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A MIXED-METHODS INVESTIGATION OF TRAJECTORIES OF PATIENT-REPORTED FUNCTIONAL MOBILITY IN PEOPLE WITH PARKINSON'S DISEASE

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A mixed-methods investigation of the trajectories of patient-reported functional mobility in people with Parkinson's disease

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CHAPTER 1

General introduction

1.1 DEFINITION OF HEALTH FROM A NURSING SCIENCES PERSPECTIVE

According to the nurse scientist Lyon (2012), "Health is an elusive term. It is a term that many people think they understand until they are asked to define or describe it and then asked how they would measure it. It has been described as a value judgment, as an objective state, as a subjective state, as a continuum from illness to wellness, and as a utopian state (rarely achievable).". The World Health Organisation defines health as: "A state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity." (World Health Organisation, 2006).

While the definition by the World Health Organisation (2006) represents an utopian state, it contains in addition to physical, mental and social aspects of health. Since the 1950s, nurses offered different conceptualisations of health but inherent in all definitions was that it is a subjective experience that encompasses how a person is feeling and doing (Keller, 1981). This subjective orientation to a definition of health differs from the medical definition of health as an objective phenomenon manifested by the absence of disease or pathology (Lyon, 2012). The nurse scientist Tripp-Reimer (1984) proposed an etic, i.e., objective interpretation of health and an emic, i.e., subjective perspective of health. According to her, this approach could be useful when perceptions of health differ between scientifically educated healthcare providers and the client. Lyon (2012) described that the understanding that both illness and wellness can be experienced in the presence or absence of a disease is a fundamental cornerstone of nursing, enabling nurses to see possibilities for people to experience wellness in the presence of a chronic disease. Thus, knowledge about factors that can contribute to physical or emotional discomfort and declines in functional ability increases a nurse's intervention possibilities to support people with chronic diseases like Parkinson's disease (PD) (Lyon, 2012).

1.2 PARKINSON'S DISEASE

Epidemiology

First described by Dr. James Parkinson in 1817 (Parkinson, 1817), PD is currently the fastest-growing neurodegenerative condition, affecting over six million people worldwide (Dorsey and Bloem, 2018, Dorsey et al., 2007). Incidence and prevalence have risen sharply in the past two decades and the numbers are expected to double by 2040 worldwide (Dorsey et al., 2018). In Luxembourg, the prevalence of PD, based on data collected between 2007 and 2017, was estimated at approximately 1032 per 100,000 men and 831 per 100,000 women aged 50 years and older (Schmitz et al., 2022) leading to an estimated prevalence of 2137 people living with PD in Luxembourg by 2023 where each year, between 57 and 100 new

cases of PD are expected to be diagnosed (Hipp et al., 2018). While PD is rare before 50 years of age (Twelves et al., 2003), a meta-analysis showed a rising prevalence of PD with age reaching from 41/100,000 in 40 to 49 years to 1903/100,000 in > 80 years (Pringsheim et al., 2014). The average age of onset is in the late fifties, with a broad range from below 40 to more than 80 years of age (Poewe et al., 2017). Although, they may phenotypically look similar, especially in the early disease stages typical PD and atypical parkinsonism can be distinguished based on certain key features, so-called "red flags", appearing along with disease progression (Schroter et al., 2023). This dissertation focusses on individuals with typical PD or PD dementia (PDD).

Pathophysiology and clinical features

PD is a movement disorder and is clinically defined by the presence of bradykinesia and at least one additional cardinal motor feature (rigidity or rest tremor) (Postuma et al., 2015). In addition to those cardinal motor features, a majority of people with PD also have non-motor symptoms that add to overall disability, i.e., disorders of sleep-wake cycle regulation, impaired cognition, mood and affect, autonomic dysfunction (orthostatic hypotension, urogenital dysfunction, constipation and hyperhidrosis) as well as sensory symptoms (hyposmia) and pain (Chaudhuri and Schapira, 2009). While some non-motor symptoms can occur years or even decades prior to the onset of motor symptoms, they become increasingly prevalent over the course of the illness and are a major determinant of the progression of overall disability (Poewe et al., 2017). The progression of motor and non-motor symptoms is illustrated in Figure 1. Progressive disability includes treatment-resistant motor symptoms (freezing of gait, described as feet glued to the floor), postural instability, falling and choking. These milestones of progression are key events in the long-term evolution of PD (Poewe et al., 2017).

