fewer years in education, being of younger age and having a higher LED predicted poorer QoL. The model also shows that persistent depression was a significant predictor of poorer QoL. Decreasing PD severity over time, but not cross-sectional disease severity, predicted decreasing QoL (β=0.2, $p<0.001$ vs β=0.1, $p>0.05$, respectively). Interestingly, the model suggested that time predicted improved QoL (β=-3.5, $p<0.01$).

Table 5-11: Significant predictors of longitudinal quality of life: basic model using linear mixed effects

	β	Std. Error	t	p	
Gender (Female)	3.7	1.3	2.7	0.007	**
Education (Years)	-0.7	0.2	-3.6	0.000	***
Age	-0.3	0.1	-4.4	0.000	***
LED	0.02	0.0	3.8	0.000	***
GDS-15	3.3	0.4	8.2	0.000	***
Time (Assessment)	-3.5	1.3	-2.6	0.009	**
UPDRS III	0.1	0.1	0.3	0.785	
Time x UPDRS III	0.2	0.0	5.1	0.000	***
Time x GDS-15	-1.1	0.1	-8.2	0.000	***

** p<0.05, ** p<0.01, *** p<0.001*
GDS-15 = Geriatric Depression Score, UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LED = Levodopa equivalent dose.

Cognitive scores and their interaction with time were individually added to the basic model (Table 5-12). MoCA scores over time but not cross-sectional MoCA scores significantly predicted greater decline in QoL. Having a classification of PD-MCI or PDD at a particular time point were not significant predictors of QoL. However, the interaction of PDD over time, but not PD-MCI over time, was a significant predictor of decreasing QoL scores (β=10.3, $p<0.05$ vs β=0.0, $p>0.05$, respectively). This could suggest that developing PDD over time significantly reduces an individual's QoL. Adding the factor scores for Memory/Executive function, Attention and Global cognition did not significantly predict cross-sectional QoL at all time points. However, changes in Attention over time were significant predictors of decreasing QoL (β=-2.3,

p<0.001). This could suggest that cognitive decline in Attention is predictive of decline of QoL in people with PD.

Table 5-12: Summary of the association of measures of cognition with quality of life using linear mixed effects modelling

	β	Std. Error	t	p	
MoCA	0.2	0.3	0.8	0.448	
Time x MoCA	-0.4	0.1	-3.1	0.002	**
PD-MCI (2 SD)	2.1	2.6	0.8	0.433	
PDD	-16.6	10.9	-1.5	0.129	
Time x PD-MCI (2 SD)	0.0	1.2	0.0	0.973	
Time x PDD	10.3	4.0	2.6	0.011	*
Memory/executive function (Factor score)	1.0	1.3	0.7	0.457	
Attention (Factor score)	1.9	1.3	1.5	0.130	
Global Cognition (Factor score)	0.1	1.3	0.0	0.971	
Time x Memory/executive function (Factor score)	-1.1	0.6	-1.6	0.107	
Time x Attention (Factor score)	-2.3	0.7	-3.5	<0.001	***
Time x Global Cognition (Factor score)	-0.4	0.6	-0.7	0.492	

** p<0.05, ** p<0.01, *** p<0.001*
MoCA = Montreal Cognitive Assessment, PD-MCI 2 SD = PD-MCI classified using the Movement Disorder Society with 2 standard deviation (SD) cut off, PDD = Parkinson's disease dementia

Log-likelihood ratio tests were used to determine whether these three models were an improved fit compared to the basic model when measures for cognition were added. All three models significantly improved the fit of the model compared to the basic model (MoCA: χ^2=228.5, p<0.001; cognitive classification: χ^2=32.0, p<0.001; PCA factors: χ^2=610.7, p<0.001). Fits between the three models were then compared using log-likelihood ratio tests to examine which of the three measures of cognition produced the model with the best fit. The model which measured cognition using the factor scores from the PCA analysis was a significantly better fit compared to MoCA or cognitive classification (χ^2=578.8, p<0.001). Therefore, changes in Attention may be more accurate in predicting poorer long term QoL compared to MoCA scores or a cognitive classification.

5.4 Discussion

This study has shown that cognitive impairment does contribute to longitudinal QoL in people with PD. Between baseline and 36 month evaluation, participants with PD-MCI at diagnosis reported a mean increase of nine points in PDQ-39 scores, indicating QoL worsened over time. This magnitude of change has been shown to be clinically significant (Peto *et al.*, 2001; Clarke *et al.*, 2009). This is in comparison with smaller increases in QoL scores (three points) over time in participants classified as PD-NC at baseline, with a degree of change felt to not be clinically meaningful (Clarke *et al.*, 2009). Moreover, baseline PD-MCI was a predictor of QoL at 36 months. In another longitudinal study, albeit with a shorter duration of follow-up, baseline cognitive impairment was also a significant predictor of future poorer QoL (Visser *et al.*, 2009). This suggests that those with PD-MCI at time of diagnosis would be more likely to experience a clinically meaningful decline in QoL over time.

Additionally, cognitive impairment, using cognitive classification (PD-NC, PD-MCI, PDD), MoCA scores or factor scores of principal components, predicted future poorer QoL in newly diagnosed people with PD. Multilevel modelling showed that declining MoCA scores over time was a significant predictor of decreasing QoL. In addition, MoCA was found to be a consistent predictor of QoL, both as a baseline predictor of future QoL and on cross-sectional analysis, although the percentage of the variance explained was small. The MoCA is a frequently used clinical measurement of global cognition as it is quick and simple to administer (Zadikoff *et al.*, 2008). Furthermore, it may be more sensitive to cognitive impairment in PD that other brief cognitive tests, such as the MMSE (Hoops *et al.*, 2009; Litvan *et al.*, 2012). Therefore, the predictive value of lower MoCA scores as an indicator of poorer QoL in the future could potentially be useful to clinicians in terms of QoL, trajectory and anticipating future difficulties for the person with PD.

However, greater predictive accuracy may come from the use of more specific cognitive assessments. The use of PCA enabled the analysis of clusters of cognitive tests in relation to QoL. The results showed that decline in factor scores for attention were significant predictors of declining QoL and had a stronger predictive power compared to MoCA over time or cognitive classification over time. Baseline attention

factor scores were also significant predictors of QoL at 36 months and accounted for the largest change in variance between models. This is an important result as few studies have evaluated what domains of cognitive impairment have an impact on QoL. Combinations of deficits in attention, memory and executive function negatively impacting on QoL have been suggested by previous studies (Klepac *et al.*, 2008; Barone *et al.*, 2009). Deficits in executive function may also contribute to instrumental ADL functions (Cahn *et al.*, 1998), where preparation of meals, correctly taking medication and handling finances require better executive functioning (Klepac *et al.*, 2008). Activities of daily living (ADL) have been shown to be important in QoL in PD (Jenkinson *et al.*, 1997b; Lawrence *et al.*, 2014).

Interestingly, attention was the only significant predictor of the principal components of cognition of poorer QoL, both at baseline and longitudinal analysis, but there is a paucity of research in this area. Klepac *et al.* (2008) found that poorer visual attention/memory was associated with poorer QoL, while another study also found participants with attention/memory deficits to report poorer PDQ-39 scores (Barone *et al.*, 2009). However, neither study looked at attention as an isolated cognitive domain. One study found that attentional deficits in PDD were significantly detrimental to both basic and instrumental ADL, which included physical functioning and social interactions (Bronnick *et al.*, 2006). Another study in participants with dementia with Lewy bodies (DLB) found fluctuations in attention were associated with significantly impaired ADLs (Ballard *et al.*, 2001b). As DLB and PDD have many similarities, and may even be part of the same spectrum of disease, there may be a similar impact of attention on QoL in PD.

The cross-sectional results showed a similar pattern of results reported in Chapter 4, where QoL decreased as cognitive impairment increased between groups, such that those classified as PD-NC reported better QoL to those with PD-MCI, and those with PD-MCI had reported better QoL than those with PDD. This was particularly evident at 36 months where significant differences were observed between all three groups and the differences in QoL between the groups were more pronounced. This is further evidence of a transition effect between those with PD-MCI experiencing worse QoL as they convert to PDD (Williams-Gray et al., 2009). This finding also supports the findings of Leroi et al. (2012b), which compared QoL between participants with PD-NC, PD-MCI

(MDS Level I criteria (Litvan et al., 2012)) and PDD. The authors reported that as cognitive impairment increased, QoL became more impaired across the three groups, although only PDD QoL was significantly poorer.

There was an interaction effect with PDD over time as a significant predictor of poorer QoL, but not with PD-MCI over time. This could reflect that those who develop PDD over the 36 month assessment period are the participants who experience a more rapid decline in QoL compared to those with PD-MCI. Thus, the extent of impairment is the important aspect of reduced QoL due to the impact of dementia on functional ADLs, which is part of the diagnostic criteria for PDD (Emre *et al.*, 2007; Leroi *et al.*, 2012b).

It could also reflect the instability of PD-MCI where some participants improved between time points and were later classified as having normal cognition. Koepsell *et al.* (2013) found that in non-PD populations, diagnosis of MCI was unstable compared to diagnosis of dementia in a longitudinal multi-centre study. Similarly, a recent retrospective study found that 25% of participants classified as multi-domain PD-MCI were later re-classified as having normal cognition at longitudinal evaluation (Loftus *et al.*, 2015). The authors suggest that these subjects who change classification from PD-MCI to PD-NC may therefore appear to have "recovered" from having PD-MCI; however, this may not be the case and instead it may be evidence of the instability of PD-MCI, or may be the result of false-positive results.

Consistent with the baseline findings in Chapter 4, younger age, higher depression scores and increased disease severity were associated with poorer QoL, both in cross-sectional and longitudinal analysis. This is consistent with previous studies (Schrag *et al.*, 2000; Schrag *et al.*, 2003; Soh *et al.*, 2011; Leonardi *et al.*, 2012; Santos-Garcia and de la Fuente-Fernandez, 2013; Kudlicka *et al.*, 2014). Interestingly, being female predicted having poorer QoL, as did increased LED score, while years in education seemed to be a protective factor. Several other studies have also reported that pre-morbid IQ and increased number of years of education have predicted better QoL (Cubo *et al.*, 2002; Bronnick *et al.*, 2006; Klepac *et al.*, 2008). This could possibly be indicative of the role of education and IQ in cognitive reserve having a protective role (Armstrong *et al.*, 2012). Gender as a predictor of QoL has led to mixed findings in the

literature with better QoL being reported in males, females or no significant differences all reported (Schrag *et al.*, 2000; Marras *et al.*, 2004; Behari *et al.*, 2005; Heller *et al.*, 2014; Lubomski *et al.*, 2014). Therefore, gender differences in QoL scores may be due to social and cultural contexts (Behari *et al.*, 2005).

Interestingly, increasing time as a variable predicted improved QoL scores. This could indicate a degree of successful adjustment and coping. It has been suggested that after a chronic disease has been diagnosed the individual has new stressors to deal with. For people with PD there are motor and non-motor symptoms to cope with, as well as psychosocial stressors, which challenge habitual coping mechanisms and negatively impact on QoL (Lazarus and Folkman, 1984; Stanton *et al.*, 2007; de Ridder *et al.*, 2008). However, post-diagnosis adjustment theories suggest that people with chronic illnesses often find a new balance or equilibrium to their lives (de Ridder *et al.*, 2008) and may return to a state of QoL similar to before the chronic illness began (Moos and Holahan, 2007; Moss-Morris, 2013). Thus, the results of this study could indicate successful adjustment to PD in the absence of new stressors.

This study has several strengths which include the large cohort of newly diagnosed PD participants and the range of validated instruments used to assess motor and non-motor symptoms, including a detailed schedule of neuropsychological tests, which were repeated at three time points. This enabled causal relationships to be explored. There was also a relatively small dropout rate, with only 11.8% of participants not returning at 18 months and an additional 18.4% of participants at 36 months. This is comparable to other longitudinal studies (Visser *et al.*, 2009; Williams-Gray *et al.*, 2009; Erro *et al.*, 2014; Hobson and Meara, 2015). As demonstrated in the results section, there were no significant differences between those who returned for 36 month evaluation and those who withdrew, were lost to follow-up or died. Mixed effects modelling enabled longitudinal evaluation of predictors of QoL, while accounting for missing data. This enabled data from all participants to be used. Furthermore, the use of principal component analysis enabled the analysis of constructs of cognition as contributors to QoL to be explored.

This study has several limitations. Firstly, as at baseline, the accurate classification of PD-MCI is challenging. As discussed in Chapter 4, this study pre-dated the MDS PD-MCI

criteria and is therefore limited in assessing language and visuospatial function. Secondly, although a high proportion of participants returned for 18 month and 36 month evaluation, it is possible that there was participation bias. Those who did not return for further evaluation may have been participants with a more rapid decline in PD, cognition and QoL and would therefore have been of particular interest to this study. However, differences in baseline scores were tested analytically and graphically and did not reveal any significant differences. In addition, the same assessment schedule was repeated at each time point for comparison and some participants improved in neuropsychological assessment scores. This could be due to a learning effect, to medication effects or normal fluctuations in cognition (Morris *et al.*, 1999; Hensel *et al.*, 2007; Yarnall *et al.*, 2013b). Our study used a time interval of 18 months between testing, which has been shown to be an appropriate length of time to negate practice effects (Stein *et al.*, 2010).

Finally, as with many longitudinal studies, missing data was a problem. The PDQ-39 questionnaire was not completed by seven participants at 18 months and 10 participants at 36 months, although four participants completed the PDQ-39 who did not at 18 months. Furthermore, at baseline 23 participants did not complete MoCA scores because this instrument was added at a later date, and 36 month CDR data was unavailable for 27 participants due to data collection problems. This reduced the statistical power of methods of analysis that require complete datasets, such as linear regression and PCA. Furthermore, the missing CDR data could have affected PD-MCI classification at 36 months with false-negative (Type I Error) classification of PD-NC in some participants. This was accounted for by the use of linear mixed effects modelling; this form of multilevel modelling has the ability to handle missing data and does not require full datasets (Verbeke *et al.*, 2009; Field *et al.*, 2012). Therefore, missing variables for individual participants at one or more time point did not "delete" all data for those participants.

In summary, this study has shown that there is a relationship between cognition and QoL. As per my original hypothesis, I found that baseline cognition and changes in cognition from baseline were significant predictors of poorer QoL at 36 months. The decline in QoL was clinically significant (Clarke *et al.*, 2009), whereas changes in participants classified as PD-NC did not show any clinically meaningful change in QoL. I

expected the presence of PD-MCI at each time point would negatively impact on QoL, however, the 18 month cross-sectional analysis and the mixed effects modelling did not show this. Therefore, it may be that decline in cognitive scores, particularly attention as suggested by the results here, or cognitive decline that affects ADLs contributes to poorer QoL, as in PDD, rather than mild cognitive impairment in itself.

This has implications for clinical practice. Clinicians may be able to use a brief test such as the MoCA to identify participants who are at risk of cognitive and functional decline. In addition, given the predictive value of attention in this study, research to devise a brief attentional task that could be used in a clinical setting could be very useful to clinicians. As attentional dysfunction was the most significant predictor of longitudinal QoL, interventions to improve concentration and attention could significantly improve QoL. Both pharmacological interventions, in the form of rivastigmine to improve attention and ADLs (Bronnick *et al.*, 2006; Mamikonyan *et al.*, 2015), and non-pharmacological interventions, such as cognitive rehabilitation focused on attention (Cerasa *et al.*, 2014), may be useful in improving cognition and therefore QoL in participants with attentional dysfunction. Further longitudinal studies are required to substantiate the findings of this study and to better evaluate the impact of treatments for attentional decline.

Chapter 6 Cognitive decline in Parkinson's disease: impact on quality of life of caregivers

6.1 Background

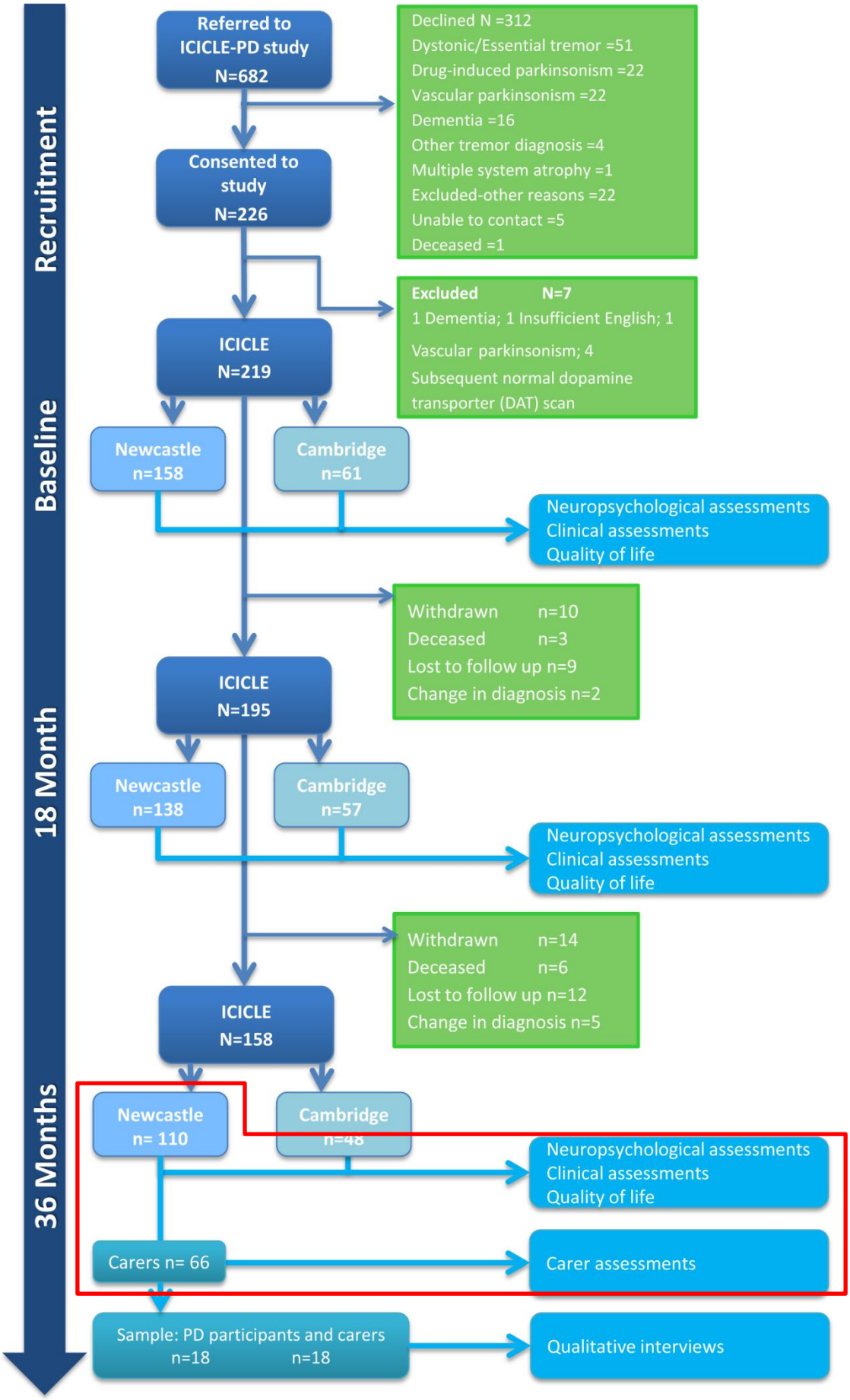
As discussed in Chapter 1, the quality of life (QoL) of informal caregivers of people with Parkinson's disease (PD) can be affected by the caring role (Rahman *et al.*, 2008). Factors that have been associated with poorer QoL in PD carers include: PD severity, PD and carer depression, burden of neuropsychiatric symptoms, reduced social activities, financial strain, perceived strain, physical health of carer and care recipient (Aarsland *et al.*, 1999; Schrag *et al.*, 2006; Leiknes *et al.*, 2010; Drutyte *et al.*, 2014; Oh *et al.*, 2015; Santos-Garcia and de la Fuente-Fernandez, 2015). However, it may be postulated that the QoL of carers of people with cognitive impairment in addition to PD may be poorer compared to those who care for a person with PD who is cognitively intact, if other factors are equal.

As outlined in Chapter 2, this work aimed to investigate whether carers of people with PD and cognitive impairment experienced worse QoL than carers of people with PD without cognitive impairment. I expected to find that carers would be typically female, spousal carers. I hypothesised that there would be a relationship between the QoL of people with PD and QoL of carers, where poorer QoL in one would be associated with poorer QoL of the other. Finally, I hypothesised that cognitive impairment in the care recipient would be detrimental to the QoL of the carer, with carers of people with PD dementia (PDD) reporting the poorest QoL.

6.2 Specific Methods

As shown in Figure 6-1, the methods and results in this chapter relate to the analysis of the 36 month follow up measures of PD participants and their carers from the Newcastle site of the ICICLE-PD study. The details of the assessments used in this study are described in Chapter 3. Carer assessments were introduced later to the study to investigate the wider effects of PD and cognitive impairment. Therefore, these assessments were not available at baseline or 18 month evaluation, although few participants at baseline had a carer.

Figure 6-1: Assessment schedule



6.3 Results

Table 6-1: Clinical and demographic characteristic of participants with and without carers

	No Carer (n=42)		Carer (n=66)		$t/Z/\chi^2$	p
	Mean	SD	Mean	SD		
Age (years)	66.1	10.6	71.3	9.0	-2.6	0.010
UPDRS III	37.5	14.7	39.6	12.4	-1.0	0.339
Hoehn and Yahr	2.2	0.4	2.2	0.5	0.0	0.984
GDS-15	2.7	2.7	2.9	2.4	-0.8	0.447
LED (mg/day)	499.1	305.5	526.3	258.8	-0.8	0.411
PDQ-39 SI	20.7	15.9	23.7	17.1	-0.9	0.363
MoCA	26.3	3.9	25.4	4.0	-1.7	0.095
MMSE	28.3	1.9	27.9	2.7	-0.1	0.887
	n	%	n	%	χ^2	p
Gender (male)	22	52	50	76	10.9	0.001
Marital status						
Married/living with partner	19	45	64	97	24.4	<0.001
Widowed	10	24	2	3	5.3	0.021
Divorced	6	14	0	0	-	-
Single	7	17	0	0	-	-
ADL, not independent	5	5	12	24	36	12.4
Cognitive classification						
PD-MCI	12	29	18	27	1.2	0.273
PDD	0	0	9	14	-	-

UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, GDS-15 = Geriatric Depression Score, LED = Levodopa equivalent dose, PDQ-39 SI = Parkinson's Disease Questionnaire Single Index Score, MoCA = Montreal Cognitive Assessment, MMSE = Mini Mental State Examination, NPI = Neuropsychiatric Inventory, ADL = Activities of Daily Living,, PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD = Parkinson's disease dementia.