The underlying molecular pathogenesis involves multiple pathways and mechanisms, among others neuroinflammation (Moehle and West, 2015, Poewe et al., 2017, Castillo-Rangel et al., 2023). Variants in leucine-rich repeat kinase 2 (LRRK2), one of the greatest genetic contributors to PD, have also been associated with increased incidence of chronic inflammatory bowel diseases (Herrick and Tansey, 2021). In addition to the neuroinflammation, sex might also play a role. Thus, a meta-analysis found a significant difference in prevalence by sex for individuals 50 to 59 years old (Pringsheim et al., 2014). According to Poewe et al. (2017), this male preponderance might be explained by a protective effect of female sex hormones, a different genetic mechanism or different exposures to environmental risk factors in males and females. Genetic variation is estimated to contribute approximately 25% to the overall risk of developing PD (Day and Mullin, 2021). This proportion is even higher in people with early onset PD before the age of 50 years (Alcalay et al., 2010). The genetic variants related to PD vary in terms of frequency and risk of PD (Manolio et al., 2009). On the one hand, some rare variants in single genes are sufficient to cause

PD while on the other hand, large numbers of common genetic variants contribute a small amount to the risk of developing PD. In the middle of this spectrum lie variants that are uncommon (but not rare) with an intermediate risk, such as glucocerebrosidase *GBA1* variants (Day and Mullin, 2021). Variants in the *GBA1* gene (*GBA1* [OMIM 606463]) can cause Gaucher's Disease, a recessive lysosomal storage disorder, lead to reduced activity of the lysosomal enzyme glucocerebrosidase (GCase), which, in turn, is linked to an increased alpha-synuclein aggregation involved in the pathogenesis of PD (Mazzulli et al., 2011, Sidransky and Lopez, 2012). While an association of these Gaucher-related *GBA1* variants with the progression of non-motor symptoms in PD has been reported (Gan-Or et al., 2015), the role of PD-risk *GBA1* variants is less clear (Goldstein et al., 2019, Menozzi and Schapira, 2021, Petrucci et al., 2020). A growing body of evidence suggests that exposure to environmental toxins (e.g., pesticides, the solvent trichloroethylene, and air pollution), are at least in part contributing to the rapid rise in the prevalence and incidence of PD. Among others, rural residents are exposed to mixtures of multiple pesticides (Dorsey and Bloem, 2024). Most genetic risk factors are by themselves insufficient to explain the majority of PD, suggesting the presence of a gene-environment interaction. Thus, environmental factors are required for these genetic factors to become pathophysiologically relevant (Ascherio and Schwarzschild, 2016, Bogers et al., 2023).

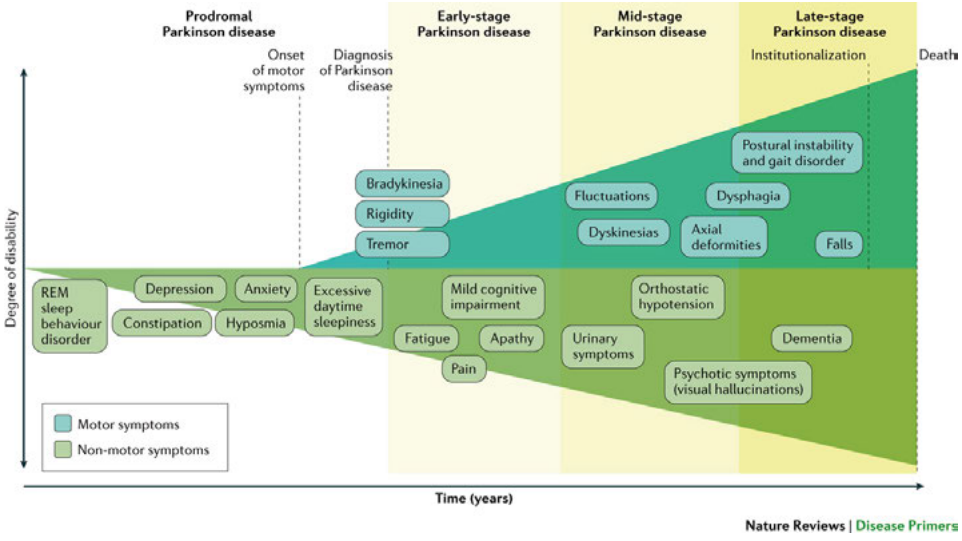

Figure 1 Clinical symptoms associated with Parkinson's disease. Reproduced with permission from Springer Nature from Poewe et al. (2017)

Diagnosis and treatment

PD is diagnosed based on expert neurological examination, cerebral imaging, and positive response to dopaminergic medication. The United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992) guide the neurological evaluation focusing on the presence of the cardinal motor symptoms, i.e., bradykinesia with tremor and/or rigidity. Since 2023 the German Association for Neurology even recommends the diagnosis of PD based on the MDS clinical diagnositic criteria (Höglinger and Trenkwalder, 2023, Postuma et al., 2015, Postuma et al., 2018). Diagnosis of PD is supported by the DopAmine Transporter Single-Proton Emission Computed Tomography (DAT SPECT) and an assessment of the response to dopaminergic medication (Stoessl et al., 2014, Pirtosek et al., 2020, Berardelli et al., 2013, Poewe et al., 2017). Only the identification of the presence of Lewy bodies in affected brain regions of a person clinically presenting as PD during a neuropathological examination of post-mortem brain tissue (Gibb and Lees, 1988) allows a definitive diagnosis of PD.