As shown in Figure 6-1, 110 people with PD returned for 36 month evaluation at the Newcastle site. Of the returning PD participants, 60% (n=66) reported having an informal carer. Demographic differences in PD participants with and without carers were explored (Table 6-1). Participants with carers were significantly older than participants with no carers (71.1±9.0 vs. 66.1±10.5, respectively, p=0.01) and proportionally more were male (77% vs. 52%, respectively, p=0.01). There were no significant differences in PD with or without carers in terms of disease severity, depression scores, levodopa equivalent dose (LED), QoL score or global cognition (Table 6-1). There was also no significant difference in the proportion of mild cognitive impairment in PD (PD-MCI) between the two groups. However, all participants who

were diagnosed as PDD had a carer (although the total number was small, n = 9). Comparing demographic data (Table 6-1), 96% of PD participants with carers were married, which was significantly more than those with no carer (45%). Conversely, those without a carer included a higher proportion of widowed participants (24% vs. 3%, respectively, p=0.02), divorced participants (14% vs. 0%, respectively) and single participants (17% vs. 1 %, p=0.03). A significantly greater proportion of PD participants with a carer reported not being independent in activities of daily living (ADL); 37% compared to 12% of participants without a carer (p=0.01). Therefore, PD participants with an informal carer tended to be older, male, married and more likely to be dependent in ADLs.

6.3.1 Quality of life in carers

In total, data was collected from 66 carers; a small number of subjects did not complete all carer assessments and were coded as missing data (Table 6-2). For example, three participants could not complete the PDQ-Carer because it was introduced into the study at a later stage.

Table 6-2: Missing carer data

	Demographic data	PDQ-Carer	SQLC	HADS	NPI-D	OARS Physical health
Number missing	9	6	6	10	6	13
Reason for missing data	Introduced later in study (n=4), missing data (n=5)	Introduced later in study (n=3), missing data (n=3)	Missing data	Introduced later in study (n=7), missing data (n=3)	Missing data	Introduced later in study (n=7), missing data (n=6)

PDQ-Carer = Parkinson's Disease Questionnaires for Carers, SQLC = Scale of Quality of Life of Care-Givers, HADS = Hospital Anxiety and Depression Scale, NPI-D = Neuropsychiatric Inventory, OARS Physical Health = Older Americans Resources and Service Physical Health Checklist.

Table 6-3 shows carers had a mean age of 67±11.5 years with a range of 32 years to 85 years. Eighty-one percent of carers were female and 93% were spouses, with small percentages of carers being adult children (daughters, 3%), another relative (granddaughter, 2%) or a friend (3%). The majority of carers were retired (70%). Only 28% of carers had other caring responsibilities, which included children, grandchildren or another relative. Therefore, the "typical carer" profile was a woman in their late 60s and retired. They were married to men with PD in their early 70s who they had known

for over 40 years. They cared for their husbands over the last two years and spent around 50 hours per week as a caregiver.

Table 6-3: Carer demographic characteristics

	Mean	SD	I-Q Range
Carer age (Years)	67.1	11.5	14.0
Education (Years)	12.2	2.8	4
Years known participant	46.2	15.0	15
Time as a carer (months)	23.5	24.5	36
Hours per week as caregiver	50.5	69.1	108
	n	**%**	
Gender, female	55	81	
Relationship to PD			
Spouse or partner	63	93	
Daughter	2	3	
Other relative	1	2	
Friend	2	3	
Employment status, retired	41	70	
Other caregiving responsibilities	19	28	
Children	4	6	
Grandchildren	12	18	
Other relative	3	4	

n=57, SD = Standard deviation, I-Q = Inter-quartile range, PD = Parkinson's disease.

The QoL of carers, and possible contributing factors, was explored. QoL was measured by the PDQ-Carer single index score (SI, mean 20.2±18.6), where higher scores indicate poorer QoL, and the SQLC (mean 109.0±17.2) where lower scores suggest poorer QoL (Table 6-4). Mood disorders in carers were explored using the Hospital Anxiety and Depression Scale (HADS). Carers reported higher scores of anxiety compared to depression (mean HADS-A 5.0±4.4 vs. HADS-D 3.5±3.3), although the scores were below suggested cut-offs, with scores above seven indicating "possible" anxiety and depression (Bjelland *et al.*, 2002).

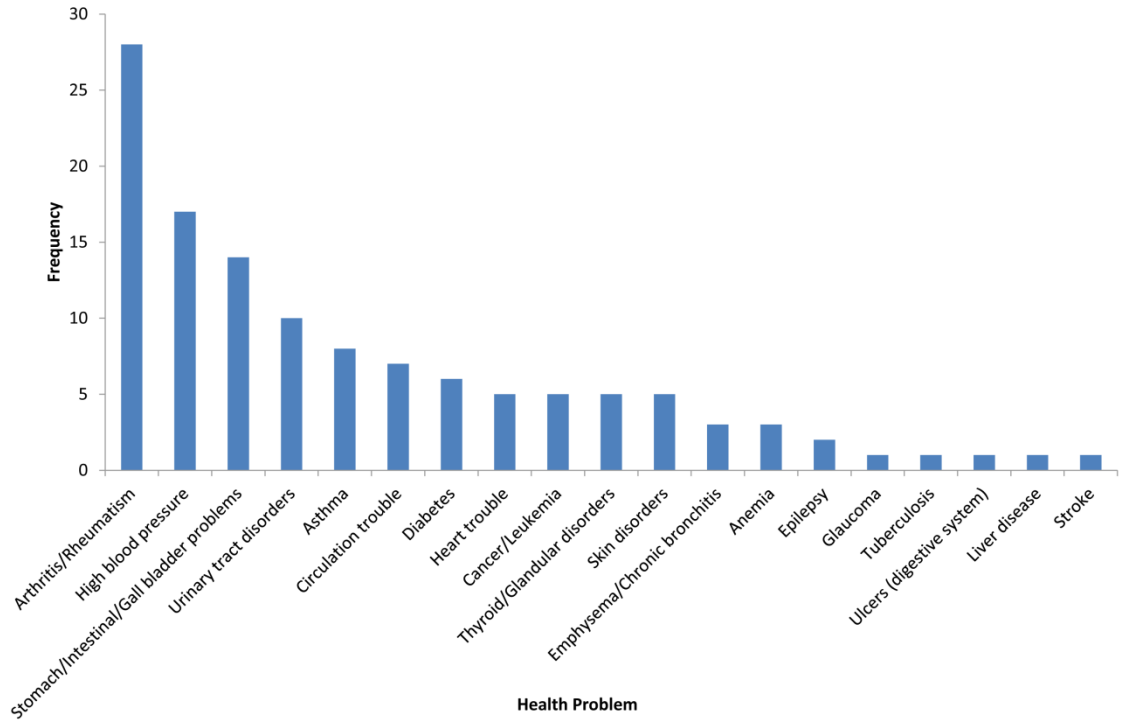
Table 6-4: Mean and standard deviation of carer quality of life questionnaires

	Mean	SD	Minimum	Maximum
PDQ-Carer SI	20.2	18.6	0	76
SQLC	109.9	17.2	51	135
HADS-A	5.0	4.4	0	17
HADS-D	3.5	3.3	0	12
NPI-D Total	9.2	9.9	0	41
NPI-D Carer distress total	4.7	5.5	0	23
Carer sleep quality (%)	59.5	23.3	5	100
Number of health problems†	1.9	1.8	0	10

PDQ-Carer SI = Parkinson's Disease Questionnaires for Carers Single Index, SQLC = Scale of Quality of Life of Care-Givers, HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale, HADS-D = Hospital Anxiety and Depression Scale – Depression subscale, NPI-D = Neuropsychiatric Inventory.
† From the Older Americans Resources and Service (OARS) Physical Health Checklist.

Using the OARS physical health checklist, the mean number of health problems reported by carers was 1.9±1.8. The majority of carers had one or two physical health problems, 38% and 25%, respectively. Only 15% (n=8) of carers reported no physical health problems. Frequencies of the reported health problems are shown in Figure 6-2, where arthritis or rheumatism were the most commonly reported health complaint, followed by high blood pressure and stomach, intestinal or gall bladder problems. The least common health problems included: glaucoma, tuberculosis, ulcers of the digestive system, liver disease and effects of stroke.

Figure 6-2: Frequency of health problems in carers



6.3.2 Cognitive impairment in Parkinson's disease and quality of life in carers

Consistent with the findings in previous chapters, PD-MCI at 2 SD was the cut-off used to classify PD-MCI. Participants were classified as PD-NC (n=39, 59%), PD-MCI (n=18, 27%) or PDD (n=9, 14%) using the neuropsychological data at 36 months. Table 6-5 shows the comparison of carer questionnaires based on the cognitive classification of the care recipient with PD. Comparisons using the PD cognitive classification did not show significant differences in age, carer anxiety, carer distress, carer sleep quality, carer physical health, neuropsychiatric problems in the person with PD or carer distress at neuropsychiatric symptoms ($p>0.05$ for all). However, NPI-D total score increased as cognitive impairment increased, but given the small number of participants in the PD-MCI and PDD groups there was likely to be a lack of sufficient power to detect subtle differences between groups.

Table 6-5: Comparison of carer questionnaires between cognitive groups

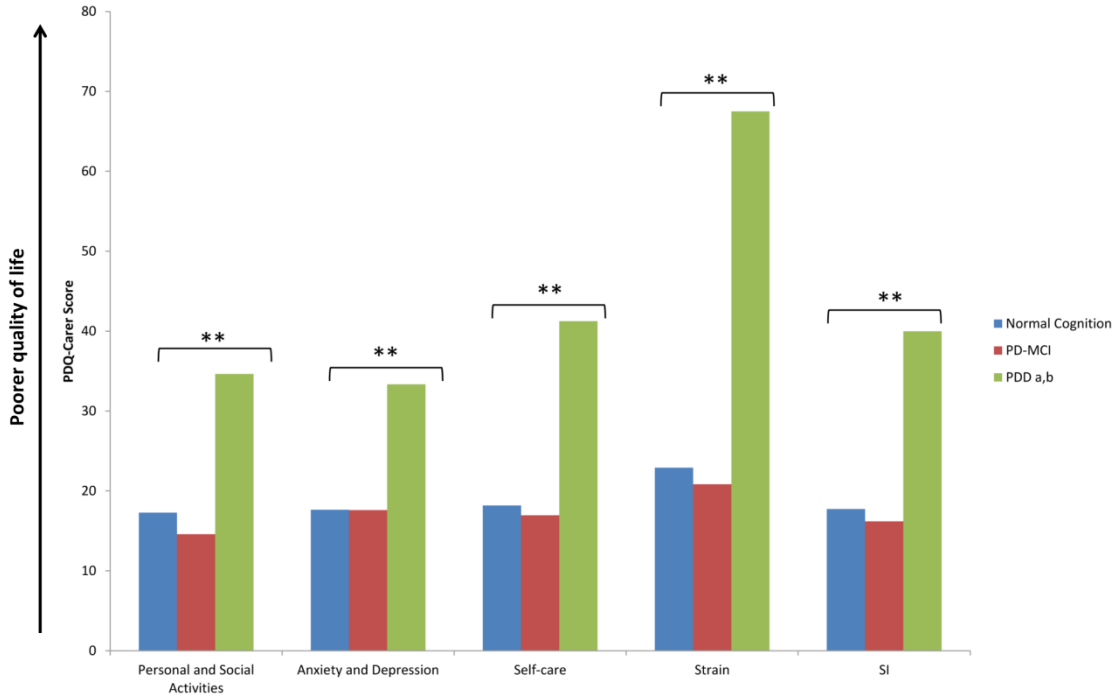
	Normal Cognition (n=39)		PD-MCI (n=18)		PDD (n=9)		X^2	p	
	Mean	SD	Mean	SD	Mean	SD			
Carer Age	65.7	13.6	70.2	6.5	67.3	11.2	0.8	0.672	
Time Caregiving (Hours/Week)	37.8	63.0	35.2	61.0	123.6	64.0	10.9	0.004	a,b
PDQ-Carer SI	17.7	16.6	16.2	17.0	40.0	20.3	9.0	0.011	a,b
SQLC	115.6	12.9	109.8	14.2	88.8	21.2	13.1	0.001	a,b
HADS-A	5.2	4.2	4.3	4.5	6.0	5.3	1.0	0.611	
HADS-D	3.2	2.7	3.1	3.9	6.3	3.8	4.8	0.092	
NPI Total	7.5	7.5	9.6	11.6	14.6	13.1	1.7	0.429	
NPI Carer distress total	4.0	4.3	5.1	6.6	6.8	6.9	1.0	0.645	
Sleep quality	60.6	21.3	60.9	24.9	52.8	23.3	0.6	0.757	
Total number health problems	2.0	2.0	1.9	1.8	1.6	1.5	0.3	0.880	

Post hoc Bonferroni correction for three group comparison at p< 0.0167; a = PD-NC vs. PD-PDDI; b= PD-MCI vs. PDD. PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD = Parkinson's disease dementia, SD = Standard deviation, PDQ-Carer SI = Parkinson's Disease Questionnaires for Carers Single Index, SQLC = Scale of Quality of Life of Care-Givers, HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale, HADS-D = Hospital Anxiety and Depression Scale – Depression subscale, NPI = Neuropsychiatric Inventory.

Only three variables reach significance between the three groups: hours per week caregiving, PDQ-Care SI and SQLC score ($p<0.05$ for all). Hours per week care giving was more than three times higher in carer of subjects with PDD compared to those caring for PD-NC or PD-MCI subjects (123.6±64.0 vs.37.8±63.0 vs. 35.2±61.0, $P<0.01$). Post hoc analysis, with Bonferroni correction for multiple comparisons, showed that

hours per week caregiving for PDD carers was significantly higher than both PD-MCI and PD-NC carers ($p<0.0167$ for both), but not between PD-NC and PD-MCI carers. A similar pattern of results was found for the QoL measures, where between group differences were significant ($p<0.05$ for both). Carers of PDD subjects reported significantly poorer QoL than PD-NC and PD-MCI carers for both the PDQ-Carer and the SQLC ($p<0.0167$ for both with Bonferroni correction). Again, post hoc analysis showed no significant differences between PD-NC carer scores and PD-MCI carer scores.

Figure 6-3: Comparison of carer quality of life scores between cognitive groups



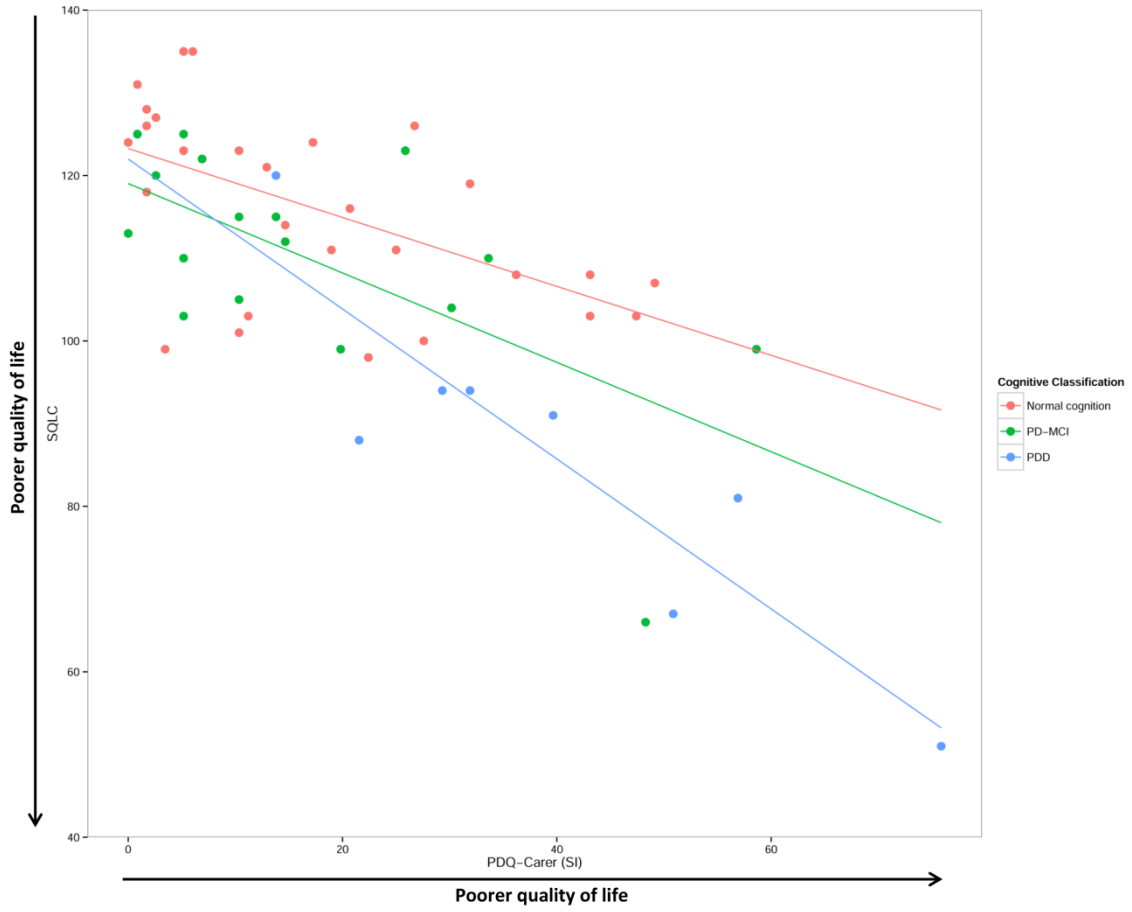
*** = p<0.01*
Post hoc Bonferroni correction for three group comparison at p< 0.0167; a = PD-NC vs. PDD; b = PD-MCI vs. PDD. PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD = Parkinson's disease dementia.

To investigate the differences between carers of different cognitive groups, the subscales of the PDQ-Carer were examined. Figure 6-3 shows significant differences between PD-NC, PD-MCI and PDD carers for each QoL subscale ($p<0.001$ for all). However, as with the previous measures, the PDD carers were the only group that reported significantly poorer QoL compared to the other two cognitive groups on each PDQ-Carer subscale ($p<0.0167$ for all). Increased strain scores were observed in all groups compared to the other sub-scores. However, the PDD carers reported the highest mean strain scores (67.5±29.6) compared to PD-NC carers (22.9±20.9) and PD-MCI carers (20.8±24.2, $p<0.01$ for all). Therefore, while PDD carers reported poorer

QoL in terms of personal and social activities, anxiety and depression and self-care, perceived strain may be the biggest contributor to poorer QoL scores.

6.3.3 Correlates of quality of life in carers

Figure 6-4: Scatter plot of PDQ-Carer scores vs. SQLC scores between cognitive groups



PD-MCI = Mild cognitive impairment in Parkinson's disease using the 2 standard deviation cut-off, PDD = Parkinson's disease dementia.

To further explore the relationship of carer QoL with PD and cognition, Spearman's rank correlations were used. First, the inter-correlations between the measures of carer QoL were determined. A moderately strong relationship was found between the PDQ-Carer score and carer anxiety (HADS-A; ρ=0.67, p<0.001), carer depression (HADS-D; ρ=0.66, p<0.001) and a weak relationship with carer rated sleep quality (ρ=-0.30, p<0.05). The SQLC was found to have a moderate relationship with carer depression (HADS-D; ρ=-0.38, p<0.01) and carer rated sleep quality (ρ=0.37, p<0.01), but not with carer anxiety (HADS-A; ρ=-0.28, p=0.051). Both measures of carer QoL, the PDQ-Carer and the SQLC were highly correlated with each other (ρ=-0.67, p<0.001). Figure 6-4

shows that carers of people with cognitive impairment consistently indicated poorer QoL in both measures compared to those with normal cognition.

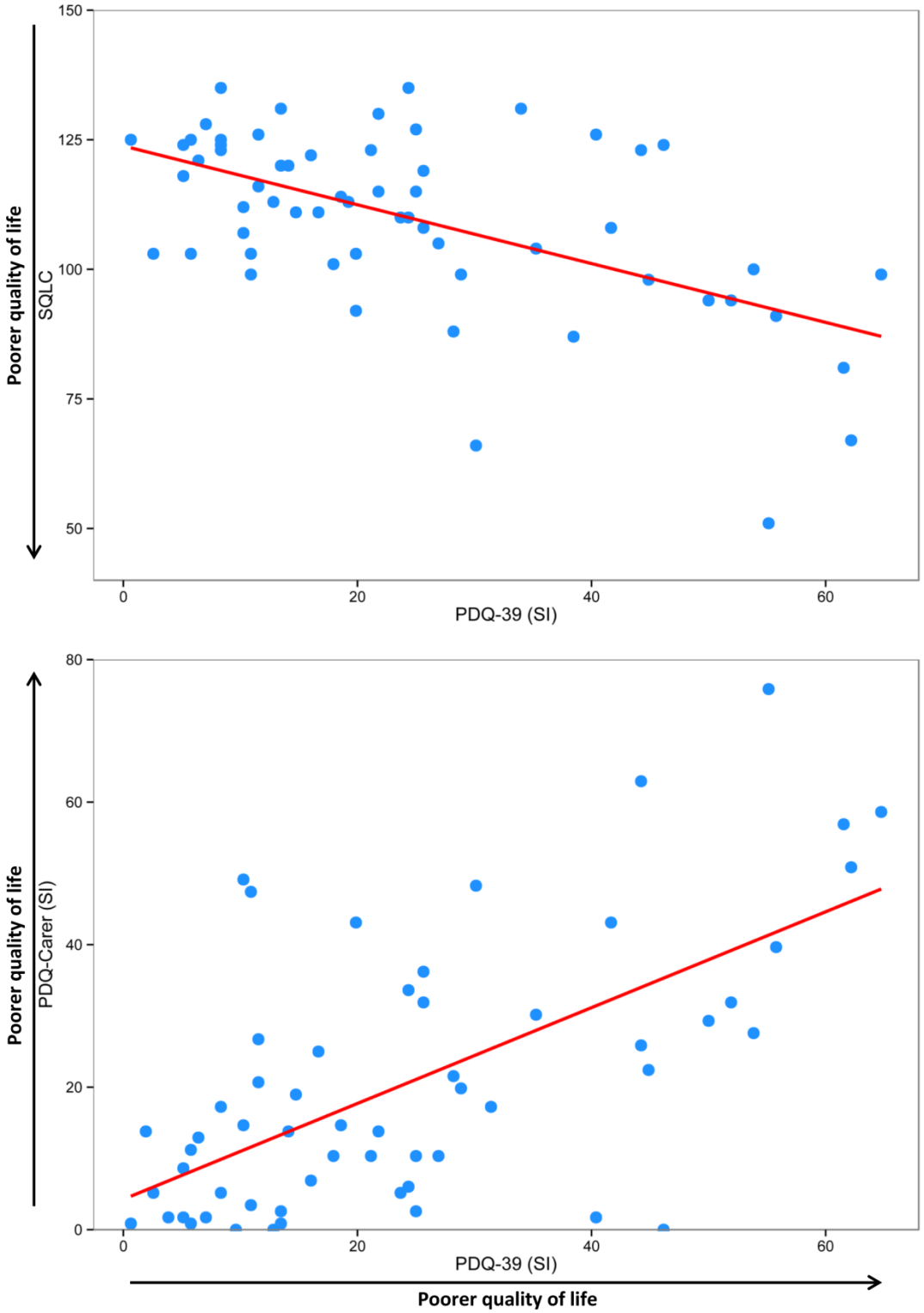
Table 6-6 shows correlations between measures of carer QoL and the clinical characteristics of the PD care recipient. After correcting for multiple comparisons, PD motor severity (UPRDS Part III) and neuropsychiatric symptoms (NPI) were significantly associated with carer QoL. Disease severity had the strongest association with both PDQ-Carer (ρ=0.56, p<0.001) and SQLC (ρ=-0.52 p<0.001), where carer QoL worsened with increasing PD motor severity. Neuropsychiatric symptoms were moderately correlated with PDQ-Carer (ρ=0.48, p<0.001) but not with SQLC (ρ=-0.17, p>0.05). Interestingly, the PDQ-Carer Strain sub-score had a moderate association with patient depression scores (GDS-15, ρ=0.43, p<0.001) and carer sleep quality was associated with neuropsychiatric symptom severity in patients (ρ=-0.51, p<0.001).

Table 6-6: Correlations between carer quality of life and clinical characteristics of the care recipient with Parkinson's disease

	PD Age		UPDRS III		LED		GDS-15		NPI Total	
	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
PDQ-Carer										
SI	0.11	0.421	**0.56**	**<0.001**	0.04	0.761	0.39	0.003	**0.48**	**<0.001**
Personal and Social Activities	0.05	0.705	**0.53**	**<0.001**	0.10	0.433	0.31	0.017	**0.48**	**<0.001**
Anxiety and Depression	0.09	0.476	**0.50**	**<0.001**	0.02	0.900	0.39	0.002	0.40	0.002
Self-care	0.09	0.483	**0.51**	**<0.001**	-0.04	0.767	0.35	0.006	**0.49**	**<0.001**
Strain	0.10	0.457	**0.55**	**<0.001**	0.08	0.545	**0.43**	**<0.001**	**0.45**	**<0.001**
SQLC	-0.36	0.005	**-0.52**	**<0.001**	0.06	0.636	-0.26	0.045	-0.17	0.212
HADS-A	0.11	0.409	0.29	0.034	0.09	0.516	0.26	0.052	0.27	0.056
HADS-D	0.11	0.419	0.29	0.032	0.20	0.145	0.24	0.074	0.40	0.004
Carer Sleep Quality	0.06	0.690	-0.11	0.416	0.17	0.231	0.00	0.972	**-0.51**	**<0.001**

Bonferroni correction for multiple comparisons at p< 0.0011; significant results after correction highlighted in bold. ρ = Spearman's correlation coefficient, PD = Parkinson's disease; UPDRS III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III, LED = Levodopa equivalent dose, GDS-15 = Geriatric Depression Score, NPI = Neuropsychiatric Inventory, PDQ-Carer SI = Parkinson's Disease Questionnaires for Carers Single Index, SQLC = Scale of Quality of Life of Care-Givers, HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale, HADS-D = Hospital Anxiety and Depression Scale – Depression subscale.

Figure 6-5: Comparing carer and care recipient quality of life



SQLC = Scale of Quality of Life of Care-Giver, PDQ-39 (SI) = Parkinson's Disease Questionnaire Single Index, PDQ-Carer (SI) = Parkinson's Disease Questionnaires for Carers Single Index

The association between carer QoL and care recipient QoL was then explored. PDQ-39 had a significant and moderately strong relationship with SQLC scores (ρ=-0.48, $p<0.001$) where poorer QoL in the person with PD was associated with poorer QoL in

the carer (Figure 6-5). The SQLC had a moderately strong relationship with the PDQ-39 Mobility and ADL subscales (ρ=-0.59, p<0.001 and ρ=-0.48, p<0.001, respectively), but not the other subscales. The correlations between PDQ-39 and PD-Carer also showed poorer PD QoL associated with worse carer QoL (Figure 6-5) but the association was stronger (ρ=0.59, p<0.001). Interestingly, the PDQ-Carer score was significantly correlated with five of the PD QoL domains as measured by the PDQ-39; Mobility (ρ=0.68, p<0.001), ADL (ρ=0.38, p<0.01), Emotion (ρ=0.37, p<0.01), Social Support (ρ=0.46, p<0.001) and Cognition (ρ=0.36, p<0.01). This could suggest that the PDQ-Carer is a more sensitive measure to subtle differences in the QoL of PD participants than the SQLC.

Table 6-7: Correlations between carer quality of life and PD neuropsychological measures

	SQLC Total Score		PDQ-Carer SI	
	ρ	p	ρ	p
MoCA	**0.40**	**0.002**	-0.32	0.014
Memory/Executive function (Factor score)	**0.47**	**<0.001**	-0.35	0.007
Attention (Factor score)	**0.51**	**<0.001**	**-0.39**	**0.003**
Global cognition (Factor score)	**0.43**	**<0.001**	-0.25	0.052

Bonferroni correction for multiple comparisons at p< 0.005; significant results after correction highlighted in bold. SQLC = Scale of Quality of Life of Care-Giver, PDQ-39 (SI) = Parkinson's Disease Questionnaire Single Index, PDQ-Carer (SI) = Parkinson's Disease Questionnaires for Carers Single Index, ρ = Spearman's correlation coefficient, MoCA = Montreal Cognitive Assessment.

The relationship between carer QoL and PD cognition was determined using the MoCA as a measure of global cognition commonly used in clinical settings, and the factor scores for Memory/Executive function, Attention and Global cognition, as determined from the principal commonest analysis (PCA), which was described in Chapter 5. Table 6-7 shows that SQLC was significantly correlated with all four measures of cognition, with the Attention factor score having the strongest association (ρ=0.51, p<0.001). The PDQ-Carer, however, was only significantly correlated with the Attention factor after correcting for multiple comparisons, although the relationship was moderate (ρ=0.39, p<0.01).

6.3.4 Predicting carer quality of life

Backwards stepwise regression was used to find a basic model for the SQLC and PDQ-Carer. Variables included in the model were: carer age, carer gender, years of education of carer, number of hours spent caregiving per week, carer sleep quality, number of health problems of carer, carer HADS-A score, carer HADS-D score, age of person with PD, UPDRS III score, LED, GDS-15 score and PDQ-39 SI. The model for SQLC scores accounted for 56% variance (R^2=0.56, p<0.01); significant predictors included increased time spent caregiving, higher carer depression scores and higher PD severity (Table 6-8). The model predicting PDQ-Carer scores accounted for 66% of the variance (R^2=0.66, p<0.001) and also included increased time spent caregiving and higher carer depression scores, in addition to increased carer anxiety scores and neuropsychiatric symptoms (Table 6-8).

Table 6-8: Significant predictors of carer quality of life

Measure of quality of life	Predictors in model	β	t	p	95% CI for β	
					Lower Bound	Upper Bound
SQLC[a]	*Time caregiving (hours/week)*	-0.5	-4.1	0.000	-0.2	-0.1
	HADS-D	-0.2	-2.3	0.025	-2.3	-0.2
	UPDRS III	-0.3	-2.9	0.007	-0.7	-0.1
PDQ-Carer[b]	*Time caregiving (hours/week)*	0.4	3.8	0.001	0.1	0.2
	HADS-D	0.2	2.0	0.048	0.0	2.6
	HADS-A	0.3	2.4	0.021	0.2	2.2
	NPI Total	0.2	2.3	0.029	0.0	0.8

a: R=0.75, R^2=0.56, Adjusted R^2=0.54, F=28.6, p=<0.01
b: R=0.81, R^2=0.66, Adjusted R^2=0.63, F=18.90, p<0.001
CI = Confidence Interval, SQLC = Scale of Quality of Life of Care-Giver, PDQ-39 (SI) = Parkinson's Disease Questionnaire Single Index, PDQ-Carer = Parkinson's Disease Questionnaires for Carers, HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale, HADS-D = Hospital Anxiety and Depression Scale – Depression subscale.

Measures of cognition in the person with PD were then added to the basic model to determine whether cognitive impairment was a significant additional contribution to carer QoL as measured by the SQLC and PDQ-Carer. Three measures of cognition were used: MoCA score as a measure of global cognition that is commonly used in clinical settings; cognitive classification as PD-NC, PD-MCI using 2 SD below normative cut offs

and PDD; and the factor scores from the PCA analysis for Memory/Executive function, Attention and Global cognition. Table 6-9 shows the models for SQLC scores. MoCA score of the person with PD significantly improved the model by 4% (ΔR^2=0.04, p<0.05) whereas cognitive classification improved the model by 5% of the variance explained (ΔR^2=0.05, p<0.01). The addition of the factors scores to the model for Memory/Executive function, Attention and Global cognition accounted for the largest change in the proportion of variance explained at 11% (ΔR^2=0.11, p<0.01). However, only the Attention factor was a significant predictor (β=0.25, p<0.05), thus the analysis was repeated with Memory/Executive function and Global cognition removed from the model. The model showed that attentional deficits accounted for 9% of the total variance of SQLC scores (ΔR^2=0.09, p<0.001).

Table 6-9: Regression coefficients and model fit of cognitive predictors of SQLC scores

Predictors in model	β	t	p	95% CI for β		R	R^2	Adj R^2	Std. Error	ΔR^2
				Lower Bound	Upper Bound					
MoCA	0.3	2.2	0.030	0.1	1.9	0.82	0.68	0.65	10.4	0.04
Cognitive classification	-0.3	-2.8	0.008	-10.8	-1.7	0.83	0.70	0.67	10.2	0.05
Factor scores	-	-	-	-	-	0.87	0.76	0.72	9.3	0.11
Memory/Executive function factor score	0.23	1.54	0.130	-1.03	7.72	-	-	-	-	-
Attention factor score	0.25	2.02	0.049	0.01	7.97	-	-	-	-	-
Global cognition factor score	0.02	0.12	0.906	-3.78	4.25	-	-	-	-	-
Attention factor score	0.4	3.9	0.000	3.0	9.5	0.86	0.73	0.71	9.52	0.09

SQLC = Scale of Quality of Life of Care-Giver, CI = Confidence Interval, MoCA = Montreal Cognitive Assessment

The above analysis was repeated for PD cognitive predictors of PDQ-Carer scores as a measure of QoL of carers (Table 6-10). The results showed that all measures of cognitive impairment accounted for negligible changes in the variance explained which were not significant. MoCA accounted for 1% of the variance (ΔR^2=0.01, p>0.05), cognitive classification accounted for less than 1% (ΔR^2<0.01, p>0.05) and the PCA factors scores accounted for 2% of the variance (ΔR^2=0.02, p>0.05).

Table 6-10: Regression coefficients and model fit of cognitive predictors of PDQ-Carer scores

Predictors in model	β	t	p	95% CI for β		R	R^2	Adj R2	Std. Error	ΔR^2
				Lower Bound	Upper Bound					
MoCA	-0.1	-0.9	0.357	-1.4	0.5	0.82	0.67	0.62	11.6	0.01
Cognitive classification	0.0	0.4	0.678	-4.4	6.7	0.81	0.66	0.62	11.7	<0.01
Factor scores	-	-	-	-	-	0.83	0.68	0.62	11.6	0.02
Memory/Executive function factor score	0.0	0.2	0.824	-5.0	6.3	-	-	-	-	-
Attention factor score	-0.1	-0.5	0.627	-6.0	3.7	-	-	-	-	-
Global cognition factor score	-0.2	-1.0	0.311	-8.1	2.6	-	-	-	-	-

PDQ-Carer = Parkinson's Disease Questionnaires for Carers, CI = Confidence Interval, MoCA = Montreal Cognitive Assessment

6.4 Discussion

Almost two thirds of PD participants in this study had an informal carer at their 36 month evaluation. Those without carers tended to be younger, female and had no spouse or partner (widowed, divorced, single). Carers tended to be spousal carers and were predominantly women in their late 60s. 85% of carers had one or more physical health problem. The demographics of carers and care recipients in this study is consistent with previous research (Glozman, 2004; Schölzel-Dorenbos *et al.*, 2009; Lavela and Ather, 2010; Peters *et al.*, 2011; Tew *et al.*, 2013; Santos-Garcia and de la Fuente-Fernandez, 2015).

This study has shown that carer QoL was worse for carers of people with PDD compared to PD-NC and PD-MCI. No significant differences in carer QoL scores, using both the PDQ-39 and SQLC, were observed between carers of people with PD-NC and PD-MCI. This is consistent with the findings of Leroi *et al.* (2012b), who reported that carer burden was significantly higher in PDD carers compared to PD-NC or PD-MCI carers. Interestingly, significant differences between reported QoL of PD-NC, PD-MCI and PDD carers for each subscale of the PDQ-Carer were also observed. However, strain was higher in PDD carers compared to the subscales measuring Personal and Social Activities, Anxiety and Depression and Self-care. Cognitive function in people with PD has been significantly associated with carer strain (Carter *et al.*, 2008; Oguh *et*

al., 2013; Martinez-Martin *et al.*, 2015). Furthermore, perceived carer strain has been associated with nursing home placement of the person with PD (Goetz and Stebbins, 1993; Abendroth *et al.*, 2012) and poorer psychosocial outcomes for the carer (O'Reilly *et al.*, 1996; D'Amelio *et al.*, 2009).

Carer QoL as measured by the SQLC was significantly associated with MoCA score and was found to be a significant predictor of carer QoL, such that carers of people who scored poorly on the MoCA were more likely to report worse QoL. Factor scores from the PCA analysis were also significantly associated with SQLC scores, however, only poorer Attention was found to be a significant predictor of carer QoL. The PDQ-Carer was only significantly associated with Attention factor scores, but no measures of cognition were found to be significant predictors. Nonetheless, the results suggest that attentional deficits may play a role in reduced carer QoL.

There is a paucity of studies that have investigated how cognitive impairment may contribute to carer QoL. One study found that poorer attention scores were a significant predictor of carer burden in PD carers (Leroi *et al.*, 2012a). Only serial sevens from the MMSE were used to measure attention. Furthermore, apathy and impulse control disorders, not cognitive impairment, in PD participants were the focus of this study. Kudlicka *et al.* (2014) found that behavioural problems related to executive dysfunction in people with PD contributed to carer burden. Fluctuations in cognition in people with PDD and dementia with Lewy bodies (DLB) were associated with increased carer distress (Lee *et al.*, 2013). Poorer cognition, as measured by the MMSE, in PD patients was associated with poorer physical health of their carer, increased stress and higher psychosocial burden (Aarsland *et al.*, 1999; D'Amelio *et al.*, 2009; Benavides *et al.*, 2013). Conversely, one study found that cognition, as measured by the MMSE, did not predict carer burden (Marsh *et al.*, 2004). However, the MMSE may not be a sufficiently sensitive measure to capture the different facets of cognitive impairment in PD, particularly executive dysfunction (Hoops *et al.*, 2009; Litvan *et al.*, 2012; Burdick *et al.*, 2014).

The difference in association of the SQLC and PDQ-Carer with cognition was surprising, given the reasonably strong correlation between the two measures. However, the difference may be explained by domains of QoL assessed in the two measures. QoL is

difficult to define with many different definitions and a variable subjective meaning to individuals (Martinez-Martin, 1998; Canam and Acorn, 1999; Glozman, 2004; Den Oudsten *et al.*, 2011). This makes QoL difficult to quantify and quantitative assessments may not be able to measure all aspects of QoL accurately. The PDQ-Carer includes subscales for Personal and Social Activities, Anxiety and Depression, Self-care and Strain (Jenkinson *et al.*, 2012), while the SQLC encompasses Professional Activity, Social and Leisure Activities and Responsibilities of the Caregiver to help the patient in their everyday living (Glozman *et al.*, 1998). The domains of QoL assessed are different and so may be measuring difference aspects of carer QoL; the SQLC may be more cognitively orientated and sensitive to cognitive impairment in people with PD. For example, caring responsibilities for the person with PD and cognitive impairment may prevent the couple from socialising. Therefore speculatively, the SQLC may measure how cognitive impairment disrupts the carer work patterns, carer leisure activities and how it may increase carer responsibilities.

Exploration of the relationship between the PDQ-39 and the measures of carer QoL showed a moderately strong relationship between carer QoL and PD QoL. Previous studies have also found significant correlations between PD and carer QoL (Miyashita *et al.*, 2011; Peters *et al.*, 2011). Morley *et al.* (2012) found that the Mobility and Cognitive Impairment domains of the PDQ-39 were significant predictors of carer QoL in the domains of Personal and Social Activities, Anxiety and Depression, Self-care and Strain of the PDS-Carer. This study also found that PDQ-39 domains of Mobility and Cognition were significantly associated to PDQ-Carer scores, in addition to the domains for ADL, Emotion and Social Support. In another study, PD and carer QoL were significantly correlated (Martínez-Martín *et al.*, 2005); furthermore PD QoL was a significant predictor of carer QoL as measured by the SQLC. However, PD QoL was not a significant predictor of carer QoL in the present study. Nevertheless, there is evidence to suggest that carer and PD QoL are associated either directly or indirectly. Two possible mechanisms for this have been proposed. Firstly, PD QoL may be a primary stressor for QoL in their carer, or alternatively, there may be a mutually dependent, dyadic relationship between carers and the person with PD, where the biopsychosocial functioning in one person is dependent on the same underlying features in the other person (DeVellis *et al.*, 2003; Lewis *et al.*, 2006; Greenwell *et al.*,

2015). These potential relationships between PD and carer are explored more in Chapter 7.

Carer QoL, as measured by the PDQ-Carer, was significantly predicted by the NPI-D total score, suggesting that neuropsychiatric symptoms were associated with carer QoL. Some studies indicate that neuropsychiatric symptoms, which are common in people with PDD, have a significant impact on carer QoL. Neuropsychiatric symptoms have been associated with increased carer burden, particularly in carers of people with PDD (Shin *et al.*, 2012b; Martinez-Martin *et al.*, 2015; Oh *et al.*, 2015). Conversely, one study suggested that while carer burden increased with neuropsychiatric symptoms, neuropsychiatric symptoms did not predict carer QoL (Martinez-Martin *et al.*, 2008).

Carer QoL was also significantly associated with PD disease severity, the number of hours spent caregiving per week, carer anxiety and carer depression. Severity of PD has been shown to be associated with carer burden, stress and strain in previous studies (Schrag *et al.*, 2006; D'Amelio *et al.*, 2009; Rodriguez-Violante *et al.*, 2015; Santos-Garcia and de la Fuente-Fernandez, 2015) but not directly to carer QoL. The number of hours spent caregiving has previously been reported to affect carer wellbeing, burden and distress (Chappell and Reid, 2002; Hirst, 2005). The number of hours of caregiving is influenced by cognitive impairment in people with PD, while a greater number of carer breaks has been associated with better carer QoL (Goldsworthy and Knowles, 2008). During the development of the PDQ-Carer, qualitative research identified anxiety and depression in the carer as factors affecting carer QoL (Jenkinson *et al.*, 2012). However, most studies seem to focus on anxiety and/or depression in the person with PD, rather than the carer (Goldsworthy and Knowles, 2008), with only a few studies investigating the effect of depression (Caap-Ahlgren and Dehlin, 2002; Martínez-Martín *et al.*, 2007; Sarandol *et al.*, 2009; Shin *et al.*, 2012a; Shin *et al.*, 2012b; Tanji *et al.*, 2013). Therefore, our findings are consistent with previous studies.

The strengths of the present study include the range of neuropsychological tests used to comprehensively measure cognition in people with PD, the range of carer measures including mood, physical health and QoL, and the range of validated instruments to assess PD symptoms. However, there are several limitations. Missing data was a

problem in this study. As discussed above, a small number of carers did not complete all measures as some were introduced at a later data and some carers did not return all questionnaires. This may have reduced the power of the statistical analysis, particularly regression analysis which excludes participants list-wise when data is missing. Thus, subtle differences or associations may not have been detected. The cross-sectional nature of this study was also a limitation; as these measures were introduced at the 36 month assessment, no longitudinal analysis was possible to determine any causal relationships. However, few participants had carers at baseline assessment as all participants were newly diagnosed with PD. Furthermore, some participants did not return for 36 month evaluation; these participants may have had more severe PD and/or greater cognitive decline. Therefore, it is possible that participants who did not continue to participate in this study may have been of greatest interest to this study as their carers may experience more strain, burden or poorer QoL. However, as described in Chapter 5, there were no significant differences in baseline scores between those who completed all assessments and those who did not return. Finally, protective factors were not accounted for in this study. Several studies have suggested that perceived social support, self-esteem, personality, coping styles and relationship between carer and care recipient are protective of carer QoL (Goldsworthy and Knowles, 2008; Tew *et al.*, 2013; Greenwell *et al.*, 2015). Further research is needed to determine how such factors can help protect carer QoL from deteriorating. Protective factors were explored as part of the qualitative work of this thesis; the results and interpretations are discussed in Chapter 7.

In summary, this study has shown an association between cognitive impairment in people with PD and carer QoL. Carers of people with PDD reported the poorest QoL. Attentional deficits were the strongest predictor of carer QoL compared to other cognitive predictors, which were also the strongest predictor of QoL in people with PD as discussed in Chapter 5. However, these conclusions should be viewed with caution, as only one of carer QoL measures was significantly predicted by PD cognition measures. Qualitative research into the effects of cognition on carer QoL and wellbeing may be able to account for some of the inconsistencies in this research, particularly regarding protective factors.

Nonetheless, these results suggest that targeted interventions focusing on attention in the person with PD may improve carer QoL. However, interventions to reduce the number of hours the carer spends per week as a caregiver, such as respite, may be a more readily implemented means of improving carer QoL. Similarly, reducing motor severity in people with PD via optimisation of drug regimens or psychological therapies to improve mood in carers may also further impact on carer QoL.