According to Damier et al. (1999) and Fearnley and Lees (1991) in certain types of susceptible neurons within particular brain regions, neuronal degeneration occurs. Even in early disease stages, different types of neurons (enteric, olfactory bulb) are affected and explain the early onset of prodromal symptoms as illustrated in Figure 1. However, the mechanism behind the cardinal motor features of PD is the loss of dopaminergic neurons in the substantia nigra leading to a depletion of striatal dopamine (Damier et al., 1999, Fearnley and Lees, 1991, Dijkstra et al., 2014, Iacono et al., 2015, Poewe et al., 2017). According to Poewe and colleagues (2017), the treatment of PD consists of pharmacological substitutes of striatal dopamine, in addition to non-dopaminergic treatments to address motor- and non-motor symptoms. Deep brain stimulation is offered to those developing burdensome motor complications of long term dopaminergic treatment (Poewe et al., 2017). The authors further describe discontinuous drug delivery due to the short half-life of L-DOPA and the variability in its gastrointestinal absorption and blood-brain barrier transport leading to complications (fluctuations of the motor response and drug-induced dyskinesias). Sustained-release and continuous delivery formulations of L-DOPA (via percutaneous endoscopic gastro-jejunostomy tubes or subcutaneously via mini-pumps) should address this problem (Poewe and Antonini, 2015, Olanow et al., 2024). According to Chaudhuri and Schapira (2009) in some individuals with PD, selected non-motor symptoms (such as pain, anxiety, panic, depression and restlessness) can fluctuate in response to dopaminergic therapy (non-motor fluctuations). Moreover, many non-motor symptoms did not respond to dopamine replacement therapy while some were even aggravated by this treatment (Chaudhuri and Schapira, 2009).

1.3 IMPAIRED FUNCTIONAL MOBILITY IN PEOPLE WITH TYPICAL PARKINSON'S DISEASE

Definition and measurement

Functional mobility in PD can be defined as:

> *"the physiological ability of people to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living, at home, work and in the community." (Bouca-Machado et al., 2018)*

By incorporating functional, societal and contextual factors this definition goes beyond body structures and functions allowing a better understanding and description of functional mobility in PD. The experience of functional mobility differs according to the disease stages. People in the early stages reporte not being worried by functional mobility and mainly associated it with the ability to move and easy perform tasks, whereas people in late stages associate functional mobility with autonomy in daily life, not needing others and the fact of not getting out on the street without anyone noticing that they have PD (Bouca-Machado et al., 2020b). The importance of autonomous decision-making in switching between places in the process of mobility decline has also been highlighted by Zegelin (2008) as people move with intentionality. Carp (1988) even conceptualised mobility as fundamental to independently meet life-maintenance needs (food, clothing, health care), and fulfil higher order needs (social relationships, recreational activities). Maslow (1943), in his theory of human motivation, described a hierarchy of priorities of five sets of basic needs (Figure 2). When the most important need is satisfied, the next higher needs emerge.

According to a systematic review aiming to identify measurement instruments used to assess functional mobility, only one study presented a definition of functional mobility (Bouca-Machado et al., 2020a). Bouca-Machado et al. (2020a) recommended the performance test "Timed Up and Go" as a measurement tool to assess functional mobility. During this test the participants are required to "get up from a standard chair, to walk 3 m at a comfortable and safe pace, turn and walk back to sit down on the chair" (Podsiadlo and Richardson, 1991). However, the perspective on important outcomes for functional mobility differs between health professionals and people with PD: for people with PD the capability of performing ADL is more important while the time it takes to perform specific tasks is more important to health professionals (Ferreira et al., 2015). The recommended "Timed Up and Go" test focuses on the time required to perform the task and thus represents the perspective of health professionals. Thus, the holistic assessment of functional mobility according to the values of people with PD is limited and the development of novel scales that measure functional mobility in PD has been suggested (Bouca-Machado et al., 2020a, Bouca-Machado et al., 2018).

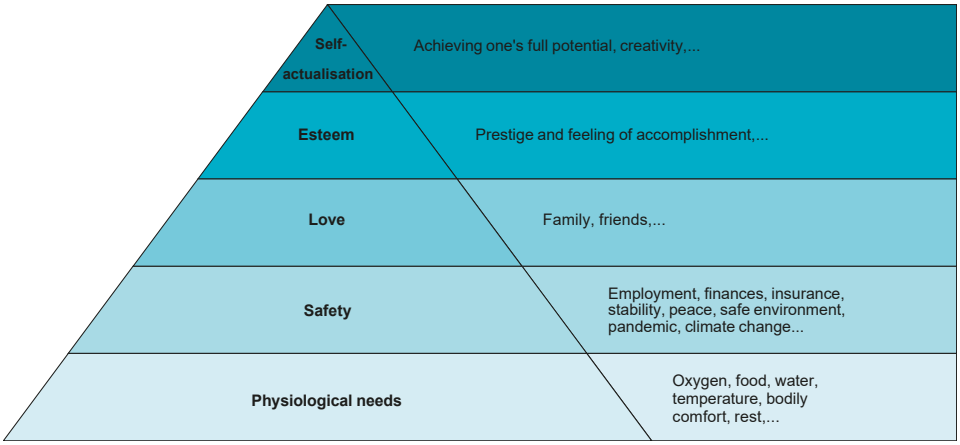

Figure 2 Hierarchy of human needs by Maslow (1943)

In a comprehensive framework for mobility in older adults, Webber et al. (2010) raised awareness of the complexity of factors that influence mobility. They describe five fundamental categories of determinants (cognitive, psychosocial, physical, environmental, and financial) with gender, culture and biography (personal life history) as critical cross-cutting influences with an increasing complexity as the environment expands farther from the home. This is also reflected in the application of functional mobility and it's determinants and consequences to the International Classification of Functioning and Disability (ICF) perspective (World Health Organisation, 2001) by Bouca-Machado et al. (2018) and Tosserams et al. (2020). The following section focuses on impaired motor- and non-motor functions and the resulting activity limitations and restrictions in participations.

Activity limitations related to functional mobility

As previously described, in addition to the experiences of functional mobility, the related limitations differ according to the disease stages. Specifically, people with PD in early disease stages mention mainly a slower rhythm in performing some tasks. While close family members notice a slowdown, friends and distant family members are unaware of the impact of functional mobility limitations on their daily lives. On the other hand, people with late-stage PD have a clear perception of functional mobility limitations as it was the most limiting factor of activities of daily living. The "OFF"-periods are described as the worst moments of the day. People with late-stage PD look for strategies to minimise the symptoms and feel ashamed for drawing others' attention as friends and colleagues have difficulties understanding the fluctuations of the disease (Bouca-Machado et al., 2020b).

This worsening of functional mobility with advancing disease stages (Bouca-Machado et al., 2018) implies a decreased ability to sit down or stand up from a chair and an overall slowing

down of motor function (Mollà-Casanova et al., 2022). Motor symptoms may directly impair functional mobility through gait impairments and indirectly due to bradykinesia, rigidity and disabling postural deformities, which affect gait of people with PD, balance and transitions (Magrinelli et al., 2016, Bouca-Machado et al., 2018). In addition, during gait initiation, turning and walking through doorways, walking problems are more pronounced due to the occurrence of freezing of gait (Morris et al., 2001). Freezing episodes are described by people with PD as having their feet "glued to the floor" (Weiss et al., 2020, Merola et al., 2016, Bouca-Machado et al., 2018). Recent work stratified individuals with freezing of gait by three freezing triggers: motor type (freezing when turning), cognitive type (freezing when dual-tasking, i.e., simultaneously carrying out a cognitive and a motor task), or the limbic type (freezing when anxious) (Ehgoetz Martens et al., 2018, Weiss et al., 2020). In addition to freezing of gait, dysautonomia (orthostatic hypotension) affects functional mobility in people with PD (Merola et al., 2016, Bouca-Machado et al., 2018). Furthermore, postural control and reflexes are impaired in PD (Mollà-Casanova et al., 2022). As a result, falls are common among people with PD, with approximately 60% of individuals falling each year (Allen et al., 2013, Bloem et al., 2001, Pickering et al., 2007). Fall and hip fracture frequency is at least twice as high as in the general older population (Kalilani et al., 2016). Given this high fall risk and activity limitations, maintaining functional mobility becomes crucial.

Relevance of functional mobility

PD is a movement disorder and as previously described, functional mobility is one of the disease-related features most relevant to people with PD (Bowring et al., 2022). Specifically, people with PD, their relatives and health professionals in Luxembourg and the Greater Region identified balance problems, falls and functional ability as main research priorities (Bowring et al., 2022). As a co-author in this priority setting study, this served as the starting point for this dissertation. Similarly, a survey aiming to identify potential issues of importance to individuals with PD found the lack of mobility as one of the most bothersome problems (Uebelacker et al., 2014).