Chapter 7 The impact of cognitive impairment in people with Parkinson's disease and caregivers: a qualitative study

7.1 Background

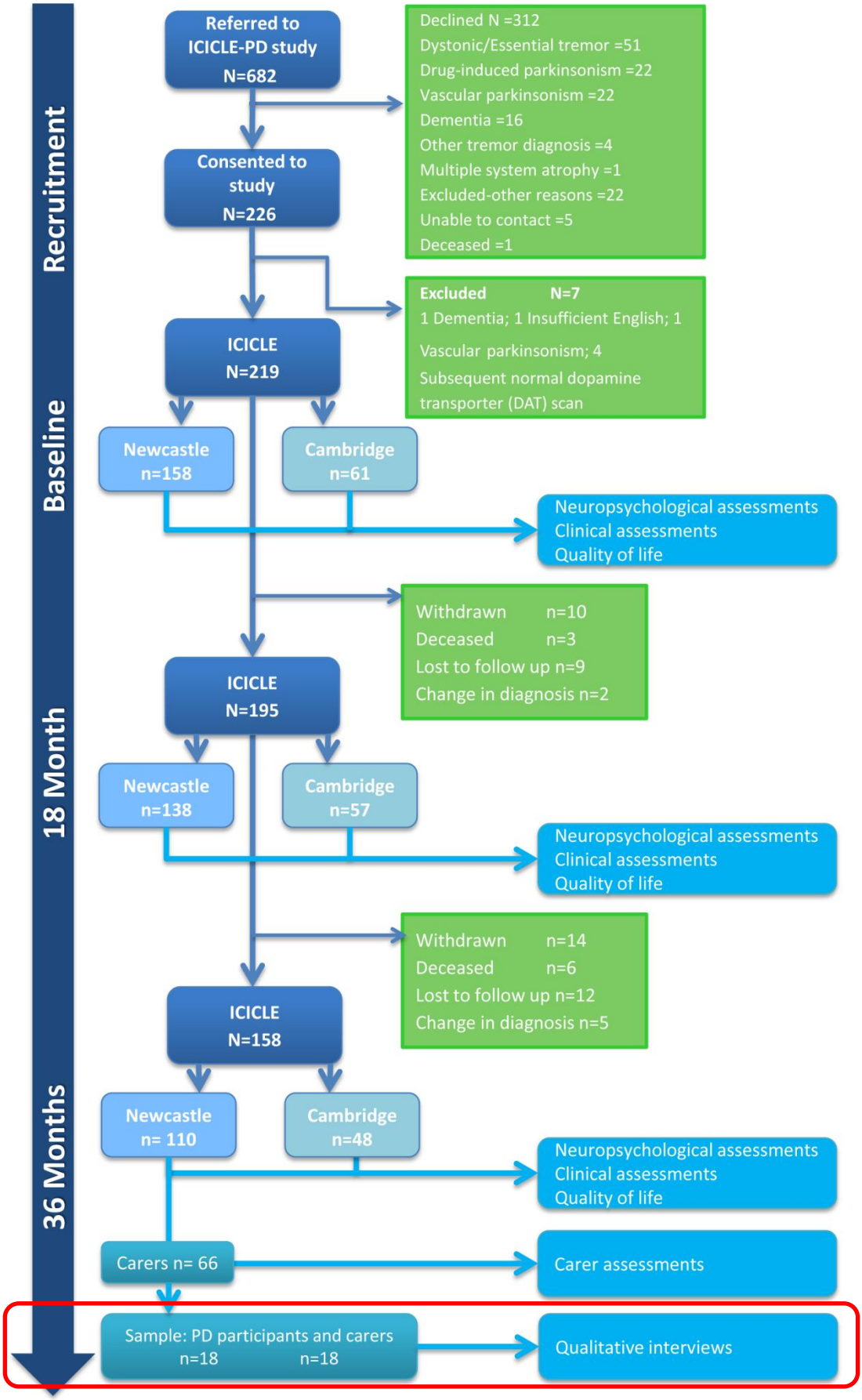
As discussed in Chapter 1, quality of life (QoL) is complex, difficult to define and difficult to measure. Furthermore, it is subjective and encompasses a wide range of concepts such as: culture, environment, social relationships, psychological issues and health (World Health Organization, 1993; Felce and Perry, 1995; Martinez-Martin, 1998; Bond and Corner, 2004). Therefore, quantitative methods may not be able to fully explore the impact of Parkinson's disease (PD) and cognitive impairment on patients and carers. Qualitative methods may be useful to explore in detail the effects of PD and cognition on individuals, and may be able to explain some of the variation in results found in the previous chapters.

As outlined in Chapter 2, the aims of this chapter were to explore the impact of cognitive impairment in PD on the QoL and wellbeing of people with PD and their carers, and whether cognitive impairment was an additional stressor, as either mild cognitive impairment (PD-MCI) or dementia (PDD). A further aim was to use qualitative analysis to provide in depth insight into the effect of PD and cognitive impairment and how this related to the experiences of individuals.

7.2 Specific Methods

As shown in Figure 7-1, the methods and results in this chapter relate to the qualitative analysis of interviews conducted with people with PD and their carers as part of the 36 month assessment within the ICICLE-PD study. The details of the methods used in this study are described in Chapter 3.

Figure 7-1: Assessment schedule



7.3 Results and Findings

In total, 36 interviews were completed with 18 people with PD and 18 carers. The three groups that were sampled were normal cognition (PD-NC), mild cognitive impairment (PD-MCI) and PD with dementia (PDD); six people with PD and six carers were in each group. The demographic information relating to each participant with PD and their carer are described in Table 7-1. The majority of people with PD were male, which is representative of PD as studies have reported a higher prevalence of males with PD (Foltynie *et al.*, 2004; Marras *et al.*, 2004; Wooten *et al.*, 2004; Heller *et al.*, 2014). Most caregivers were spousal, with only one carer being an adult child of the person with PD and another who was an acquaintance of the person with PD who became an informal carer through mutual agreement. Thus the majority of caregivers were wives or female partners. This is consistent with other carer studies (Glozman, 2004; Schölzel-Dorenbos *et al.*, 2009; Lavela and Ather, 2010).

The principal themes were: 1) the experience of PD, 2) changes in identity, and 3) coping mechanisms and adjustment. Across these inter-linked themes were also two other important overarching issues. Firstly the different experiences between carers and people with PD; and secondly the effects of cognitive impairment. These themes and overarching issues are discussed below.

Table 7-1: Demographics of participants with Parkinson's and their carers

	Age	Sex	Occupation	Carer Relationship	Carer age	Carer sex	Carer Occupation
PD-NC	62	Male	Retired engineer	Partner	66	Female	Retired care assistant
	69	Male	Retired housing director	Wife	70	Female	Homemaker
	74	Female	Retired dinner lady	Husband	74	Male	Retired electrical engineer
	75	Male	Retired air traffic controller	Wife	67	Female	Retired air traffic controller
	80	Male	Retired medical lab technician	Wife	69	Female	Retired nurse
	81	Male	Retired doctor	Wife	78	Female	Retired radiographer
PD-MCI	65	Male	Retired HGV driver	Wife	64	Female	Retired physiotherapist
	66	Male	Retired solicitor	Wife	61	Female	Solicitor
	66	Male	Retired nurse	Carer/friend		Female	Carer (retired PA)
	67	Female	Retired catering technician	Husband	71	Male	Retired maintenance electrician
	67	Male	Semi-retired sound recording engineer	Wife	64	Female	Audio services
	68	Male	Retired salesman	Wife	67	Female	Retired psychiatric nurse
PDD	67	Male	Retired fitter	Wife	66	Female	Retired shop assistant
	70	Female	Retired lab technician	Husband	77	Male	Retired boiler plater
	72	Male	Labourer	Wife	72	Female	Retired care assistant
	79	Female	Retired shop assistant	Daughter	52	Female	Carer
	69	Male	Retired Local government officer	Wife	56	Female	Teacher
	87	Male	Retired sales engineer	Partner	68	Female	Retired

PD-NC = Parkinson's disease with normal cognition; PD-MCI = Parkinson's disease with mild cognitive impairment; PDD = Parkinson's disease dementia.

7.3.1 The experience of Parkinson's disease

As outlined in Chapter 1, individuals with PD face illness specific factors that can disrupt their emotional equilibrium and QoL (de Ridder *et al.*, 2000; Moss-Morris, 2013). Therefore I explored PD related stressors with the potential to disrupt the QoL in people with PD and their carers. Participants and carers described their experiences of diagnosis. Both participants and cares described the experience as "devastating." The diagnosis of a chronic disease, particularly a progressive disease such as PD with many uncertainties, can be a stressful event that causes distress (Pinder, 1992). Phillips (2006) compared the experience of being diagnosed with PD to "a bomb being dropped," where it is a potentially life shattering experience where the individual has to pick up the pieces and rebuild.

Participants without cognitive impairment focused on the physical aspects of PD when describing what symptoms affected their lives; motor symptoms seemed to be more salient. Walking and balance were predominant issues among those without cognitive impairment; tremor, slowing of movements (bradykinesia) and speech were also commonly described. Physical symptoms associated with PD significantly affected individuals in various aspects of their lives. Restrictions seemed to vary depending on severity of PD symptoms and the type of symptoms.

> *"Well I was very active, I am quite active now, but then I was a member of the ramblers club and every fortnight I would go out for a ten mile hike, and I don't trust myself to go out for a ten mile hike now because I don't want to make a fool of myself if I fell down, I would hate to think that I had to call the air ambulance or anything like that"*

PD 12, 74 year old female, PD normal cognition

Participants described how the physical symptoms of PD influenced everyday activities and QoL, such as going for walks or getting in and out of bed. PD 12 described how she enjoyed walking but it had been restricted due to PD and was no longer able to participate in the local rambling club. In addition, these were sources of social interactions which had become less frequent.

> *"The dizzy turns are the most annoying aspect of the condition… they're restrictive, they're unpredictable, you don't know whether they're, I mean I can*

go for a day, have a heavy meal and feel perfectly alright and then the next day have not such a heavy meal and it comes on, it's not, so you can't predict it"

PD 9, 81 year old male, PD normal cognition

Secondary to motor symptoms, non-motor symptoms (NMS) were also described, included drooling, increased urinary urgency and postural hypotension or feeling dizzy. Several participants also reported sleep problems in some form, which seemed to significantly impact on their wellbeing. Some participants described PD symptoms as annoying or frustrating, as PD 9 described above. The unpredictability of the physical symptoms was also a source of disruption in terms of QoL, impairing social functioning, creating feelings of embarrassment and causing distress. Thus non-motor symptoms had varying effects on participants, affecting not just them, but also their carers. Cognition and cognitive features were also discussed.

7.3.1.1 Living with Parkinson's disease: Is cognitive impairment an additional stressor?

Participants and carers were asked about their experiences with cognitive impairment to explore whether the presence of cognitive impairment was an additional stressor that could impact on QoL. Through the interviews, it became apparent that many participants were aware of changes in cognition, although some of these changes were subtle. Furthermore, the degree to which they were affected seemed to be eventuated in those with dementia. Difficulties with cognitive impairment were generally expressed more frequently by the carer than the person with PD. This could suggest that carers were more aware of changes in cognition than was the care recipient, or cognitive impairment had more of an impact on carers than the person with PD.

Short term memory was the feature most discussed. However, the context or way in which they were discussed varied.

"I notice now I'll go into a room to do something but I forget what I'm going to, I'm standing there looking into the room for a couple of minutes before I remember what it is I've, instead of automatically going straight into the room and doing it I have to stop sometimes and think what was it I was going to do… maybe that's because I'm getting old anyway, older"

PD 7, 69 year old male, PD normal cognition

Those with normal cognition often acknowledged some subjective memory problems but often dismissed them as "just old age." This was usually forgetting to do certain tasks, household chores or the names of people, such as friends or celebrities. These were sometimes described as "frustrating" but were often not troublesome to participants at all.

Participants with PD-MCI and PDD found memory problems to be more troublesome.

> *"It's certainly affected my memory, I can watch the same film over and over again and it's fresh every time, there's the usual thing about forgetting names… I don't like going to parties where there's people who I ought to know and remember their names because the chances are I don't"*

PD 14, 67 year old male with PD-MCI

> *"Basically, most mundane aspects of life, I need to write down, I couldn't go shopping or go to see somebody down the road, without writing it down first, I just forget everything"*

PD 18, 69 year old male, PDD

These participants with PD and cognitive impairment were aware that they had prominent memory problems. They recognised that their memory problems were more than just old age and attributed them to PD. PD 18 described, with difficulty, that his memory impairment prevented him from socialising and running errands. He lived in an isolated, rural setting and thus was prevented from going out of the house on his own due to his cognitive impairment. Instead he relied on his wife and visitors for social interaction. Both participants described how they felt despondent, often feeling frustrated or even angry with themselves. Carers also described memory problems in the care recipient as a source of worry.

> *"I really really am starting to get very very worried about him now, I mean I know we've been to see the psychologist as well and had all the memory tests taken so far but his short term memory is, he soon forgets, every morning it's what are we doing today… where at one time you know he would never forget something that's very important but now he does and I've got to keep reminding him every day, and sometimes it will be two or three times during the day I've got to keep reminding him of things"*

Carer 6, 67 year old female, care recipient has PD-MCI

This carer of a person with PD-MCI explained how she became worried about her husband's memory. She described that it was a noticeable change since he was

diagnosed with PD which required her to remind him of planned events or redirecting him when he was lost when driving in once familiar areas. She explained that he would soon have to stop driving, which was potentially upsetting. Due to PD and cognitive impairment, eight participants have given up driving, either through choice or through intervention. This has had an impact on their social lives and restricted their freedom or ability to take trips to visit family or friends. Furthermore, this could potentially result in social isolation for some, particularly if their cognitive impairment was such that they were unable to use public transport (Taylor and Tripodes, 2001).

Conversely, two of the participants with PDD did not attribute their memory problems to having PD but instead thought it was old age; and a further PDD participant denied having any memory problems despite her daughter stating that she had very noticeable memory problems.

> *"I've got a good memory, but I do seem to be losing a lot of it… I remember a lot of what happened in the past and I remember what happens now is probably combined with the two, you know, I don't have a problem with my memory really, it's not as bad as I thought it was"*

PD 2, 79 year old female, PDD

> *"Just not good, not good at all… I'll tell her "oh I've just made this" or "we did that" and then the next day I'll say "oh do you remember," "you never told me that," so just complete did not recall it at all, you know, things she sees on the telly things we've done she just doesn't remember them"*

Carer 2, 52 year old female, carer of PDD

It was unclear whether these participants were unaware that they had significant cognitive impairment or whether they were using denial as a coping mechanism.

Concentration, slowed thinking, reasoning problems and confusion were also aspects of cognitive impairment that affected people with PD and their carers.

> *"Concentration, I used to be an avid reader, I can't get past two or three pages now, I've got to keep going backwards and picking it up… I think, oh, I'll come back to you, it's taking me a long, long time to read now, as I say, concentration"*

PD 13, 66 year old male, PD-MCI

As described by PD 13, several participants with cognitive impairment mentioned reading difficulties due to concentration or sustained attention problems. They described reading the same passages over and over and becoming frustrated.

> *"Crosswords, I'm a fanatic, I always have been most of my life, now it takes me that bit longer to complete them, I used to do some of them you know it's fast and like they were a challenge every day, but not now, I just take my time, so that's slowed things up, I mean it's not a big thing to you but to me it was, you know what I mean, slower altogether I think"*

PD 6, 68 year old male with PD-MCI

This gentleman with PD-MCI explained how he had always enjoyed crosswords, but he noticed it took considerably more time complete them and found it much harder to work out the answers. Although this was a mild problem that he felt other people would dismiss as trivial, it was an important difference from his perspective because it was something he habitually did as a pastime. This differed from the way those with PDD experienced thinking difficulties, which seemed to be a more intrusive to their daily activities.

> *"…the other things I find I find is that I can't express myself as easily as I could do I have to stop and think more often and in some cases not not too often I just don't know how to finish an answer to a question maybe, it just tails off"*

PD 1, 87 year old male with PDD

> *"If you were saying something interesting and I knew something to add on to it I don't like to do that now because I will start talking and then I'll be thinking "what was I going to say," and you don't want to show yourself up so I can tend to sit back a bit now"*

PD 4, 70 year old female, PDD

Some expressed getting more confused and "mixed up" at times. However, those with PDD seemed to experience this to a greater extent. Those without cognitive impairment acknowledged slightly slower thinking when prompted, but again it was not important or detrimental. However those with PDD found it disrupted and affected their confidence, as described by PD 4.

The carer of PD 1, who was diagnosed with PDD, described her observations of how he was often confused and disorientated:

"…he'll go to sleep in the lounge and he'll wake up and he'll look all way around as if it's a bit strange to him, he woke up the other night, and he said it was at 8 o'clock in the evening, "oh there's something going to happen, quick let's get to bed," and I thought what does he mean, you know, or he'll come out with little odd conversations that has got nothing to do with what we were talking about... I feel as if I'm losing him a bit"

Carer 1, 68 year old woman, care recipient has PDD

This carer described the change in her partner as uncharacteristic of him and found these changes distressing. He was frequently confused to the point where he couldn't follow conversations; brought up topics that weren't relevant to the conversation or was disorientated to the point his behaviour became peculiar. Carers disclosed observing the person with PD to be confused or disorientated more frequently than the person with PD. This could be that carers are more aware of episodes of confusion than the person with PD and cognitive impairment, or they are more disposed to talk about them; carers of people with PDD describing more frequent and severe episodes.

One gentleman with PDD described his feelings about dementia.

"It takes the gloss away from life"

PD 18, 69 year old make, PDD

He described other aspects of PD as being easily managed but that the dementia caused some emotional distress. PD 18 had more advanced dementia compared to the other interviewees, but he was able to articulate that he felt angry and frustrated about having PD and dementia, although the conversation was disjointed at times due to problems with concentration and memory. Feelings of anger and frustration were commonly expressed by those with cognitive impairment.

"Frustrating, again you see that word keeps coming into this, frustration and not being able to do things in one form or another, yeah that's it it's frustration but not sufficient to cause real big problems, yeah that's how I would put it"

PD 10, 66 year old male, PD-MCI

"I get mad with myself sometimes you know, I think "bloody hell why did I do that," you know, well what did I fetch this out for when I didn't go in for it like, that sort of thing like you know, what did I fetch this back for, and I was always I was always very tidy, in the garage I knew where everything was, everything had to be just so I can get it, well I cannot find a thing now"

PD 8, 75 year old male, PDD

These individuals shared feelings of frustration relating to cognitive difficulties, with memory problems being the most frequently referred to, although other motor symptoms were also sources of frustration. Frustration was most expressed by those with PD-MCI.

7.3.1.2 Neuropsychiatric features and cognitive impairment

Neuropsychiatric symptoms, particularly sleep disturbances, mood disorders, hallucinations and delusions have been associated with cognitive impairment and dementia in PD (Aarsland *et al.*, 2001; McKeith and Mosimann, 2004; Leroi *et al.*, 2012c; Oh *et al.*, 2015). These symptoms may be additional stressors to those with PD plus cognitive impairment, and their carer. Hallucinations were present only in participants diagnosed with dementia.

> *"I'll go through to [my husband] and I'll say how many is for dinner because I think [my grandchildren] are going to have their dinner, well they just disappear… when the meal comes they disappear, they go, and even though I go through you see if you were in the room with me I'd come through to you and I would say "who is for dinner," and you would say two and I would think there was four but I know they're not"*

PD 4, 70 year old female with PDD

This female PDD participant described vivid hallucinations and often saw her grandchildren or deceased mother, having conversations with them and even making meals for them. She did not find them frightening or distressing and described seeing her mother as comforting, as if she was being "watched over". She described how she tried to reason with herself, for example that she knew her granddaughters did not live nearby and it could not be them; however the hallucinations would persist.

> *"but it's hallucinations it's like there's a presence of one or two people in the house, even when you tell her that and she explains it and you've told her "oh no [the grandchildren are] up Scotland" but an hour later she'll come back and say "how many is in the room" you know, so as I say it's difficult with it being a mental thing, not physical it's just mental"*

Carer 4, 77 year old male, husband to PDD

Her husband, however, found this behaviour distressing; he described repeatedly trying to reason with his wife but found he was unable to "get through" to her which was frustrating.

"The elves, is just my nickname for what happens at teatime, it's really quite simple, at dusk, the elves come out to play and at the bottom of our garden, there's quite a lot of back garden, you can get up to five, six, maybe occasionally more, creatures, in inverted commas, who dance around in the dark, apparently illuminated at times… they never attempt to bite, touch, poke, shout, or anything inappropriate, they just arrive and they're soundless and touchless… and, of course, it's not an elf really, I do know what I'm talking about, really, an elf sounds more interesting than hallucinations."

PD 18, 69 year old male with PDD

In comparison, this gentleman with PDD was aware that the "elves" he saw at the bottom of his garden were hallucinations. He was able to describe them vividly and said they often wore pink tutus. As with PD 4, he did not find the hallucinations threatening or distressing, instead he found them amusing and harmless.

Of the six people with PDD, three carers described hallucinations in the care recipient. All carers found hallucinations to be disturbing and unsettling. Hallucinations included animals, small children, deceased relatives and elves. Three carers also described delusions in the carer recipient, which was more distressing than the hallucinations. Carer 10 explained some of the specific features she found most difficult and upsetting:

"One winter when [our daughter] was home she was coughing quite a bit and it was no more than a cold and I knew it was no more than a cold but [my husband] reckoned it was cancer and he thought that maybe there was asbestos that had affected all of us, that was pretty terrible as well (crying)"

Carer 10, 61 year old female, wife of male PD-MCI

As described above, Carer 10 described her husband having delusions, where he believed the house was infested with asbestos and had given his daughter cancer. Carer 10 was very distressed by her husband's delusions and found it difficult to cope with. This form of misidentification or delusion is not commonly reported in PD (Emre *et al.*, 2007; Pagonabarraga *et al.*, 2008). However, as described by Carer 18, it was very upsetting particularly when it occurred on holiday and support was not available. Other studies have found the presence of psychosis, including hallucinations and delusions to be detrimental to QoL (McKinlay *et al.*, 2008; Barnes *et al.*, 2013; Aarsland *et al.*, 2014; Goldman and Holden, 2014).

"…in the dream like I give him a good hiding like, that sort of thing like… I was just telling the wife about it and but I didn't feel sorry after it I just thought to myself well why did I dream that like you know I mean I've dreamt before I mean I've hit the wife… I've bit her and all sorts like, it's a bit frightening at times I mean I don't know like but they reckon she's no, I'm really hitting this bloke in my dream…"

PD 8, 72 year old male with PDD

Some participants and carers described sleep disturbance, including restless legs syndrome and acting out dreams. These features are common in PD and has been shown to significantly impact on an individual's QoL and also to frequently disrupt sleep quality of spousal caregivers (Whitehead *et al.*, 2008). PD 5, who had no cognitive impairment, described how he and his wife found it necessary to resort to single beds as it was so disruptive. Sleep disturbances were more extreme in people with PDD, as described by PD 8; he admitted to accidentally injuring his wife when acting out dreams. In the interviews, sleep disturbances were reported more by participants with cognitive impairment, which has also been found in other studies (Erro *et al.*, 2012; Pistacchi *et al.*, 2014).

7.3.1.3 Increased caring responsibilities

As a result of the motor and non-motor symptoms associated with PD, all except one carer described an increase in responsibilities. For carers of recipients without any cognitive impairment, this tended to be more physical tasks such as increased housework, gardening, getting dressed, talking on the telephone and driving.