Functional mobility of people with PD worsens as the disease progresses (Lindh-Rengifo et al., 2021, Mirelman et al., 2019) and impacts daily life. In particular, impaired functional mobility is associated with a loss of independence (Shulman et al., 2008), activity limitation (Tan et al., 2012, Tan et al., 2011), falls (Creaby and Cole, 2018), decreased social participation (Hammarlund et al., 2014), increased self-stigma (Hanff et al., 2021), and decreased quality of life (Perez-Lloret et al., 2014). Limitations in activities range from minor fine motor coordination tasks to major activities of daily living. In the transition between Hoehn and Yahr stages II and III gait impairment occurs, while in the transition from stages III and IV loss of independence in performing activities starts (Hoehn and Yahr, 1967, Goetz et al., 2004). People with PD describe gait disorders as "a loss of confidence in walking, a feeling of imbalance or reduced ability to negotiate uneven terrain or stairs" (Bouca-Machado et al., 2018). In addition, they

report changes in physical activities since diagnosis limiting their favourite activity (Burgess and Rasmusson, 2016) and restricting their participation in leisure, work or social aspects of life in both household and community settings (Bouca-Machado et al., 2018).

People with PD have an increased risk of long-term institutionalisation, independent of socio-demographic confounders (Nihtila et al., 2008). The increased risk of nursing home admission is mainly driven by the person's functional limitations (Bjorkstedt et al., 2023, Shih et al., 2020). Consequently, in Europe, in intermediate and advanced disease stages, the largest component of the estimated annual cost are professional care and nursing home costs. Yearly costs per individual increase with disease progression, from €454 / €1712 (26.5%) in an early disease stage, over €3,147 / €5,865 (53.7%) in an intermediate disease stage to €10,179 / €15,682 (64.9%) in an advanced disease stage (Chaudhuri et al., 2024). Most importantly, people with PD typically express a strong desire to remain in their homes for as long as possible (Habermann and Shin, 2017). Also, the presence of a spouse is associated with a lower risk of being institutionalised (Nihtila and Martikainen, 2008). Thus, a promotion of mobility and functionality taking account the environment could help to delay institutionalisation and respect the desires of people with PD.

1.4 LIFE WITH PARKINSON'S DISEASE AS A CHRONIC DISEASE

Progression of Parkinson's disease

Hoehn and Yahr (1967) designed the widely used Hoehn & Yahr scale, a simple descriptive staging scale providing a general estimate of clinical function in PD, combining functional deficits (disability) and objective signs (impairment) and it is frequently used to stage the severity of PD. It is based on the twofold concept that the severity of overall parkinsonian dysfunction is related to bilateral motor involvement and compromised balance/gait. Increasing PD-related motor impairment therefore can be charted from unilateral (Stage 1) to bilateral disease (Stage 2) without balance difficulties, to the presence of postural instability (Stage 3), loss of physical independence (Stage 4) and being wheelchair- or bed-bound (Stage 5). People with PD are staged at their current level of function. The authors did not presume that people with PD necessarily start PD at Stage I and decline sequentially to Stage 5 or death. The MDS-taskforce recommends the use of the H&Y scale for demographical presentation of patient groups, for definition of in- and exclusion criteria at baseline and as a validation standard for other rating instruments (Goetz et al., 2004).

Twenty years ago, Lunney et al. (2002) described three illness trajectories for people with progressive chronic illnesses, among them a trajectory with prolonged gradual decline, from a low baseline typically in older age, advanced neurological disease, or dementia. The trajectories

(Figure 3) correspond to a different rhythm and set of priorities in care. They described this trajectory as being of progressive disability from an already low baseline of physical functioning with a substantial contribution to health care costs. Accordingly, these individuals may lose weight and functional capacity and cannot adequately react to minor physical events or daily challenges that can be fatal when occurring in combination with declining reserves (Lynn and Adamson, 2003). In addition, research involving people with multiple health conditions (Mason et al., 2016) points to an additional trajectory of functional decline, i.e., the multimorbidity trajectory as illustrated in Figure 4. With PD progression, the number of comorbidities increases (Minar et al., 2019). Thus, individuals with PD may have two trajectories running in parallel, with the more rapidly progressing trajectory typically taking up the largest effort. This leads us to the next section discussing different dimensions of illness progression.