"I'm not really caring for my wife no she does nearly all the housework and the washing, I mean I wash up occasionally and if she wants any odd jobs done I do them but and we go out shopping together you know things like that"

Carer 12, 74 year old male, husband of PD normal cognition

However, carers of people with cognitive impairment, both PD-MCI and PDD, seemed to have increased responsibilities compared to those with normal cognition, although PDD carers had more numerous responsibilities. In addition to the motor symptoms of PD, they also had additional responsibilities due to cognitive problems.

"So every day I go over and cook them lunch, help with washing, ironing cleaning shopping… she has a shower, blow drying her hair, cut her hair, sometimes help her get ready, take her to see her friends, take her to the town, take her shopping, remembering what things they need in the house, buying

them things that would make their lives easier for example a walkabout telephone… so basically what happens when you're a carer I think unless you live with the person you end up having another house to look after"

Carer 2, 52 year old woman, daughter of PDD

Carer 2 is the daughter of a woman with PDD. As she describes here, her responsibilities significantly increased since her mother was diagnosed and she became an informal carer. She described a long list of duties she has undertaken to care for her mother, including giving her father some respite. She was a child caregiver, rather than a spouse or partner, and thus she had the added responsibility of two homes to maintain: her house and her mother's house. She went on to describe how she found this stressful at times.

"So at the start that was quite hard and that's where you think it's becoming overwhelming, I think I used to think I'm overwhelmed… I'd go our house is just not, I need to dust and hoover not that I'm even slightly house proud but when you can write your name in it…. so you just think I can't it's too much there's too much and then [my husband] talks to me and then I'm fine again so it's I think, it's stress it's obviously stress."

Carer 2, 52 year old female, daughter of PDD

Carer 2 described herself as feeling "overwhelmed" by her increased responsibilities, which suggested she was not coping with caring for her mother. She described feeling stressed and being put under strain from the extra responsibilities she acquired as a carer of someone with PDD. She explained that she had to readjust her priorities, and as a consequence the upkeep of her own household at times became neglected. Another carer said caregiving had changed her priorities and joked she had a new perspective: "pay somebody to do it or you've got to accept lower standards."

"Oh well I'm responsible for everything, he can't make decisions anymore, he doesn't want to make decisions, it sounds a bit disrespectful to him, but it's sometimes like having a child because he'll say, "can I have?" if we're out and he sees something he'll say, "can I have that?" as if a child would. I'll say, "you're a grown man, if you want it do what you want," so he relies on me to do everything, he doesn't make any decisions at all, well I sometimes feel he's asking my permission to do things, which he would never have done"

Carer 16, 64 year old female, wife of PD-MCI

"Well most things, I mean he can't work the cooker now where he would you know do a meal, the cooker is like a…he just doesn't know how to do it at all, and like the running of the house you know, he hasn't got a clue with the money

side of things and so I do all that as well, where I mean direct debits are wonderful things (laughs)… so I've took over most things really… he doesn't know how to do so many things, he even he gets mixed up putting his clothes on and just little things you know like that, gets mixed up with the shower gels and the shaving foams and all that sort of thing, I just feel as if you know you have to be there all the time"

Carer 11, 66 year old female, wife of PDD

Carer 16 explained how her husband no longer felt able to make decisions and so she made all decisions to the point where he asked her permission to do things. As described above, taking over financial matters was often referred to by carers of recipients with both PD-MCI and PDD as the person with PD no longer had the ability to keep track of bills or bank accounts. One participant described how her husband was confused about amounts of money, such as calling one hundred pounds one thousand pounds, which led to her taking control of the finances. Carers also described how they observed the care recipient becoming "mixed up" about everyday activities. Carer 11 explained how her husband needed her help getting dressed as he often put clothes on incorrectly or used incorrect products for showering and shaving.

Some cares found being a carer more stressful than others; these tended to the carers of people with more salient cognitive impairment. Many carers described subtle shifts in their priorities and found that they had less time for chores or even leisure activities due to the demands of caregiving. Restrictions were reported most frequently in carers of people with PDD, and to a lesser extent those with PD-MCI.

"Well you can't go very far for too long, if you do go anywhere you've got to let him know that if you're going to be late you've got to let him know because he gets very worried"

Carer 8, 72 year old female, wife of PDD

Carer 8 described how she felt her time on her own was curtailed by husband; she described him as becoming anxious when he was separated from her for long periods of time. This prevented her from meeting friends, going for walks or seeing her mother.

Spousal carers and the care recipient were prevented on going on holidays due to the person with PD.

"Life is not normal anymore, I would like to be able to say, right, come on, we will go here, or we will do this, we will go there, or book a holiday, but with the Parkinson's now I would always be fearful if we were abroad and something was to happen I'm conscious of that, because I wouldn't want her to take ill or be bad abroad, and have to find that she's hospitalised abroad"

Carer 15, 71 year old male, husband to PD-MCI

This individual had stopped going on holiday with his wife since she had been diagnosed with PD. He worried that something would befall his wife related to PD while they were abroad, particularly that she would be hospitalised in a country far away from home. Therefore, they no longer went on holiday at all. Other carers felt they were unable to go on holiday as they felt worry or even guilt at leaving the person with PD and cognitive impairment. This could be a potential problem for carers and could contribute to feelings of being overburdened if they feel unable to take sufficient breaks or respite from caring (Goldsworthy and Knowles, 2008).

Anxiety was the most commonly mentioned psychological outcome and was expressed to some extent by all carers, usually in terms of worry, panic or feeling frightened. A common anxiety expressed by carers related to the future of the care recipient if they were no longer able to care for them. This was predominantly expressed by carers of people with cognitive impairment who, as explored above, had more numerous caring responsibilities.

"It's a big worry, if anything happens to me, I don't know how he would survive, he'd have to take a few steps back, I can't see him coping with internet banking and all sorts of things, and using a computer, he used to be the one who told me what to do, but not anymore, it's the other way around"

Carer 14, 64 year old female, wife of PD-MCI

"it really worries me if anything happens to me I really get scared about that if I was to take ill and something was to happen to me, so if there's, if I think there's something wrong I go to the doctors now, because I want to keep myself healthy"

Carer 11, 66 year old female, wife of PDD

These carers described their worries and fears about their own health deteriorating or possible death and how it would affect their spouses. As with many spousal informal carers, these cares were older adults and prone to age-relegated illnesses or general health problems (Berry and Murphy, 1995). Thus possible future ill health and how

their spouse, who was reliant on them, would manage was a cause of anxiety. The carers shared the fear that their spouse would not be able to cope on their own and that there would not be anyone else to care for them. Although some had family around them, they did not feel able to rely on others to look after their spouse.

Thus carers of people with cognitive impairment in addition to PD seemed to have an increased number of responsibilities compared to carers of people with PD and normal cognition. The tasks carers of people with PD and cognitive impairment helped with were more ranging and often involved taken on tasks that involved memory, planning, reasoning and decision making.

7.3.1.4 Cognition vs. motor symptoms: the fear of dementia

The attitudes of individuals to dementia were similar between groups, where the prospect of having dementia was a more alarming concept than having just PD.

> *"It makes me wonder if I'll end up like that, my twin brother is in hospital at the moment, he's got lung problems and there's a guy in the next bed and he's he hasn't been diagnosed with Parkinson's but he has got Parkinson's, but he's got dementia as well like and yeah it's a bit upsetting when I see what it can do"*

PD 3, 62 year old male, PD normal cognition

This participant without cognitive impairment discussed cognition and dementia in terms of something worse than PD. He found seeing other people with dementia more distressing, particularly when he envisioned dementia as part of the progression of PD. He described that, although he had found the experience of being diagnosed as difficult at the time, he had come to terms with PD. However he found the prospect of being diagnosed with dementia in addition to PD as disturbing. Several other participants had witnessed the effects of dementia in family members or friends and described it as "cruel," "upsetting" and "distressing."

This attitude was also explored in carers.

> *"Dreadful, I think it's probably the worst thing you can get, I mean I would, the thought of getting dementia just terrifies me"*

Carer 12, 74 year old male, husband of PD normal cognition

As with the people with PD, this carer expressed his fear and negative views of dementia. Several other carers also discussed their views and experiences of dementia; one carer described it as "a living death sentence" while others expressed distress at seeing family members with dementia.

> *"Scared, actually, I actually try not to think about it, because I think the thing that scares me most is the thought that [my husband] could end up with dementia and I know that one in three people with Parkinson's get dementia, and I cared for my dad with dementia, and it was horrible, I worry that I won't have the energy to do that again"*

Carer 17, 67 year old female, wife of PD normal cognition

Carer 17 took care of her father when he had dementia before her husband was diagnosed with PD. She was fearful of dementia and found taking care of her father with dementia very stressful to the point where she would struggle to cope if she had to repeat a similar experience with her husband. For some carers they expressed being aware of future dementia.

> *"I worry about that because my dad had Alzheimer's and I thought that that was what [my husband] was getting to be honest, I was thinking should we go to the doctor and see about this? I've not broached it with [my husband], now I just put it down to the Parkinson's"*

Carer 14, 64 year old female, with of PD-MCI

> *"I am fully expecting [dementia] to happen… we've all seen dementia and Alzheimer's and they end up in homes don't they, so I do worry about that one especially if he's done something out of character I think oh is this the start of it? …it's only happened once, he did get a bit violent, it was the medication but at the time I didn't know it, that frightened me"*

PD 16, 64 year old female, wife of PD-MCI

Most carers of people with PD and cognitive impairment expressed anxiety or fear relating to dementia; whether it was in terms of the care recipient developing dementia or whether dementia would progress further, for example resulting in nursing home placement. The shared belief between carers was that the occurrence of dementia would end in that individual going into a nursing home as they wouldn't be able to cope with looking after someone with dementia.

In addition to this, Carer 16 discussed previous violence which was out of character for her husband. Although this had not reoccurred it was nevertheless a source of worry

of future dementia and institutionalisation. Carers of people with PDD were worried about the hallucinations and delusions their spouses or partner experienced becoming more frequent and more disruptive. Nursing home placement has previously been associated with behavioural problems, aggression, hallucinations and delusions in people with dementia (Sury *et al.*, 2013).

Fear was shared by some participants with dementia.

> *"…the dementia frightens me more than Parkinson's I think, Parkinson's I've got sewn up, well I'm not going to say sewn up, the other one is the unknown quantity really"*

PD 11, 67 year old male, PDD

This person with PDD again explains that he finds dementia more frightening than the physical symptoms of PD. He mentioned that it was the "unknown quantity" of dementia that he found most disturbing. This has also been found in other studies (Carpenter *et al.*, 2008; Robinson *et al.*, 2011).

In order to compare the motor symptoms of PD to cognitive impairment, questions were introduced to explore these differences from the carers' perspective. The perspectives on these differed between carers.

> *"I think they're on a par actually, I can live with his memory problems because I think I've got used to it, I do worry about the Parkinson's getting worse, thinking, is he going to do this or heaven above that he has to go in a home at any point, which I hope is years and years, at the moment I'm quite capable of dealing with anything that has to be dealt with, but I think the Parkinson's worries me more than the memory because he's not silly, he knows what he's doing, he's quite capable of logical thought at the moment… so I think I worry about both of them"*

Carer16, 64 year old female, wife of PD-MCI

Carer 16 thought the PD symptoms and the cognitive symptoms were equal to each other and she worried about both. This is in contrast to the attitudes of carers of people with PDD who were also asked what they thought of the dementia compared to PD symptoms:

> *"It's like nothing on earth is it, the Parkinson's you think, a piece of cake, the dementia is the real tricky one, actually it's that rollercoaster with the dementia that you've got and you think, oh life is okay, half an hour later you know*

they've gone again and it's not okay, you have to, I don't know, have sort of strategies where you try not to react, try to think, well it will be okay and then you think well actually you are fooling yourself, but no it doesn't compare actually, I think the physical side of the Parkinson's is a bugger really … but compared to the cognitive impairment they are opposite ends of the scale in having to deal with them, I think really, yes I find that a more, a scarier a prospect"

Carer 18, 56 year old female, wife of PDD

Carer 18 described finding dealing with the cognitive difficulties associated with dementia very difficult. She acknowledged that the motor-symptoms of PD were problematic and they restricted the leisure activities they both enjoyed, however in comparison these difficulties were "a piece of cake" compared to dementia.

7.3.2 Identity: "I just feel a lesser person"

Identity, predominantly change in identity, was a central issue. Participants with PD-MCI and PDD discussed how they were not the same person and that their image of themselves had changed as a result of Parkinson's disease. Being diagnosed with PD to many participants was a life changing event that split their lives into "before" and "after."

"I almost had a breakdown because I couldn't remember who I used to be, I literally couldn't, I found that whatever was going on in my life it all revolved around Parkinson's, even when I dream now I've got Parkinson's, to me it's as if it's always been like this… I think what a lot had been wrong with me too was I think I was grieving for somebody I'd lost, which was myself, I found a lot of similarities in grieving the things that you feel"

PD 13, 66 year old male, PD-MCI

PD 13 explains how having PD had altered his perception of himself to the point where he struggled to remember his life and identity before the onset of PD. He detailed psychological distress and a near "breakdown" which is often a colloquial term that can encompass acute psychiatric disorders manifesting as depression and/or anxiety (Shorter, 2013). This individual with PD-MCI likened this change to grief, a feeling that was shared by other participants with PD-MCI.

"I feel that since I got Parkinson's I have lost something and I can't get it back, it is hard to describe how I feel in that way, I felt angry when I first got it because I thought, why have I got it? I can't think of anything more to say, my life has changed a lot since I got it"

PD 15, 67 year old female, PD-MCI

This lady felt that she had lost something within herself and blamed PD as the source of her anger and grief at this loss. Through both these interviews, they suggested that periodic deteriorations in PD caused a crisis which disrupted their emotional wellbeing and QoL; this is a concept previously described by Moos and Schaefer (1984). Through illness and disability, their previous self-image is no longer congruent with their current physical and mental state. Such crises have been proposed to trigger a grief-like mourning period (Livneh and Antonak, 2005). In chronic illness this has been coined as 'chronic sorrow' (Davis, 1987) and has been observed in a previous study in people with PD (Lindgren, 1996).

For several participants, this change in identity and the loss of self was centred on a lack of confidence due to cognitive impairment.

"it's stopped me from speaking out because what I do do is I get into conversation say with you now and then half way through I start to think why am I saying this, and I don't know why and I forget what I was going to, so it knocks my confidence"

PD 4, 70 year old female, PDD

This lady with PDD described how she felt less confident and it prevented her from joining in discussions. She was able to articulate how her confidence had been affected by cognitive aspects of PD, particularly concentration and memory. She described how she lost confidence in conversing with friends and in groups because she had difficulty in maintaining the thread of a conversation or her own thoughts. Other participants with PD-MCI shared this experience.

"Some people that I've known for 20 years, I've forgotten their name… [I feel] stupid, yes, it would be nice to confidently go to places and meet people and call them by their names and it's always, "hi," this can be people I should know really well"

PD 14, 67 year old male, PD-MCI

"Attention, yes same thing again, I wander off, say you go out with people and someone you know, I just wander away… people must think I'm pig ignorant

because they'll turn around, "I'm not going out with him anymore," trying to hold a conversation with someone who doesn't listen, it's a bit one sided, isn't it?"

PD 16, 65 year old male, PD-MCI

These participants with cognitive impairment described how difficulties with concentration and memory made them feel inadequate around other people. PD 16 described how he thought other people might perceive him as being rude not paying attention to conversations or even walking away mid-conversation. Similar experiences were also expressed by other participants, where they lacked the "confidence" to partake in discussions or seemed "stupid," particularly in large groups.

One gentleman with PD-MCI described feeling as though his friends "don't take as much notice" of him or sometimes his wife "ignored" him which inhibited him taking part in social events. These people with cognitive impairment felt that other people did not understand how they were affected by PD and it was not just a physical illness. Social participation as a result of cognitive impairment was a significant issue that emerged from the data. Social factors have also been shown to be important contributors to QoL These include: social isolation, break down of relationships, marital disharmony, stigmatisation and role change (Singer, 1974; Schrag *et al.*, 2003; Livneh and Antonak, 2005; Phillips, 2006; Calne *et al.*, 2008; Knipe *et al.*, 2011; Hinnell *et al.*, 2012; Murphy *et al.*, 2013)

Conversely, people without cognitive impairment did not tend to define themselves by PD.

"…there wasn't sort of a dividing line where that's pre-Parkinson's and post-Parkinson's it seemed to be from my point of view it seemed to be a gradual thing… I know I've been diagnosed but nothing dramatic has happened, I think that's what I've been trying to tell the tale throughout I can't see any dramatic change yet"

PD 7, 69 year old male, PD normal cognition

Some felt that they were not "poorly" and did not think of themselves as being ill. Some people said that they felt no different to how they were before being diagnosed with PD. Those who did not define themselves by PD tended to describe their conditions as "mild" and expressed that most people would not know they had PD.

This could be due to the symptoms of PD, either physical or cognitive, not being salient to these individuals and thus there they have not had to incorporate their disease as part of their identity.

7.3.2.1 Role reversal

In some participants and carers, their sense of identity had changed in terms of role reversal with spouse, partner or family member. Minor changes in perceived role and position among friends and family were expressed by participants without cognitive impairment.

> *"More and more the responsibility for decisions are hers, I think, from that point of view, our roles have been, kind of reversed…. when it comes to maintenance about the house, I think she does most of that now, as I say my role is reduced to laundry, making cups of tea... [it makes me feel] worthless… it's very difficult to cope with when it's obvious that you're becoming such a burden and a drag"*

PD 17, 75 year old male, PD normal cognition

PD 17 was dissatisfied with the change in role and identity within his marriage. He described himself as feeling reduced to simple tasks around the house because of the motor symptoms he experienced due to PD. He perceived himself of having low self-worth and a burden to his wife, who had become increasingly responsible in many aspects of their lives to compensate for her husband. The expression of role reversal was expressed more in people with PD-MCI and PDD and their carers.

> *"I used to you know I felt head of the family, not that that means, I didn't wield a stick but you know I couldn't I could never do that, but I felt as though I had a position in the family, but now I don't, I feel downgraded a bit, whether that's paranoia setting in or not I don't know but I just feel a lesser person… I feel as though she's the boss now, really and it's quite rightly is too because she's got me to put up with, so there you are"*

PD 6, 68 year old male, PD-MCI

PD 17 described himself as "downgraded" and "a lesser person." He drew a distinction between who he was before cognitive impairment began to have a noticeable impact, and who he was afterwards. This resulted in the carer taking charge in most cases, with some male participants with PD and cognitive impairment describing their wives as "the boss."

"She is boss, we make it clear that she's boss, so that she can do things really quickly and get things done"

PD 18, 69 year old male, PDD

This individual with PDD explained how his wife had become the boss in the household. His dementia had advanced to the point where his incoherent thought processes interfered significantly with daily activities, including planning and executing ideas. Through assuming the role of the person in charge it enabled his wife to "do things really quickly" such as efficiently making decisions and taking charge of all the domestic arrangements.

This suggestion that the wife or female partner of male PD participants had become in charge was echoed in other interviews. Participants with awareness into this role reversal suggested they found this demoralising. This could reflect the stereotyped gender roles held by older generations and the accepted norm: that men were head of the household and the wife was secondary. For example, those who previously looked after their family either through caring of them financially or in a nurturing role were no longer able to do so, resulting in a diminished sense of identity (Julia, 2003).

"…they don't let me do very much, they think I should just sit in a chair and watch them and not worry about whether the shopping gets done or the housework gets done or the shopping gets done, cause they're there and they're in charge and I'm not"

PD 2, 78 year old female, PDD

This participant who had PDD felt that she was no longer in charge of her own household and went on to describe how she was "told off" for doing tasks such as ironing. Many caregivers, particularly those PDD carers, were also aware of a change in role or role reversal with the care recipient.

"I never had children and I never wanted children but now I have two children. i.e. my mam and dad… I think that's probably one of the hardest things is that your parents don't become your parents you become the parent and they become the child."

Carer 2, 52 year old female, daughter of PDD

The carer of PD 2 was her daughter who described how she had reversed roles with her mother with PDD and she assumed the role of the parent. Carer 2 found that due to memory impairments in her mother, she could not rely on her mother's judgement

for day to day tasks and she was "actually not capable of doing it," such as financial issues and dealing with utility companies Furthermore, she described how she protected her mother from things she knew she could not do. This change in role between parents with dementia and adult children has also been reported in previous research (Cecchin, 2001; Barca *et al.*, 2014; Toepfer *et al.*, 2014).

> *"I think we've reversed roles, I've gone from being spoilt, looked after, always have been, and [my husband] did most things and whatnot, and I saw it as if I have to do everything now, and I have to, I don't tell him everything where before we always told each other everything, you know like something with the family I don't tell him because I think eeh he'll just worry about that, he'll just get you know it'll, so I keep a lot to myself"*

Carer 11, 66 year old female, wife of PDD

As with Carer 2, Carer 11 explained how their roles had reversed, although this was in the context of their marriage. Before the diagnosis of dementia her husband took care of her and did most things around the home. Since the onset of dementia she explained that that was no longer possible and she had become the person who took care of her husband. She went on to explain that she no longer discussed family problems with her husband to protect him from anxiety, which was also a significant change in their relationship and role as a couple.

7.3.2.2 Pre-death grief: feelings of loss in carers

Some carers, predominantly those with partners with PDD, spoke of feelings of loss and grief. This was in terms of who they were and their lives with their partner. Perceptions of the self and that of their partner were altered by dementia.

"It undermines your confidence actually and you start to question your life as it was, you think I've had as I say a very charmed, wonderful, happy marriage, life and then it, sort of, it makes you question everything (crying) you are not sure anymore… you know intrinsically that you have had a wonderful, happy relationship, but it just makes you question so much, I don't know, it's draining because you can't really do anything without having to consider it, that sounds awfully self-pitying doesn't it? You know, you just have to think about it all the time, you can't get away from it, so it's a big change what it's done to us, from feeling that I was a very happy, loving person, I don't think I am and sometimes I don't think I have been, so I can't work that out really, I don't know why it makes you question what's happened in the past, but it does, it sort of changes your confidence I think, it makes you less able to deal with stuff; I think that's just basically less confident"

Carer 18, 56 year old female, wife of PDD

This carer spoke of her self-image in terms of incongruence and grief. She described grieving for the life she lost due to her husband's dementia, which was very happy; the change in circumstances made her question whether she really was happy previously. She perceived herself as being less confident, unhappy and indifferent, which was in contrast to the view she previously held of herself. This was a source of obvious distress to her and she was very tearful during this part of the interview.

"It's that change from that dual partnership of having that rock beside you to being the carer really and it changes the balance obviously in the relationship which you will know from everybody else, that's hard actually to deal with and try, not to mask it but to try, you use up a lot of energy trying to make things better, to try and regain that balance, you know, and sort of refocus it, to try and help self-esteem and keep trying to keep, almost maintain the status quo, but it's not"

Carer 18, 56 year old female, wife of PDD

Carer 18 explained the loss of the partnership she had with her husband, her "rock," to becoming a carer was a source of unhappiness as her husband's dementia progressed. This carer described the grief of interpersonal loss in her relationship with her husband, which has also been observed elsewhere (Noyes *et al.*, 2010).

Another carer who cared for her husband with PDD was asked how she had been affected by Parkinson's and dementia.

"He was just totally different, he just you'd think he'd been unplugged, it's the only way I could describe it, he was it just wasn't [my husband] at all, he was totally different, his movements and he just wasn't right at all"

Carer 11, 66 year old female, wife of PDD

Carer 11 implied that her husband was a different person and described him as "unplugged." Interestingly, a key theme discussed by carers was how the person with PD was no longer themselves, particularly those who also had dementia. Several wives described how they felt they were "losing" their partner.

"I suppose they make me feel a little bit depressed at time because I feel as if I'm losing him a bit… I know we've still got a wonderful relationship we've always had a great relationship, sometimes I feel, oh it sounds horrible, as if I'm love, living with an old man which has never been [him], so I do get depressed over it yes"

Carer 1, 68 year old female, partner of PDD

These spousal carers of people with PDD expressed their unhappiness. Carer 1 described her sadness and depression as dementia was taking away the man she had fallen in love with.

This concept of pre-death grief felt by carers has been reported in previous studies (Dempsey and Baago, 1998; Ghesquiere *et al.*, 2011; Lindauer and Harvath, 2014). In participants with cognitive decline where, although the person with dementia is still physically present, they are no longer cognitively or emotionally present, which has been found to be a cause of feelings of loss and grief in the carer (Sanders *et al.*, 2008; Carter *et al.*, 2012). Sweeting and Gilhooly (1997) described "social death" in people with dementia, where the person with dementia was treated as dead before they were actually deceased by carers. Meuser and Marwit (2001) argued that the pre-death grief in caregivers of people with dementia is real grief and is equivalent to death-grief in terms of intensity of feelings.

To a lesser extent, these feelings of grief were also experienced by carers of people with PD-MCI and one carer whose husband had no cognitive impairment.

"I think it's taken the man I married, the man that I thought I was going to spend my old age with, the life we planned which we had it all planned, it's gone, and Parkinson's took it, definitely, at first I was frightened of it I was frightened what it was going to do to us both emotionally and financially,

because that made a vast difference to our life when [my husband] finished work"

Carer 16, 64 year old woman, wife of PD-MCI

"I feel like I've lost my partner, he's become very self-absorbed, it feels like life revolves around him now, it feels like he's living so much in a bubble that he has stopped noticing how things impact on me completely... I actually just feel really lonely… I can't quite find the words to describe how much it's changed our relationship really, I feel like I've lost him in lots of ways (Crying)"

Carer 17, 76 year old female, wife of PD normal cognition

Although these individuals care for someone without dementia, they both described PD as having taken their husbands, although this was expressed by more carers of people with PD-MCI than those without cognitive impairment. Carer 16 described how the life she planned with her husband had gone, again suggesting chronic sorrow and pre-death grief in carers of people with PD-MCI as well as those with dementia (Lindgren, 1996). Carer 17, however, was distressed by changes in his personality. Non-motor symptoms in her husband included apathy which she found upsetting as he no longer seemed like the same person. As with the carers of PDD participants, they suggested feeling something akin to grief at the perceived change in their loved one.

7.3.3 Coping and adjusting to Parkinson's and cognitive impairment

I have outlined the experience of having PD as described by people with PD and carers of people with PD, including the psychosocial impact of the disorder. All participants discussed stressors, whether motor, non-motor or cognitive, which challenged habitual coping mechanisms (Lazarus and Folkman, 1984; Stanton *et al.*, 2007; de Ridder *et al.*, 2008). This led to a disruption in individuals' emotional equilibrium and caused psychological distress (Moos and Schaefer, 1984; Stanton *et al.*, 2007; Moss-Morris, 2013). Coping and adjustment in PD, both in those with and without cognitive impairment, did not seem to be fixed where interviewees detailed periods of both successful adjustment and adjustment difficulties. However the severity of the stressors differed between groups with people with PD-MCI and carers of people with cognitive impairment describing more difficult and distressing situations that affect their QoL. This section explored the extent to which cognitive impairment affected successful coping and adjustment.

7.3.3.1 Coping with cognitive impairment and successful adjustment

Successful adjustment seemed to be discussed more by participants without cognitive impairment.

> *"I can talk about it now, I found that I couldn't talk about it when I got diagnosed I don't know why like, it's just I didn't want to talk about it as well like you know, but now I can talk to people about it like you know and mainly to say look I've got Parkinson's but I get on with life and I'm doing fine"*

PD 3, 62 year old male, PD normal cognition

This gentleman without cognitive impairment described how initially it was difficult to accept he had PD but overtime he learned to adjust, which required good coping strategies. However, in people with cognitive impairment, they may not have adequate cognitive reserve to implement these coping strategies (Hindle *et al.*, 2014; Kudlicka *et al.*, 2014). Social support seemed to be the most frequently utilised; caregivers were central to helping the person with PD cope.

> *"Well [my wife]'s a great coper, she thinks positive all the time, and she just gets on with it, she won't allow me to be defeatist, you know she makes light of things"*

PD 5, 80 year old male, PD normal cognition

> *"He's not too bad at the moment, how it affects us in the future I don't know, it's something I've got to deal with you know, so I know he's got it so therefore it's up to me to take care of him as best I can"*

Carer 3, 66 year old woman, partner to PD normal cognition

The carer tended to the main source of social support. Participants often described how they would be "lost" without their carer and that they would not know how to cope without their partner being there. They described how the support from them helped them cope with PD and that this has had a positive effect. High perceived social support has been shown to be a factor in successful adjustment to chronic illness and to better QoL in general (Schreurs *et al.*, 2000; Bond and Corner, 2004; Brettschneider *et al.*, 2013). Social support had been suggested as a stress buffer and can be useful to aid active coping and finding meaning or benefits from chronic disease (Thoits, 2011).

Carers frequently helped with dressing, putting on shoes socks and particularly with fastening small buttons. For most, physical help tended to be mild such as helping

them out the car or taking charge of medication. Carers also reported implementing items around the home to help, such as medicine boxes, grab rails and night lights. The interviews with carers suggested that they compensated for the cognitive impairments in the care recipient.

> *"He's more forgetful, he leaves things and I just automatically put them away, I don't make a fuss about it, like he'll do a job and he'll leave all the things and I just automatically put things away because at least he's trying to do the job and that's how I look at it"*

Carer 7, 70 year old female, wife of PD normal cognition

Some carers discussed "protecting" the care recipient from the realities of their condition and did not disclose changes in their memory or what efforts they made to protect their feelings. However, evidence suggests this may lead to increased perceived stress in carers (Drutyte *et al.*, 2014).

Another key coping mechanism was adaptation; participants described ways they had developed strategies to adapt and cope with the changes associated with PD. These individuals described being able to adapt to having PD and found that these modifications to daily life were beneficial and made challenges or difficulties easier to cope with.

> *"I cannot remember things, so I write a lot of things down, we've got a calendar and we write we both write in it, so the theory being that we'll glance at it and remind each other what's going on"*

PD 6, 68 year old male, PD-MCI

> *"I've got to write on the calendar or, or I just wouldn't I just wouldn't attend like half of them I wouldn't be here… and I'm always checking them to see if I've put the right dates on like you know, just checking and checking and checking just to make sure"*

PD 8, 72 year old male, PDD

These participants with cognitive impairment described adapting to their memory problems by writing this down. By writing down appointments and events on the calendar and developing the habit or regularly checking it, they suggested that they felt more in control. Other methods of adapting to memory impairment were described such as alarms or pill boxes to regulate medication. Adapting in this way to cognitive stressors has been described as problem-focused coping as described by the

stress and coping model of adjustment (Lazarus and Folkman, 1984). Problem-focused strategies involve trying to find a solution to a chronic illness related stressor. The use of problem-focused coping strategies has been suggested to increase perceived control and decrease feelings of uncertainty (Sanders-Dewey *et al.*, 2001; Moos and Holahan, 2007). It has been suggested that cognitive impairment is a barrier to task orientated coping strategies (Hurt *et al.*, 2012). However, with encouragement of carers, some participants with cognitive impairment were able to implement these strategies to minimise the distress of memory problems.

Those displaying positive attitudes and optimism seemed to have more perceived control of the situation; they were able to identify and implement changes that they could make and thus adapt to the situation.

> *"I have an upbeat personality, I get on quite well with people, the majority of people, I get on with, I'm a good organiser, so I can organise things so that things run smoothly, as best I can, just shrug off things that go wrong"*

Carer 13, female carer of PD-MCI

This sense of control and empowerment was clearly demonstrated by those displaying positivism and finding meaning as a carer, particularly in carers of people with cognitive impairment.

> *"When she's come out the shower and I wrap her in the towel and I dry and she's like, "oh you're angel I don't know what I'd do without you," and that's like more than if you'd won the lottery to be honest, it's like more than anything so so yeah… I think you realise how lucky you are and how health is more important than money or how you look or what house you live in what things you own, it makes you a better person, that's what I believe, it's made me a better person, it's enriched my life, yeah without a doubt"*

Carer 2, 52 year old woman, daughter of PDD

> *"I wouldn't say it's affected our marriage at all you know I think it sometimes draws you closer doesn't it you know so no"*

Carer 8, 72 year old female, wife of PDD

> *"[Our relationship] probably has had its dips but overall I think it's probably better than it would have been without it, probably, because you tend to have highs related to the lows don't you, so sometimes you've got to have the lows before you appreciate the highs, and I think overall I would say it's probably a better relationship than it would have been"*

Carer 10, 61 year old female, wife of PD-MCI

These carers expressed increased appreciation for the care recipient and felt their relationships had improved. Carer 2 expressed an enrichment to her life from caring. Finding appreciation and meaning in caring for a loved one has been reported in previous research. Netto *et al.* (2009) found that informal familial carers of people with dementia exhibited positive personal growth, where they become more patient, understating and resilient as a result of caring for a loved one. They further observed gains in the relationship, where the relationship improved with the care recipient. Personal growth in spouses of people with PD was found to have a positive effect on the relationship (Mavandadi *et al.*, 2014). Furthermore, in spousal carers a good relationship with the care recipient has been shown lower strain and may have protective factors (Lyons *et al.*, 2009).

To a lesser extent, several participants suggested they were able to find meaning and appreciation in life since they were diagnosed with PD.

> *"I think as well you know in life you learn to just cope don't you I mean especially at my age and [my wife's] age, you've been through most of your life you know there's nothing much surprises you and there's so much good things in our life as well that's the main thing you see, the good outweighs the indifferent and the bad, we're just I'm lucky to be alive and we seem to enjoy life together and a lovely family and I love being around them,"*

PD 6, 68 year old male, PD-MCI

> *"I think it might have brought us a bit closer together because we're we try to we try to do more by ourselves than we used to like you know, just to have a bit of time to ourselves like"*

PD 8, 72 year old male, PDD

Other participants felt they were "lucky" that their PD was not more severe and that "it could have been worse." A few participants mentioned that having cancer would be worse or that PD would not cause death and were thus were able to find some comfort in this. Finding meaning, as described by the participants above, can include the perception of the impact of the illness on the self or changes in priorities and future goals, for example the appreciation of family and being happy may become a priority over money or material possessions (Walker *et al.*, 2004). The cognitive adaptation model states that successful adaptation is centred around the search for meaning, regaining perceive control and restoring self-esteem (Taylor, 1983). It has

been proposed that finding meaning is a key component of psychosocial adaptation (Fife, 1995).

Expressions of optimism and positivism, despite the degenerative properties of PD, were expressed by most people with PD.

> *"I feel very positive about the future… I feel that if I can go on like this for the next 10, 20 years, I would be quite happy and I feel great at the moment, I've never felt better"*

PD 3, 62 year old male, PD normal cognition

> *"Well, the main thing is we stay optimistic and don't let the buggers get you down… dementia, weak or strong or Parkinson's weak or strong, will get all of us, at some point over the coming years, so keep smiling"*

PD 18, 69 year old male, PDD

As detailed in Chapter 1, individual differences are central to how successfully a person adapts to chronic illness (Stanton *et al.*, 2007). Personality traits of optimism have been found to be protective of negative illness beliefs and predictive of better QoL (Hurt *et al.*, 2014). Optimism has been suggested to facilitate coping and adaptation due to the individual having positive expectation and thus may be more motivated to achieve specific goals (de Ridder *et al.*, 2000; Wrosch and Scheier, 2003) as detailed by the self-regulation model of adjustment (Leventhal *et al.*, 1998).

Acceptance was an important issue in successful adjustment to PD.

> *"I suppose I have a rather slap happy regard to it, there's no point in being miserable, people are doing their best to help me so you get involved along with the same thing so if I do something stupid I just laugh."*

PD 1, 87 year old male, PDD

This participant indicated he had good psychosocial adjustment; he had made efforts to adapt to the situation and accepted social support from others. Furthermore, he displayed using humour as a coping mechanism, which can act as a buffer for stress and stressful situations.

> *"Well I'm well I feel that it would be nice if it lasted longer, I still look forward, I mean I still plan things and sort of quite interested in the house and how it's sort of furnished and decorated and that sort of thing you know I look forward to the future, we realise it's going to be that it's limited in quality and time"*

PD 9, 81 year old male, normal cognition

"Well I haven't got a crystal ball, I don't know what's round the corner, I try and keep us happy and as mobile as you can… I've got enough common sense to know that I've got [Parkinson's and dementia] and you cannot you cannot really beat it but you learn to live with it and accept it, and I think if you've got a positive attitude you'll struggle by, the Parkinson's I never dreamt I would finish up with something like that but it's here and we've got to live with it, I suppose if you didn't accept it you've got a problem"

PD 11, 67 year old male, PDD

Acceptance, of physical and cognitive difficulties, seemed to be central in successful adjustment and perceived QoL. This shift in priorities has also been observed in other studies (Hounsgaard *et al.*, 2011; McLaughlin *et al.*, 2011). Participants who described acceptance of their condition, the impact this had on their lives and that the condition would deteriorate seemed to demonstrate that a new equilibrium in QoL had been reached. They reported less psychological distress and used a number of coping strategies to maintain their new equilibrium, which suggested successful adjustment. (Moss-Morris, 2013).

7.3.3.2 Adjustment difficulties

Interviewees disclosed psychological disturbances, such as fear, anger, anxiety and depression, which are possible indicators for unsuccessful adjustment and accommodation (Moos and Holahan, 2007). This may negatively impact on QoL (Suzukamo *et al.*, 2006). Others suggested that coping was an ongoing process and there were times when they struggled to as cope well compared to others.

Only two people with PD without cognitive impairment described repeated difficulties adjusting particularly when regarding the future.

"I'm not sure I am coping with them… I tend to be more and more negative about what I can and can't do, you know, yes, I go to an exercise class on a Tuesday which is sponsored and organised by Parkinson's UK, the physios are specially trained, they see people there who have got more advanced Parkinson's than mine, I think two things one, how lucky I am not to be in their state, the second thing is this is what I'll become eventually, I find that a bit depressing"

PD 17, 75 year old male, PD normal cognition

The interview with this gentleman gave the impression he had not successfully adjusted to having PD. Throughout the interview he seemed to vent his emotions and

repeatedly voiced feelings of helplessness and low self-worth. This can be indicative of poor psychosocial adjustment (Moss-Morris, 2013). There was also evidence that he catastrophized, which was also displayed by two other individuals who seemed to have poor adjustment. Participants with normal cognition who gave the impression of adjustment difficulties tended to be younger.

Participants with PD-MCI seemed to disclose more frequent periods of adjustment difficulties compared to those with either PDD or no cognitive impairment.

> *"It's Parkinson's, anybody who has got an illness of that or any nature it's going to if it is a serious illness, they're going to get upset by it and wake up in the morning and think oh bugger, (laughs) because that's the sort of feeling you do get occasionally especially if you wake up and it's a lovely day like today, fantastic, and then you wake up properly and you remember that you've got Parkinson's"*

PD 10, 66 year old male, PD-MCI

> *"It governs your whole life from the minute you wake up in the morning to when you go to bed at night, you can never stop thinking about it because it's always there"*

PD 13, 66 year old male, PD-MCI

Both PD 10 and PD 13 suggested that PD was salient in their lives and they were often reminded of it. PD 10 described feeling upset and frustrated by having PD and the stressors associated with having it, while PD 13 was at times depressed. Crisis theory states that successful adjustment to chronic illness is mediated by illness stressors, the extent to which the illness intrudes on your life (Leventhal *et al.*, 1998). Therefore it could be supposed that those who have adjusted more successfully have less intrusive or salient symptoms than those who have not successfully adjusted to having PD and/or cognitive impairment. However, neither of these participants described psychological distress as a constant feature of their lives and they used adaptive or constructive coping mechanisms to help them adjust to their condition at least in the short term.

Interviewees who seemed to struggle to cope successfully seemed to demonstrate more frequent low mood and worry than those describing positive coping mechanisms and successful adjustment.

"I was angry and bitter… it took me a long time to get used to saying I have got Parkinson's… but I just couldn't believe it at the time I just couldn't believe it, I still can't at times, I think, how am I going to cope if I haven't got [my husband] here? …I don't feel bitter and I don't feel angry now, I really did then I thought it is not fair, I am just coming up to retirement as well and [my husband] and I were going to go on holiday and just please ourselves"

PD 15, 67 year old female, PD-MCI

This lady with PD-MCI described having PD as unfair and had stopped her and her husband enjoying their retirement. She described herself as angry and bitter initially, although these feelings had dissipated. Nonetheless she gave the impression of still struggling to cope at times and was frustrated at needing her husband to take care of her. The impact of chronic disease on interfering with life roles and relationships, as described by PD 15, has been suggested to be a factor of disequilibrium and poor adjustment (Lazarus and Folkman, 1984).

Some individuals who found it difficult to adjust explained how they did not feel they had anyone to talk to.

"Nobody, I mean the wife is as good as gold like but she's not a very good listener, I mean she's not, she's sympathetic but well at the same time I've always kept a lot of things to myself like that, I'm pretty inward like, even before I had the Parkinson's I kept a lot of things to myself like, just I find it hard to express myself like you know"

PD 8, 72 year old male, PDD

Some participants described how they "bottled things up". As PD 8 described, some participants did not feel they were able to talk to their partner or to other people about their feelings and the difficulties they experienced. Sometimes this was because they did not want to worry their loved ones, whereas other individuals described themselves as having always been less inclined to seek social support. Not disclosing their worries and concerns may lead to low perceived social support and repression of emotions, leading to continued disequilibrium, difficulties adjusting and poor QoL (Moss-Morris, 2013).

A few participants described how the uncertainty of PD was difficult to adjust to.

"It's changed in that looking to the future is not good, in fact a bit bleak at times if I do get upset about the possible prospects… I get a bit miserable, just I

mean it's difficult to describe and put your finger on, just I suppose depressed is the only word that easily springs to mind"

PD 10, 66 year old male, PD-MCI

"…a bit depressed, I'd feel a lot better if I knew it was getting better rather than worse, but it can't be helped that's it… [I'm] a bit uncertain about [the future] not knowing how things are going to turn out… my mother had dementia and her sisters… so it makes me think you know there's a chance I might get dementia"

PD 12, 74 year old female, PD normal cognition

PD was described as unpredictable in terms of day-to-day life and in terms of the future. A qualitative study by Stanley-Hermanns and Engebretson (2010) found that uncertainty and unpredictability, both in terms of daily life and the future, to be a main theme in their exploration of experiencing PD. Previous studies have found that uncertainty can lead to psychological distress (Sanders-Dewey *et al.*, 2001).

Three people with PDD described repeated problems with coping.

"I feel as if I'm a burden I don't want to be a burden… I'm not doing what I should be doing, like I should be doing house work and I should be doing washing and ironing and I'm not…"

PD 2, 78 year old female, PDD

PD 2 described herself as a burden to her family and also suggested feelings of guilt and frustration about being cared for, which she seemed to find difficult to cope with as they were outside her control. According to the cognitive appraisal model of coping (Taylor, 1983), loss of perceived control can be a barrier to successful adjustment. She also suggested coping by wishful thinking, which has been shown to contribute to life dissatisfaction and poorer perceived QoL (Lazarus and Folkman, 1984). One gentleman with PDD described how he had recurrent thoughts of suicide since his diagnosis.

"That does worry me a bit like where am I going to end up like, what am I you know will I be carried out like that you know, will I end up in this like this you know, if if I thought if I was going to end up like that I'd rather go now like not I would never overdose myself or nothing like that like, that has come in my mind before like but I wouldn't have the nerve to do it I don't think… if you have a couple of [drinks] like and you could think about harming yourself like you know, easy like you know"

PD 8, 72 year old male, PDD

PD 8 described repeated low mood and psychological distress over the last few years. The uncertain future of PD and dementia progressing to the point of dependency made him feel he would rather die than live dependent on others and had contemplated overdosing in the past. Although he had dismissed the probability of committing suicide, he acknowledged that when he was low or had occasional alcoholic drinks, these feelings returned. Suicide and suicidal thoughts in people with dementia, predominantly within one year of diagnosis, has been observed in previous studies (Purandare *et al.*, 2009; Möller *et al.*, 2013). However, two other people with PD but without dementia also disclosed past suicidal thoughts.

7.3.3.3 Do cares find cognitive impairment more difficult to cope with?

The premise of whether cognitive impairment was an additive difficulty to caring for someone with PD was explored. As described above, carers used a variety of coping mechanisms to adjust to the caregiving role, and in most cases adjust to the change in their partner. Most carers who did not have to cope with cognitive impairment in addition to PD suggested they had successfully adjusted to their spouse having PD.

> *"…if I have problems I cope, I'm a coper… but you can't avoid people getting ill and causing anxiety and upset, you cannot avoid that, it's part of life isn't it and everybody got to deal with it, and I do deal with things"*

Carer 5, 69 year old female, PD normal cognition

However, some carers of people without cognitive impairment found it difficult to cope at times. A fundamental issue was the changes in the lives of the carer were a source of distress and depression.

> *"It has affected our lives tremendously, I get very depressed about it but I try not to let him see and make light of it, but it's I don't think people realise outside the disease how it does affect you"*

Carer 9, 78 year old female, wife of PD normal cognition

> *"It feels like our quality of life has been destroyed, it has impacted on our lives far more than any of the other things that he's had wrong, really, and the plans we had… it feels that we're just sitting waiting to die, I just think we should be getting on with our lives really"*

Carer 17, 76 year old female, wife of PD normal cognition

Carer 17 described her QoL as "destroyed" by her husband's PD. Throughout the interview with this carer, it was implied and sometimes stated that she had poor

psychological adjustment since her husband was diagnosed with PD. She at times stated worry, anxiety, frustration and anger. Both Carer 9 and Carer 17 explored the concept of being depressed by their husband having PD, which could indicate an adjustment disorder with depressed mood (American Psychiatric Association, 2000).