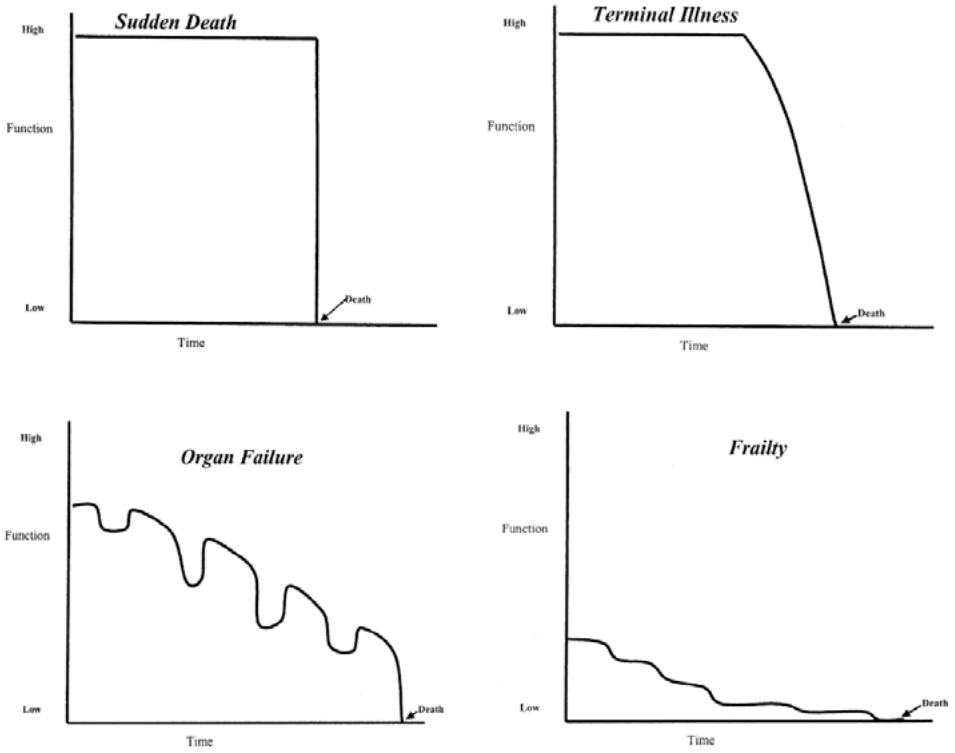

Figure 3 Trajectories of functional decline. Reproduced with permission from John Wiley and Sons from Lunney et al. (2002)

Dimensions of illness progression in Parkinson's disease

The trajectories as illustrated in Figure 4 can relate to physical wellbeing while other trajectories may exist regarding dimensions such as the spiritual or existential domain

(Murray et al., 2024). Although people with multiple conditions reported managing the cumulative effects of their various illnesses, individuals and families often thought changes were part of ageing (Mason et al., 2016). Like in people with chronic heart failure, spiritual distress (reflecting a gradual loss of identity and growing dependence) could be present throughout the trajectory in people with PD. Parallel psychological and social trajectories may also be mapped (Lynn and Adamson, 2003). The challenges of managing fluctuating and unpredictable illnesses can lead to social concerns and trigger an emergency hospital admission (Bielinska et al., 2021, Gill et al., 2015). Psychological concerns reflect periods of greater anxiety or depression associated with physical or social health changes alongside ongoing (mental) health problems. Spiritual distress was described a loss of control, lack of meaning and purpose, or the demands of coordinating care in the face of multiple illnesses and medications (Mason et al., 2016, Murray et al., 2024).

Finally, Murray et al. (2017) argue that holistic, person-centred care should not focus only on the deterioration of physical health but also on social, psychological and spiritual aspects of well-being to meet those multidimensional needs of people with chronic diseases. Thus, psychological and existential well-being can fall in response to changes in social circumstances, or an acute physical illness, but a decrease in social, psychological, or existential well-being can also precede global physical decline or death. Some older people reach a tipping point when they feel useless, unable to live with dignity and experience increasing psychological and existential distress. In Chapter 5 and 6 of this dissertation, we describe the progression of motor and non-motor symptoms, similar to illness trajectories. Based on this, medical doctors can develop a treatment plan aiming to manage the symptoms and control the disease trajectory.

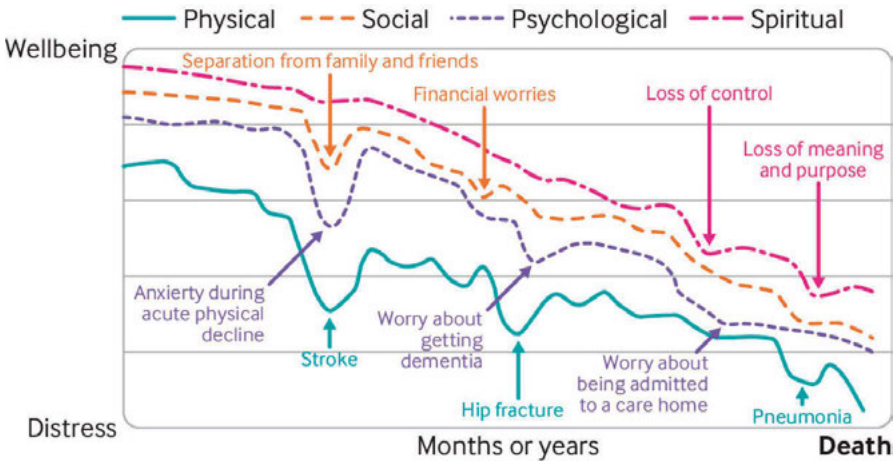

Figure 4 Wellbeing dimensions in people with multimorbidity (two or more diseases in the same person at the same time) illness trajectory. Reproduced with permission from BMJ Publishing Group Ltd. from Murray et al. (2024)