Carers of people with cognitive impairment reported more numerous and frequent difficulties. More noticeable cognitive impairment appeared to cause the greatest challenges to successful coping, with carers of people with PD-MCI disclosing fewer difficulties in coping compared to those with PDD.

> *"I suppose that's the kind of concern that I've got that I don't know whether things will be very gradual or whether there could be a sudden deterioration, I suppose that's what I'm so scared about that things would just change overnight (tearful)"*

Carer 10, 61 year old female, wife of PD-MCI

Carer 10 implied she still had episodes of low mood. Her husband had delusions in the past and cognitive difficulties were a prominent feature she had to adapt to. Furthermore, Carer 10 was worried about the future, that her husband's cognitive problems would suddenly get worse. This was shared by many carers. The alternation between acceptance and uncertainty about the future has also been found in previous qualitative research by O'Shaughnessy *et al.* (2010), who explored the effects of progression of disease in spousal carers of people with dementia.

Cognitive problems in the care recipient seemed to be a source of frustration to carers.

> *"I think I'm like a coiled spring at times, the slightest thing seems to, I'm just wound up sort of thing, and you would think oh just let it go by… as I say, I do get myself stressed up"*

Carer 15, 71 year old male, husband of PD-MCI

> *"I just turn off if I think he's being unreasonable, it's no good arguing with him because he doesn't think logically like I do now, I think, well I can stand here and have a stand up argument with him, he's going to start shaking because he's got upset, at the end of the day it won't change anything, just walk away and leave him… that's it, I don't know I just cope I just do it, I have to"*

Carer 16, 64 year old female, wife of PD-MCI

Carer 15 described himself as a "coiled spring" and could overreact to situations that would not normally affect him as he undertook increasing responsibilities to

compensate for his wife's disease. Carer 16 described her frustration in her husband where he was no longer able to think logically which caused arguments. A qualitative study also reported frustration and impatience in carers of people with mild cognitive impairment and early dementia (Adams, 2006) which can impair QoL.

For some carers, cognitive impairment became a barrier to the marital relationship.

> *"I think more about [my husband] than I would have done, I think it's as simple as that, I think I'm quite a single minded person who would probably have just you know gone on doing my own thing, thinking less about him, but because of the Parkinson's I think I have to take him into account much more, sorry" (tearful)*

Carer 10, 61 year old female, wife of PD-MCI

Carer 10 felt as though she had to change to take her husband into account more as a result of PD-MCI, whereby she put him first. However this was a source of distress for her as it impacted negatively on her self-esteem and led to higher perceived stress. She was visibly upset as she implied she was dissatisfied with her new self-image and sense of falling short of what she should be as a carer.

> *"I mean our whole life has just changed you know, everything has just changed… it does upset me but you cannot sit in a chair and cry because he would get upset if I was sitting round crying I do have a few tears mind but out the road and have a few tears, but I would never let him see that I was upset you know because he would be upset that I was upset, I would never let him see that… you just get on with it, have a few tears and roll your sleeves and get on with it"*

Carer 11, 66 year old female, wife of PDD

Carer 11 disclosed that she sometimes did not cope as well and felt distressed. For Carer 11 the presence of dementia and how it changed their lives was the source of distress. This was also discussed by other carers of people with PDD.

> *"Knowing that something is not right that you can't fully share because it's so scary for you to share what your worries are, so it's like double the burden… you, sort of, protect people really and you protect your loved one most and then it's this, sort of, this is a spiral of care or something, it's a spiral of protection as well that you have for folks over the illness I suppose and care"*

Carer 18, 56 year old female, wife of PDD

Both carers described being cut off from their partners in terms of interpersonal support. They both described wanting to protect their loved ones, which was

described as a "spiral of protection" by Carer 18. Carer burden has been shown to increase with the carer's perception of satisfaction with social support, the marital and sexual relationship (Edwards and Scheetz, 2002; Schrag *et al.*, 2006). Most carers of participants with cognitive impairment felt isolated and lacking social support; they felt unable to talk to their partner, who was their usual source of social support, as they wanted to "protect" them from their worries. Carer 18 described this as a double burden, suggesting dementia was an added barrier to interpersonal support in her relationship. The loss of the lives they had and their plans for the future as a result of dementia was also observed by Robinson *et al.* (2005). This could be inferred as evidence of chronic sorrow in carers, which has previously been found in carers of people with PD (Lindgren, 1996).

Carers of people with cognitive impairment, who also had intrusive neuropsychiatric features, suggested successful coping and adjustment was more difficult.

> *"[my husband] got it into his head that the house was falling down and that was a major anxiety for quite a while despite every reassurance from me… but it was a genuine belief at the time, he really was worried that when we got the surveyor round you know to sell the house he would probably find something like the house was subsiding or there was a major crack in it and the whole thing was going to go down like a pack of cards, and at first I just laughed at it but I stopped doing that because it's just a horrible fear (crying)"*

Carer 10, 61 year old female, wife of PD-MCI

This lady found it very difficult to deal with the delusions her husband exhibited and was unable to cope with it. She was very upset and found that she could do nothing to help him, which added to the distress. This was shared by the two other carers whose partners had delusions that were intrusive.

> *"…there's nothing much I can do about it, you see it's difficult because say if you hurt your foot I could help you with your foot and say oh I'll put a bandage on or whatever but if it's something mental the mind you don't know how to cope with that, you can talk to and I'm talking to you I can talk to her and sometimes you see well it's not getting through to her you know because it keeps happening all the time… how do you cope with that, you know?"*

Carer 4, 77 year old male, husband of PDD

Carer 4, whose wife had PDD, explained how he struggled with the frequent hallucinations his wife had. He described how he found that practical help came more

easily to him as there was something he was able to do. However, as there wasn't a tangible solution to help his wife, since reasoning with her that the hallucinations of family members were unreal had failed, he became frustrated and distressed. He seemed to find situations that were outside of his control more difficult to cope with and adjust to. Schrag *et al.* (2006) found hallucinations increased carer burden. More severe neuropsychiatric symptoms have been shown to contribute to carer burden while features such as hallucination and delusions in PD were associated with carer stress (Williamson *et al.*, 2008; Oh *et al.*, 2015).

A few carers openly disclosed that they were not coping, again these feelings were more significant in carers of people with PDD.

> *"I blame him and that's really not coping because it's not his fault, and I know it's not his fault and I say to myself it's the illness, but sometimes still you want to blame him for your change in life and that's completely wrong and cruel, (Crying) so that's really not coping and, you know, just being less than kind, you feel horrible"*

Carer 18, 56 year old female, wife of PDD

The husband of Carer 18 had dementia that had progressed quite rapidly. As described above and in previous sections, she faces numerous stressors as a result of the dementia, rather than the other motor and non-motor symptoms of PD. These were very disruptive and caused psychological disturbance including fear, anger and distress, which are all associated with unsuccessful adjustment (Moos and Holahan, 2007). She also indicated she frequently faced threats to her self-image and perceived self-efficacy in addition to the difficulty of facing an uncertain future, which have been suggested to be features of poor psychosocial adjustment (de Ridder *et al.*, 2000). As described by Carer 18, some carers who were not coping vented their frustration on the care recipient, which resulted in self-blame and guilt . This has also been found in caregivers of people with Alzheimer's disease (Pagel *et al.*, 1985). Self-blame in dementia caregivers has been associated with increased depression, anxiety and hostility (Morris *et al.*, 1988).

"I actually think we have a good quality of life, because we enjoy the time we spend together… I think our quality of life has changed, but it's not a bad quality of life that's been left in its place, it's different to what we had planned, but we still do okay, yes definitely"

PD 16, 64 year old female, wife of PD-MCI

Therefore good psychosocial adjustment in carers of people with PD and cognitive impairment seemed to depend on how intrusive and disruptive the features of cognitive impairment were. However, some carers were able to successfully adjust to minimise the impact of cognitive impairment on their QoL and sense of wellbeing.

7.4 Discussion

The aim of this study was to explore the impact of cognitive impairment in people with PD on their QoL and on the QoL of their carer. This study found that many different aspects of PD disrupted QoL, including motor symptoms, non-motor symptoms and cognitive impairment. As PD progressed, both individuals with PD and their carers discussed situations that had challenged their ability to cope, had caused psychological distress and resulted in poorer QoL. This is consistent with other studies (Charlton and Barrow, 2002; Goldsworthy and Knowles, 2008; Chiong-Rivero *et al.*, 2011; McLaughlin *et al.*, 2011; Shin *et al.*, 2012a; Shin *et al.*, 2012b; Drutyte *et al.*, 2014; Kang and Ellis-Hill, 2015).

The results of this study found that for some individuals, cognitive impairment can negatively impact on their QoL and caused emotional distress, but not for all. It seemed that, particularly for the person with PD, if they did not have an awareness of any cognitive impairment then their emotional equilibrium was not disturbed. Therefore, it was only in people who found cognitive impairment, either as PD-MCI or PDD, to be intrusive to their daily lives that were distressed and described poorer QoL.

For these people with PD and their carers, cognitive impairment affected a range of aspects of their QoL: social participation, leisure activities, employment, independence, daily activities, mood and identity. Role reversal, where the perceived roles had changed between the person with PD and the carer, was a central issue and a source of emotional distress. For example, the change in circumstances forced a change in the position of the couple in the household; the wife had assumed the head

of the household as a means of adjusting to the physical and cognitive abilities in the place of her husband with PD, which is contrary to gender stereotyped roles often held by the older generation (Pinquart and Sorensen, 2006). Role reversal in people with dementia and dissatisfaction has also been reported previously (Cecchin, 2001; Barca *et al.*, 2014; Toepfer *et al.*, 2014). However, carers adopting this role may be protective for the care recipient's QoL, where their self-esteem is protected by the carer shielding the person with PD from the change in circumstances. Nonetheless, one study suggested that this may result in increased perceived stress in carers (Drutyte *et al.*, 2014). Conversely, carers described pre-death grief towards their spouses or partners with cognitive impairment, although this was predominantly expressed by PDD carers. Pre-death grief, which has also been referred to as chronic grief, chronic sorrow and social death, has previously been described in carers of people with dementia (Dempsey and Baago, 1998; Noyes *et al.*, 2010; Ghesquiere *et al.*, 2011). Carter *et al.* (2012) however, found that in carers of people with PD, cognitive change in the care recipient was the strongest predictor of carer grief. These findings are consistent with our results in this study.

The results of this study showed that participants were able to use protective factors to prevent QoL being disrupted. Social support has been supposed to act as a buffer for stress and aids active coping (Thoits, 2011). High perceived social support has been shown to be an important factor to successful adjustment (Bond and Corner, 2004; Brettschneider *et al.*, 2013). Optimism has also been suggested as a protective factor where being optimistic may facilitate coping mechanisms to promote subjective wellbeing and good health (Wrosch and Scheier, 2003). In PD, optimism has been reported to protect against negative illness perceptions and predicted better QoL (Hurt *et al.*, 2014). Mutuality, or the quality of the relationship between the carer and the care recipient, has also been found to be protective in dyadic PD couples. Lyons *et al.* (2009) showed mutuality was protective of role strain in carers over a 10 year period. Greater mutuality between spouses and people with PD has also been associated with better mental health, lower carer burden and better carer QoL (Tanji *et al.*, 2008). Positive growth and finding benefits or meaning have also been found to be significant in successful adaptation and maintaining QoL (Fife, 1995; Walker *et al.*, 2004; Netto *et al.*, 2009; Mavandadi *et al.*, 2014).

However, this study has also shown that emotional equilibrium and adjustment are not fixed; instead QoL fluctuates as both carers and care recipients experience stressors related to PD and/or cognitive impairment. The results show a number of examples where interviewees described not coping including: uncertain futures, depression, worry, fear, guilt and anger. While not coping was described by all people with PD, those with cognitive impairment and PD seemed to express more instances of not coping. It has been previously suggested that successful coping and adjustment rely on having sufficient cognitive reserve to instigate effective coping strategies (Hindle *et al.*, 2014). Furthermore, two studies have proposed that even mild cognitive dysfunction could impair the implementation of helpful coping strategies (Hurt *et al.*, 2012; Kudlicka *et al.*, 2014).

Whether PD-MCI was more difficult to cope with for carers in comparison to only having PD was unclear; the descriptions from carers were mixed, with some coping well and others finding coping more difficult. This may be due to the severity of cognitive impairment in some people with PD having a less disruptive effect on the lives of the carer than others, as their functional ability may be more intact (Martínez-Martín *et al.*, 2007; Leroi *et al.*, 2012b). However, PDD carers seemed to describe very clearly that dementia was more difficult to cope with than having PD. PDD carers reported an increase in responsibility, greater emotional distress and feeling overwhelmed or unable to cope with the changes. Recent studies have found that neuropsychiatric symptoms in people with PDD have been associated with increased carer burden (Shin *et al.*, 2012b; Martinez-Martin *et al.*, 2015; Oh *et al.*, 2015) and carer distress (Stella *et al.*, 2009; Lee *et al.*, 2013). Furthermore, carer distress was shown to be higher in those caring for people with PDD and higher scores of delusions, hallucinations and agitation (Aarsland *et al.*, 2007a), which is similar to the findings of this study.

There are several strengths to this study. All PD participants were newly diagnosed when recruited to the ICICLE-PD study, and so at 36 month evaluation participants had lived with the diagnosed for the same length of time. Participants were purposefully sampled using theoretical criteria to give a representative sample of carers and people with PD across cognitive groups. Semi-structured interviews were used which gave

flexibility and allowed the researcher to explore new themes generated by participants. The use of qualitative interviews was also advantageous in exploring QoL, which, given the complexity and subjectivity of the concept of QoL, makes it challenging to measure, particularly as it fluctuates over time. Finally, the sample size was relatively large for qualitative studies with a total of 36 interviews used for analysis.

There are several limitations to this study. First, the gender ratio of people with PD and carers were both uneven, with more male PD participants and more female carers taking part. However, this reflects the reality of the disease, where studies show proportionally more males with PD, and a society that relies on female care provision both formally and informally (Glozman, 2004; Schölzel-Dorenbos *et al.*, 2009; Lavela and Ather, 2010; Peters *et al.*, 2011; Tew *et al.*, 2013; Santos-Garcia and de la Fuente-Fernandez, 2015). Similarly, most of the carers were the spouse or partner of the person with PD; thus the experiences of other relatives, such as adult children as carers, are underrepresented. Finally, the interviews and analysis for this study was conducted by a researcher (RAL) who had reviewed the literature around the issues discussed. Therefore, the results here were not entirely inductive, which is part of the interpretivist approach to qualitative research (Green and Thorogood, 2009), as the researcher had preconceived knowledge in this field which could not be suspended. However, this has been previously criticised as unrealistic (Bryman, 2008).

In summary, the results of this qualitative study show that cognitive impairment does seem to affect the QoL and wellbeing of people with PD and their carers, in addition to other motor and non-motor symptoms. However, the extent to which individuals are affected seemed to depend on how salient the cognitive features were, how much they impacted on their daily lives, and whether they had the personal resources to cope and successfully adapt to these changes. The results also highlighted that QoL is not a fixed state and fluctuated as the disease progressed and stressors emerged. The discussion which developed around protective factors for good QoL was not foreseen, but provides possible opportunities for future interventions to enhance coping mechanisms.

Chapter 8 Conclusions and Future Work

This study aimed to explore the relationship between quality of life (QoL) and cognitive impairment in people with Parkinson's disease (PD) and their carers using a mixed methods approach. In Chapter 4, mild cognitive impairment in PD (PD-MCI) was found to independently predict QoL in newly diagnosed people with PD in addition to PD motor severity, depression and neuropsychiatric symptoms. However, the operational cut-off of PD-MCI was found to be an important factor when determining the effect of PD-MCI on QoL. Using the Movement Disorder Society (MDS) criteria for PD-MCI, a cut-off of 2 standard deviations (SD) below normative values was the only cut-off, compared with 1 and 1.5 SD cut-offs, that was associated with meaningfully poorer QoL. This analysis also identified 22 PD-MCI subtypes using the proposed MDS PD-MCI criteria with no significant QoL differences between the most common subtypes. This suggests that the severity of cognitive impairment *per se,* rather than the nature of the impairment, may be more impactful on the individual with PD. Furthermore, the number of subtypes found in this sample would likely be impractical for clinical use.

Chapter 5 examined longitudinal changes in cognition and QoL in people with PD over 36 months. Clinically meaningful declines in QoL scores were observed in those with baseline PD-MCI (2 SD cut off), but not in those classified with normal cognition. Furthermore, baseline cognitive measures were significant predictors of QoL at 36 months. Thus, the MoCA, a commonly used clinical measure of cognition, may be a useful screening tool for predicting those at risk of poorer QoL in the future. However, poorer attention scores had a greater predictive accuracy, suggesting that if an attentional analogue of the MoCA could be developed, this might be even more useful. Factor scores from principal component analysis resolved the apparent disparity between non-significant QoL scores for PD-MCI subtypes, and permitted the analysis of groups of neuropsychological tests and QoL. Using mixed effects modelling, the interaction between time and cognition was found to significantly predict poorer QoL, but not cross-sectional cognition. However, cognitive change in this cohort was relatively modest and therefore unlikely to contribute to large changes in QoL for most subjects. As the disease progresses and cognition declines into PDD, it may have a greater relative impact. Overall, the results suggested that cognitive decline

contributes to worsening QoL, with changes in attention over time having the greatest predictive accuracy.

The effect of cognition on carers of people with PD was evaluated in Chapter 6. Most people with PD who had carers were male and married, while most carers were female spousal carers. The results demonstrated a significant association between PD QoL and carer QoL, suggesting a mutual dependence or that the QoL of both people in the relationship is dependent on the same underlying features. Carers of people with PDD reported significantly poorer QoL scores than PD-NC or PD-MCI carers. There was a significant association between cognitive scores and carer QoL, and attention scores were the strongest predictor of carer QoL compared to other cognitive measures. However, this result should be viewed with caution as only one measure out of the two questionnaires used to assess carer QoL was predicted by cognition.

Finally, the results detailed in Chapter 7 used qualitative research to explore cognition in PD and its effects on carers and people with PD. The results showed that the relationship between cognition and QoL in people with PD and their carers was complex. Some carers and people with PD spoke about how cognitive impairment had a negative impact on their QoL and caused emotional distress, but not for all and some discussed their lives more generally within the qualitative interviews. The extent to which individuals found cognitive impairment distressing depended on how intrusive they found the symptoms to their daily lives; this was predominantly expressed by PDD carers.

Furthermore, the interviews suggested that QoL fluctuated as both carers and care recipients experienced stressors relating to PD and cognitive impairment, which disrupted the emotional equilibrium of the individual and challenged successful adjustment. Interestingly, protective factors emerged from the qualitative analysis; participants who described: social support, optimism, mutuality between carer and care recipient and finding meaning from their illness experiences seemed to report better psychosocial adjustment and QoL. Therefore, QoL may not necessarily be permanently reduced by having PD and cognitive impairment, or by being a carer: in both cases a good QoL can be achieved. However it is important to be aware that QoL is not necessarily stable over time. This finding highlights the importance of regular

patient reviews by clinicians, where good QoL in patients may not be constant and subject to change.

8.1 Conclusion

Outcomes from the mixed methods approach used in this study have been complementary and combining strengths of the two methods may therefore be perceived as being advantageous. The two types of analysis, qualitative and quantitative, revealed several consistent findings and common themes. In people with newly diagnosed PD, cognitive loss played a significant but relatively small role in overall levels of QoL for them and their carers. Patients who fell into the category of PD-MCI had, on average, worse QoL scores; patients categorised as the most severe PD-MCI had were more likely to report poorer QoL.

Over the following three years, most patients were cognitively stable, and for them and their carers, QoL was not greatly influenced by cognition. However, a minority of people developed PDD over those three years, and for them and their carers, cognition had a much greater impact on QoL. Standard brief clinical tests, such as the MoCA, could predict to some degree those people at risk of declining QoL, but more sophisticated attentional tasks may have greater predictive power. Within these trends, however, there is significant individual variation with some people adjusting better than others, and adjustment varying over time. The qualitative arm of the study explored potential reasons for this variation. Awareness of cognitive loss, changes in roles, and anticipatory grief challenge QoL, while mutually supportive relationships, optimism and good support from other people mitigate these factors. Thus, QoL and its relationship with cognition is complex; currently available measures of QoL may not be able to account for the wide range of experiences and subjective meaning of "QoL".

8.2 Future work

A number of interesting findings have been detailed from this study. However, further work is needed. Only a small proportion of participants had developed dementia at 36 months. A longer follow-up period is required to observe the trajectory of cognitive impairment in people with PD and how this impacts upon QoL. As this study is part of the larger ICICLE-PD study, further evaluation will be possible at 18 month intervals in

each participant. It would be interesting to investigate further the effects of impaired attention in this cohort and whether attentional deficits continue to be a significant determinant of QoL. In addition, devising and validating a brief attentional task to be used in a clinical setting could be very useful to clinicians. Furthermore, as attentional decline is a marker for cholinergic depletion, it would be interesting to investigate whether there is an association between cholinergic neurotransmitter changes and QoL.

The findings from this study also suggest possible targets for intervention. Treatments to improve attention may improve QoL in both people with PD and by extension their carers, either pharmacologically (e.g. rivastigmine) or non-pharmacologically (e.g. cognitive training). However, it may be more feasible to improve carer QoL by reducing the number of hours caring per week, such as with respite care, or by optimising the drug regimen of the person with PD. It would be interesting to compare whether these more readily available methods would have a greater impact on carer QoL than improved cognition in the person with PD. Finally, studies investigating psychological therapies to improve mood and successful adjustment may be particularly beneficial. By promoting protective factors to enhance existing coping mechanisms, better QoL for both carers and the person with PD may be achieved to prevent longer term decline in QoL.

Appendix A: List of publications, presentations and posters

Publications relating to this thesis:

Lawson, R.A., Yarnall, A.J., Duncan, G.W., Khoo, T.K., Breen, D.P., Barker, R.A., Collerton, D., Taylor, J.-P. and Burn, D.J. (2014) 'Severity of mild cognitive impairment in early Parkinson's disease contributes to poorer quality of life', *Parkinsonism & Related Disorders*, 20(10), pp. 1071-1075.

Lawson, R.A., Yarnall, A.J., Duncan, G.W., Khoo, T.K., Breen, D.P., Barker, R.A., Collerton, D., Taylor, J.P. and Burn, D.J. (2014) 'Quality of Life and Mild Cognitive Impairment in Early Parkinson's Disease: Does Subtype Matter?', *Journal of Parkinson's Disease*, 4(3), pp. 331-336.

Other publications:

Mak, E., Su, L., Williams, G.B., Firbank, M.J., **Lawson, R.A.,** Yarnall, A.J., Duncan, G.W., Owen, A.M., Khoo, T.K., Brooks, D.J., Rowe, J.B., Barker, R.A., Burn, D.J. and O'Brien, J.T. (2015) 'Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study'*, Brain*, 138(10), pp. 2974-86.

Yarnall, A.J., **Lawson, R.A.,** Duncan, G., Breen, D.P., G.D., Khoo, T.K., Brooks, D., Barker, R.A., Taylor, J.P. and Burn, D.J (2015) 'Anticholinergic load: Is there a cognitive cost in early Parkinson's disease?', *Journal of Parkinson's Disease*, DOI: 10.3233/JPD-150664.

Lawson, R.A., Millar, D., Brown, R.G. and Burn, D.J. (2013) 'Guided Self-Help for the Management of Worry in Parkinson's Disease: A Pilot Study', *Journal of Parkinson's Disease*, 3(1), pp. 61-68.

Mak, E., Su, L., Williams, G.B., Firbank, M.J., **Lawson, R.A.,** Yarnall, A.J., Duncan, G.W., Owen, A.M., Khoo, T.K., Brooks, D.J., Rowe, J.B., Barker, R.A., Burn, D.J. and O'Brien, J.T. (2015) 'Increased rates of whole brain atrophy in Parkinson's disease with mild cognitive impairment: ICICLE-PD study', *submitted to Journal of Neurology, Neurosurgery, and Psychiatry.*

Posters and presentations

Lawson, R.A., Yarnall, A.J., Duncan, G., Breen, D.P., G.D., Khoo, T.K., Brooks, D., Barker, R.A., Collerton, D., Taylor, J.P. and Burn, D.J. Does prolonged use of anticholinergic

medication contribute to cognitive impairment in early Parkinson's disease? 19th International Congress of Parkinson's Disease and Movement Disorders, 14-18th June 2015 (Poster Presentation and Platform Presentation as part of guided poster tour).

Johnston, F., **Lawson, R.A.**, Khoo, T.K., Yarnall, A.J., Duncan, G.W., Coleman, S. and Burn, D.J. Leptin and insulin; biomarkers for cognitive impairment in Parkinson's disease? ICICLE-PD 36 month interim analysis. 19th International Congress of Parkinson's Disease and Movement Disorders, 14-18th June 2015 (Poster Presentation).

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Lawson, R.A., Yarnall, A.J., Duncan, G.D., Khoo, T.K., Breen, D.P., Barker, R.A., Collerton, D., Taylor, J.P. and Burn, D.J. Severity of cognitive impairment and quality of life in Parkinson's disease: from diagnosis to 18 months. Parkinson's UK Research Conference, 3-4th November 2014 (Poster Presentation).

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Appendix B: Parkinson's Disease Questionnaire (PDQ-39)

ICICLE-PD Subject reference no: PDQ-39
Date:

DUE TO HAVING PARKINSON'S DISEASE, how often have you experienced the following, during the last month?

Due to having Parkinson's disease, how often during the last month have you ….	*Please tick **one box** for each question*				
	Never	**Occasionally**	**Sometimes**	**Often**	**Always or cannot do at all**
1. Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2. Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3. Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4. Had problems walking half a mile?	☐	☐	☐	☐	☐
5. Had problems walking 100 yards?	☐	☐	☐	☐	☐
6. Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7. Had difficulty getting around in public?	☐	☐	☐	☐	☐
8. Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐
9. Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you ….

*Please tick **one box** for each question*

	Never	Occasionally	Sometimes	Often	Always
10. Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11. Had difficulty washing yourself?	☐	☐	☐	☐	☐
12. Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13. Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
14. Had problems writing clearly?	☐	☐	☐	☐	☐
15. Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16. Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17. Felt depressed?	☐	☐	☐	☐	☐
18. Felt isolated and lonely?	☐	☐	☐	☐	☐
19. Felt weepy or tearful?	☐	☐	☐	☐	☐

Please check that you have ticked <u>one box for each question</u> before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you ….

Please tick ***one box*** *for each question*

	Never	Occasionally	Sometimes	Often	Always
20. Felt angry or bitter?	☐	☐	☐	☐	☐
21. Felt anxious?	☐	☐	☐	☐	☐
22. Felt worried about your future?	☐	☐	☐	☐	☐
23. Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24. Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25. Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26. Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27. Had problems with your close personal relationships?	☐	☐	☐	☐	☐
28. Lacked support in the ways you need from your spouse or partner? ***If you do not have a spouse or partner, please tick here*** ☐	☐	☐	☐	☐	☐
29. Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐

Please check that you have ticked <u>one box for each question</u> before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you ….

*Please tick **one box** for each question*

	Never	Occasionally	Sometimes	Often	Always
30. Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31. Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32. Felt your memory was bad?	☐	☐	☐	☐	☐
33. Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34. Had difficulty with your speech?	☐	☐	☐	☐	☐
35. Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
36. Felt ignored by people?	☐	☐	☐	☐	☐
37. Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38. Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39. Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Please check that you have ticked <u>one box for each question</u>

Coding system for questions

All questions on the PDQ-39 are coded in the same way.
We recommend that data is entered using the following codes:

0 = Never
1 = Occasionally
2 = Sometimes
3 = Often
4 = Always (or cannot do at all, if applicable)

Dimensions and their questions

Mobility
10 questions, nos. 1 to 10

Activities of daily living (ADL)
6 questions, nos.11 to 16

Emotional well being
6 questions, nos. 17 to 22

Stigma
4 questions, nos. 23 to 26

Social support
3 questions, nos. 27 to 29

Cognitive impairment (Cognitions)
4 questions, nos. 30 to 33

Communication
3 questions, nos. 34 to 36

Bodily discomfort
3 questions, nos. 37 to 39

Scoring for each dimension

Each dimension is calculated as a scale from 0 to 100
0 = no problem at all; 100 = maximum level of problem

If the response to a question is missing, no scale score is calculated for that individual for that dimension.

Formula for scoring each dimension

$$\frac{\text{sum of scores of each question in dimension}}{\text{4 (max. score per question) x nos. questions in dimension}} \times 100$$

Mobility
(scores of questions 1+2+3+4+5+6+7+8+9+10) / (4 x 10) x 100

Activities of daily living
(scores of questions 11+12+13+14+15+16) / (4 x 6) x 100

Emotional well being
(scores of questions 17+18+19+20+21+22) / (4 x 6) x 100

Stigma
(scores of questions 23+24+25+26) / (4 x 4) x 100

Social support
(scores of questions 27+28+29) / (4 x 3) x 100

note: if respondents indicate that they do not have a spouse or partner on question 28 then social support can be calculated as follows:

Social support = (scores of questions 27+29) / (4 x 2) x 100

Cognitions
(scores of questions 30+31+32+33) / (4 x 4) x 100

Communication
(scores of questions 34+35+36) / (4 x 3) x 100

Bodily discomfort
(scores of questions 37+38+39) / (4 x 3) x 100

Appendix C: Carer questionnaires

Carer/Informant Demographics

Participant reference number: Date:

Researcher:

DOB: Relationship to participant/patient:

Ethnicity: Handedness: R / L

English proficiency Y / N English as first language Y / N

Social History

Marital state: Single/ Married (living with partner)/ Separated/ Divorced/ Widowed

Home: Own residence/ Renting/ Placement (residential care)/ Off-spring's home/ Other relative's home/ Other:

Lives with care recipient? Y/ N

Occupation: FT/PT

Highest education level:

Driver: Yes/No

Smoker/ Ex-smoker/ Non-smoker

If applicable; approximate no. of pack years: _____

Caffeine intake: _____ units/ wk (1 units = 1 cup tea/ coffee/ coke)

Alcohol intake: _____units/ week

Any history of previous alcohol excess? Yes/ No

Caregiver History

Length of time they've known participant/patient:

Length of time as caregiver/carer:

Length of time spent per week as caregiver:

Other caregiving responsibilities: Children/Grandchildren/Other relative/Other:

Sleep

Rate sleep quality

Best imaginable night's sleep

Worst imaginable night's sleep

Why? Give 3 most important factors that affect sleep quality.

1. ……
2. ……
3. ……

OARS-Physical Health Checklist for Informant/Caregiver

Participant reference number: Date:

Researcher:

Do you have any of the following illnesses?	Y/N	How much does it interfere with your activities?			Medication Y/N
		Not at all	A little	A great deal	
Arthritis or rheumatism					
Glaucoma					
Asthma					
Emphysema or chronic bronchitis					
Tuberculosis					
High blood pressure					
Heart trouble					
Circulation trouble in arms or legs					
Diabetes					
Ulcers (of the digestive system)					
Other stomach or intestinal disorders or gall bladder problems					
Liver disease					
Kidney disease					
Other urinary tract disorders (including prostate trouble)					
Cancer or Leukemia					
Anemia					
Effects of stroke					
Parkinson's Disease					
Epilepsy					
Cerebral Palsy					
Multiple Sclerosis					
Muscular Dystrophy					
Effects of Polio					
Thyroid or other glandular disorders					
Skin disorders such as pressure sores, leg ulcers or severe burns					

PDQ-Carer

ICICLE-PD Subject reference no: PDQ-Carer Date:

Due to being a carer, how often <u>during the last 4 weeks</u> have you ……

*Please **tick one box** for each question*

		NEVER	OCCASIONALLY	SOMETIMES	OFTEN	ALWAYS
1.	**Found you could not sleep through the night?**	☐	☐	☐	☐	☐
2.	**Found it difficult to get out to do the shopping?**	☐	☐	☐	☐	☐
3.	**Found the demands of caring physically difficult?**	☐	☐	☐	☐	☐
4.	**Felt anxious because of the responsibility of caring?**	☐	☐	☐	☐	☐
5.	**Been prevented from pursuing hobbies and other interests?**	☐	☐	☐	☐	☐
6.	**Felt worried about your own physical health?**	☐	☐	☐	☐	☐
7.	**Thought that your caring role was taken for granted by others?**	☐	☐	☐	☐	☐
8.	**Felt that relationships with friends have been affected?**	☐	☐	☐	☐	☐
9.	**Felt impatient with the person you care for?**	☐	☐	☐	☐	☐

Please check that you have <u>ticked one box for each question</u> before going on to the next page.

Due to being a carer, how often <u>during the last 4 weeks</u> have you ……

*Please **tick one box** for each question*

	NEVER	OCCASIONALLY	SOMETIMES	OFTEN	ALWAYS
10. Felt exhausted?	☐	☐	☐	☐	☐
11. Felt worried about the future?	☐	☐	☐	☐	☐
12. Felt you lacked the energy and motivation to do the things you enjoy?	☐	☐	☐	☐	☐
13. Taken less care with your diet?	☐	☐	☐	☐	☐
14. Felt more withdrawn because of your caring role?	☐	☐	☐	☐	☐
15. Felt depressed?	☐	☐	☐	☐	☐
16. Felt less in control of your temper than before you became a carer?	☐	☐	☐	☐	☐
17. Felt worried about what would happen if you were unwell?	☐	☐	☐	☐	☐
18. Been limited in what you can do socially?	☐	☐	☐	☐	☐

Please check that you have <u>ticked one box for each question</u> before going on to the next page.

Due to being a carer, how often <u>during the last 4 weeks</u> have you ……

*Please **tick one box** for each question*

	NEVER	OCCASIONALLY	SOMETIMES	OFTEN	ALWAYS
19. Felt that your workload around the house has increased significantly?	☐	☐	☐	☐	☐
20. Found it difficult to see friends and family?	☐	☐	☐	☐	☐
21. Found it difficult to leave the person you care for alone for more than one hour?	☐	☐	☐	☐	☐
22. Felt that your physical health has been affected by your caring role?	☐	☐	☐	☐	☐
23. Felt that you are responsible for everything at home?	☐	☐	☐	☐	☐
24. Felt that you cannot do things on the spur of the moment?	☐	☐	☐	☐	☐
25. Found it difficult to be involved in activities which require commitment (e.g. volunteering work or regularly meeting friends)?	☐	☐	☐	☐	☐

Please check that you have <u>ticked one box for each question</u> before going on to the next page.

Due to being a carer, how often <u>during the last 4 weeks</u> have you ……

*Please **tick one box** for each question*

	NEVER	OCCASIONALLY	SOMETIMES	OFTEN	ALWAYS
26. Paid less attention to your own health (e.g. put off visiting a doctor, ignored symptoms etc)?	☐	☐	☐	☐	☐
27. Felt unable to go on holiday or take short breaks?	☐	☐	☐	☐	☐
28. Felt responsible for Parkinson's disease medication being available and/or taken at appropriate times?	☐	☐	☐	☐	☐
29. Had to limit outings because you worry that the person you care for won't be able to cope?	☐	☐	☐	☐	☐

Please check that you have <u>ticked one box for each question</u>.

Thank you for completing this questionnaire!

Scale of Quality of Life of Informal Care-Givers - SQLC

Participant ID:…… Relationship to participant:……

Date:…… Researcher initials:……

I. Professional activity

1. Have you continued at your former place of work after your relative fell ill?

	Yes (5)	No (0)
Is your work (*Please circle one*):		
Full-time, for full working day	5	0
Part-time with incomplete working day	3	0
Had to start working (if hadn't worked before)	0	5
Didn't work before either	5	0

2. Do you manage to perform your duties while now being occupied with the patient's care?

	Yes (5)	No (0)
(Please circle one):		
As well as previously	5	
With difficulty	3	
Partly manage	1	
Not at all	0	

3. Did you change your work because of your relative's disease?

	Yes (0)	No (4)
If yes, your job is now *(Please circle one):*		
The same as previously	3	0
Close to previous type	2	0
In another branch	1	0
Changed the job for other reasons not related to the relative's disease	4	0

4. Are you obliged to perform any complementary job for extra money?

	Yes (0)	No (5)
(Please circle one):		
As frequently as before	5	
Rarely	4	
Somewhat less	3	
Often	2	
Very frequently	1	
Never	0	
Perform other job for reasons unconnected to the relative's disease	3	

II. Social and leisure activities

5. Do you have time for different kinds of leisure activities in spite of your involvement into the patient's care? Yes (3) No (0)

(Please circle one):

As frequently as before	3
Somewhat more than before	4
Somewhat less than before	2
Rarely	1
Never	0
Never did	3

6. Does care of the patient allow you run the household?
Yes (3) No (0)

	Now I have more to do	**As much as previously**	**Somewhat less**	**Very rarely**	**Never**	**Never did**
Buying food	2	3	2	1	0	3
Making laundry	2	3	2	1	0	3
Cleaning house	2	3	2	1	0	3
Cooking	2	3	2	1	0	3
Other (indicate)	2	3	2	1	0	3

7. Does care of patient allow you to give a hand to you parents and other relatives?
Yes (3) No (0)

(Please circle one):

More frequently than before as I have now stopped work	4
As frequently than before	3
Somewhat less frequently	2
Very rarely	1
Never	0
Never did	3
More frequently than before as now it is my responsibility	2

8. Do you continue to discuss family plans and problems with your ill relative?
Yes (3) No (0)

(Please circle one):

More often than before	4
As often as before	3
A little less often than before	2
Very rarely	1
Never	0
Never did before	3

9. Does the care of our relative let you to continue to attend to the needs of your children or the grandchildren as well as you did before? Yes (3) No (0)

	More frequently than before as I have now stopped work	**As frequently than before**	**Somewhat less frequently**	**Very rarely**	**Never**	**Never did**	**More frequently than before as now it is my responsibility**
To control and help children in scholarship	4	3	2	1	0	3	2
To take children to school, to sport activities or for a walk	4	3	2	1	0	3	2
To take children to theatres, museums, etc.	4	3	2	1	0	3	2
Other (indicate)	4	3	2	1	0	3	2

III. Responsibilities of the care-giver to help the patient in his everyday living

10. Does the regular everyday care and attention to the chronically disabled person make you depressed? Yes (0) No (3)

(Please circle one):

The mood is the same as before	5
Continuous depression (a week or more)	3
Stable depression with weight loss and insomnia	0
Depression for reasons unconnected with relative's disease	5

11. Can the patient stay at home by himself while the family members are out or away? Yes (3) No (0)

Without assistance he is able to:	**Always**	**Sometimes**	**Never**
Dress	2	1	0
Make the bed	2	1	0
Warm up food	2	1	0
Take food left for him (wrapped up or in container)	2	1	0

12. Does your patient need assistance when using public transport or car-driving? Yes (0) No (3)

(Please circle one):

Never needs assistance	3
Somewhat more often than before	2
Very often	1
Always needs assistance	0
Needed assistance before disease started	3

13. Can your patient regularly take the prescribed medicine by himself? Yes (3) No (2)

(Please circle one):

Always	2
Sometimes	1
Never	0

14. Can your relative take a bath without assistance? Yes (3) No (0)

(Please circle one):

Always	2
Sometimes	1
Never	0

15. Can your patient move around without assistance? Yes (3) No (0)

Without assistance he is able to:	Always	Sometimes	Never
Visit his therapist	2	1	0
Go for a walk or shopping	2	1	0
Move around inside the whole house	2	1	0
Go to the lavatory	2	1	0
Get seated on the bed	2	1	0

16. Can your relative call for a physician by himself? Yes (3) No (0)

(Please circle one):

Always	2
Sometimes	1
Never	0

J. M. Glozman, K. G. Bicheva, N. V. Fedorova, Scale of Quality of Life of Care-Givers (SQLC), J Neurol (1998) 245 [Suppl 1]: S39–S41

Appendix D: Interview schedule development

Interview Schedule: PD participants

V 1.0

Example questions for participants

- Has your life changed since you were diagnosed with PD?
    - In what way?
    - What tasks do you need help with?
    - How do the changes make you feel?
- How is your memory?
    - How has that changed?
- How have you coped with these changes?
- What do you enjoy doing? What hobbies/interests do you have? Has your health/PD stopped you from doing those?
- How do you feel about the future?
- How has your being diagnosed with PD affected your spouse/partner/carer?
    - How is your relationship with your spouse/partner/carer changed?
    - Do you enjoy spending time together?
    - In what way have things changed??

Interview Schedule: Carer

V1.0

Example questions for carers

- Has your life changed since your spouse/relative/friend was diagnosed with PD?
    - In what way?
    - What tasks does your spouse/relative/friend need help with?
- Describe a typical day. Has this changed over time?
- How is your spouse/relative/friend's memory?
    - How has that changed?

- How do the changes make you feel?

- How have you coped?
    - What do you do to relax?
    - What helps you deal with the challenges experienced as a result of your spouse/relative/friend's illness?

- Has your social life been affected?

    - To what extent?

    - Are you at all prevented from having visitors?

- How has caring for your spouse/relative/friend affected your health?

- How do you feel about the future?

    - Is it something you ever worry about?

Interview Schedule: PD participants

V 2.0

Example questions for participants

- **What was it like before you were diagnosed with PD?**
    - How long have you been together?
    - How would you sum up your marriage/relationship?
    - How did you spend your time?
    - What did you do for a living?
- **Tell me about when you were first diagnosed?**
    - Who first noticed the symptoms?
    - How was it diagnosed?
    - How did you feel?
- **Has your life changed since you were diagnosed with PD?**
    - In what way?
    - What tasks do you need help with?
    - Do you think your quality of life has changed?
    - In what way?
    - What would improve your quality of life?
- **How is your memory?**
    - How has that changed?
    - Does your thinking seem slowed down?
    - Can you give me an example?
    - What effect do you think these thinking problems have?
    - What do you think of the memory/thinking problems compared to the Parkinson's symptoms?
- **How do the changes make you feel?**
- **What helps you to cope with these changes?**
    - What do you do to relax?
    - What hobbies/interests do you have?
    - Has your health/PD stopped you from doing those?
- **How has your being diagnosed with PD affected your spouse/partner/carer?**
    - Has your relationship with your spouse/partner/carer changed?
    - In what way have things changed?
    - Do you enjoy spending time together?
- **How do you feel about the future?**
    - Is it something you ever worry about?
- **Some people with PD also have dementia, what do you think about that?**

- **Is there anything else I haven't mentioned that you'd like to talk about?**
    - The effects of Parkinson's, how the Parkinson's has affected you or your spouse/partner/relative?

Interview Schedule: Carer

V2.0

Example questions for carers

- **What was it like before your spouse/relative was diagnosed with PD?**
    - How long have you been together?
    - How would you sum up your marriage/relationship?
    - How did you spend your time?
    - What did you do for a living?
- **Tell me about when your spouse/relative was first diagnosed?**
    - Who first noticed the symptoms?
    - How was it diagnosed?
    - How did you feel?
- **Has your life changed since your spouse/relative was diagnosed with PD?**
    - In what way?
    - What tasks does your spouse/relative need help with?
- **How is your spouse/relative's memory?**
    - How has that changed?
    - Do you think their thinking has slowed down at all?
    - Can you give me an example?
    - What affect do you think these thinking problems have on you?
    - What do you think of the memory/thinking problems compared to the Parkinson's symptoms?
- **How has your spouse/relative's PD affected you?**
    - Is there someone who helps you?
    - What support do you get?
    - What support do you need?
- **How do the changes make you feel?**
- **What do you do to help you cope?**
    - What helps you to cope with these changes?
    - What do you do to relax?
    - What helps you deal with the challenges experienced as a result of your spouse/relative's illness?
- **Has your social life been affected?**
    - To what extent?
    - Are you at all prevented from having visitors?
- **How has caring for your spouse/relative affected your health?**
    - Do you take less care of yourself than you used to?

    - Do you feel more tired or stressed than you used to?
    - Can you give me an example?
- **Do you think your quality of life has changed?**
    - In what way?
    - What would improve your quality of life?
- **How do you feel about the future?**
    - Is it something you ever worry about?
- **Some people with PD also have dementia, what do you think about that?**
- **Is there anything else I haven't mentioned that you'd like to talk about?**
    - The effects of Parkinson's, how the Parkinson's has affected you or your spouse/partner/relative

Appendix E: Coding Frame

Main themes	Sub-themes	Descriptors
The experience of Parkinson's disease	*PD symptoms*	Motor symptoms
		Neuropsychiatric symptoms
		Non-motor-symptoms
	Cognition	Memory
		Concentration/attention
		Thinking difficulties/"mixed up"
		Dementia
	Carer responsibilities	Increased responsibility
		Burden
		Unappreciated
		Worry
		Carer health
		Source of emotional support
	Effect on daily lives	Independence
		Restricted social activities
		Hobbies
		Driving
Changes in identity	*Role reversal*	Parent/child relationship
		"Boss"
		Inadequate
		Loss of confidence
	Pre-death grief	Not the same person
		Cognitive impairment has taken their loved one
		Grief and depression
Coping mechanisms and adjustment	*Coping well and successful adjustment*	I just cope
		Social support
		Optimism and positive attitude
		Adapting to changes
		Finding meaning and personal growth
		Humour
	Adjustment difficulties	Uncertainty
		Pessimism and low mood
		Not-coping
		Intrusive symptoms
		Cognitive impairment/dementia
		Guilt
		Helplessness/loss of control

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