Manage the impact of Parkinson's disease on daily life

As described above, chronic diseases like Parkinson's have a relatively strong impact on the lives of those affected and their families. Despite medical advancements, PD remains an incurable chronic condition, and treatment currently focuses primarily on symptom control. People with PD can manage the effects of this stressful situation, e.g., minimise, avoid, tolerate, change or accept in the frame of the coping process (Lyon, 2012). In their transactional model, Lazarus and Folkman (1984) define coping as:

> *"constant changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person." (Lazarus and Folkman, 1984).*

Similarly, Corbin and Strauss (2010) and (1985) described this self-management across the illness trajectory. Compared to the previously described illness trajectory, their model adds the overall work (illness-related, everyday life and biographical) performed during this course and the burden of those, involved in the work and its organisation. Consequently, the illness trajectory is considered as only one aspect of many and their model refers to the active role of individuals with PD in shaping the illness trajectory. Thus, the progression is not defined by the disease itself, but also by the individual reaction of the people living with it and of their family, friends and health professionals. This highlights the central role of individuals with PD and their family: it is they who do the daily work of coping with the illness, who work through the problems associated with this work and who are ultimately most affected by the consequences of the illness and the work associated with it (Corbin and Strauss, 2010) and (1985).

According to Corbin and Strauss (2010), each trajectory can be analytically broken down into phases that shape the curve. These phases include acute phases, normalisation phases, stable and unstable phases, phases of deterioration, and end-of-life phases. In essence, the phases of a trajectory correspond to the physical and physiological status of the disease. Phasing indicates the type of coping work needed and the potential physical and psychological impact that could arise. This is more complex than it may initially appear. A person may indeed physically recover, but perhaps they struggle to psychologically adapt to the disease and the associated changes in their life. Alternatively, someone with an illness may believe it to be stable, experiencing an emotional high, while their physical condition slowly deteriorates (Corbin and Strauss, 2010). Overall, Corbin and Strauss (2010) defined the five phases of chronic illnesses as follows. A phase is considered **acute** when the affected individual is physically or psychologically impaired to an extent that immediate medical attention and possibly hospitalisation are necessary to prevent further deterioration. The focus then is on achieving both physical and psychological stabilisation and promoting recovery (Corbin and Strauss, 2010). **Normalisation** indicates physical and psychological recovery following an

acute phase. The trajectory overall shows an upward trend, and coping strategies aim to achieve physical well-being, regain functionality either fully or partially, and also cope with the illness and resulting disability (Corbin and Strauss, 2010). A phase is **stable** when there are no significant changes for better or worse in the course of the illness. The disease may slowly change over the years, with fewer or no noticeable signs. Coping aims to maintain this stability. Conversely, a phase is **unstable** when a disease or disability is out of control. Normal coping strategies are ineffective, so coping focuses on identifying the cause of instability and/or alternative tactics to bring the health condition under some control and maintain it. Normal life may be seriously disrupted (Corbin and Strauss, 2010). A **declining** trajectory indicates that the course of a disease is moving slowly or rapidly downward. This could be the result of a progressive disability, as seen in PD. Coping strategies here aim to control the speed and extent of the decline (Corbin and Strauss, 2010).

Occurrence of declining and stable/normalising trajectories of functional mobility

The nursing scientist Zegelin (2008) investigated factors explaining longitudinal changes of mobility by developing a model of the process of becoming bedridden. Although this dissertation doesn't focus on the topic of being bedridden ("a longer state of existence in which the affected person spends the majority of the day (and night) in bed"), the factors involved in the decline of mobility might help to find ways how to prevent a decline. Thus, she describes the phenomenon of becoming bedridden as a slow process developing in phases by which the person is increasingly confined to one location. She identified a range of factors influencing the process of becoming bedridden (underlying pathology, consequences of the restricted immobility, adaption to and coping with the restricted mobility, social support and implication, occupation, furniture, transfer situation, key events, the personality of the person itself as the skills and attitude of as the communication with the carers during mobilisation). Importantly, she highlights the central significance of the autonomous decision making in switching between places as people move with intentionality:

> *"One "takes" bed rest, but one "is" bedridden." (Zegelin, 2008).*

She recommends that research about mobility should not only focus on the physical aspects but also on the social and psychological aspects. Also, she describes that the transfer situation and the experiences during the mobilisation influence the choice to stay mobile or not. Moreover, she highlights that the fact of being bedridden is not inevitable. Instead, she recommends to rate it as a complication and that in many cases the pathology of immobility can be reversed.

While the decline in functional mobility is well-documented, it is equally important to understand the processes that can facilitate improvements in mobility.. Adlbrecht and

Mayer (2018) investigated the process of regaining physical mobility. Thus, the process of regaining mobility is initiated after a sudden reduction in mobility and independence due to an incident (surgery, critical pain, illness, and hospitalisation). Subsequently, according to a multiple holistic case study (Adlbrecht and Mayer, 2018), older people aim to improve their independence, whereas nurses focus on mobility itself. Specifically, older people evaluated their situation based on the functional restrictions caused by the mobility impairment and their goals aroused from experienced incidents, e.g., not being able to go to the bathroom by themselves. Thus, they recommend that approaches to regain functional mobility could involve strategies other than mobility training. This is in line with the discussion by Zegelin (2008) about intentional mobility of older adults. Adlbrecht and Mayer (2018) describe the process of how to regain mobility starts from a safe level, mobility and independence improve stepwise in an iterative process. More specifically, the safe levels enable older adults to move comfortably without fear and stress. Once they are confident enough they can move to a higher level for a short period of time. As this is exhausting, it is important that they can move back to their "comfort zone" whenever needed. Also, the range of mobility needs to be extended in small steps. Finally, they regain confidence, strength and the ability to extend the periods of time spent at the next higher mobility level. The process of regaining mobility might be limited by the baseline mobility status. Thus, older adults who used the walking frame before the sudden mobility reduction, do not learn to walk without the walking frame. This is in line with the cognitive-reserves research discussing that cognitive interventions should aim at maintaining and possibly restoring brain structure and functions rather than expecting that training will evoke novel brain responses in older adults (Nolan and Blass, 1992). Also, they might not exploit their capabilities to their maximum, as they tends not to overachieve their goals. If for example, the goals is "not to be a burden for anyone", they have achieved their goal when they are able to move independently in their wheelchair – they do not try to learn to walk again (Zegelin, 2008).

Understanding stable and normalising trajectories

A useful concept for further understanding stable or improving trajectories is salutogenesis, a concept defined by the medical sociologist Aron Antonovsky (Antonovsky, 1979) during a study about women in the age of menopause. The questionnaire included the question: "During World War II, were you in a concentration camp – yes or no?". Of the 287 women 77 responded with "yes". Despite having lived through the most inconceivably inhuman experience, followed by Displaced Person camps, illegal immigration etc., some women were reasonably healthy and happy, had raised families, worked, had friends, and were involved in community activities. Consequently, the fundamental question in scientific, humanitarian and philosophical terms became:

> *"How do some of these people manage to stay reasonably healthy?" (Antonovsky, 1979).*

This central question offeres three advantages over the pathogenic question "Why do people become ill?": It focuses on the common denominators of health, including individuals' subjective interpretations; it embraces the notion of multiple causations and encourages a broad approach consistent with the field of health promotion; and it measures health on a continuum (instead of the traditional dichotomous categorisation in "health" and "illness") and seeks to describe and explain factors that move individuals toward the healthy end of a health continuum. Thus, health and illness were no longer viewed as dichotomies but as a multidimensional health-illness continuum. Finally, he stated that salutogenesis could add an important new facet to pathogenesis, the traditional medical model, by researching the origins of health to identify factors that can promote health (Antonovsky, 1979). Thus, the salutogenic model is focused on human strengths to overcome vulnerability rather than weaknesses (Horsburgh and Ferguson, 2012).

Overcoming vulnerability with reserves

Webber et al. (2010) raised awareness of the complexity of factors that influence mobility. The concept of "reserves" may help in describing and explaining interindividual differences in developmental trajectories during the life course and in ageing (Cullati et al., 2018). Specifically, Cullati et al. (2018) extended the concept of cognitive reserves (Stern, 2012) to other reserves, e.g., socioeconomic or relational to better describe and explain the development of vulnerability across the life course.Spini et al. (2013) defined vulnerability as:

> *"lack of resources, which in a specific context, places individuals or groups at a major risk of experiencing (1) negative consequences related to sources of stress; (2) the inability to cope effectively with stressors; and (3) the inability to recover from the stressor or to take advantage of opportunities by a given deadline" (Spini et al., 2013).*

As illustrated in Figure 5, people with PD can show an adaptive or non-adaptive process when confronted with adverse life events. Individuals with an adaptive process show a trajectory where they regain their initial level of reserves after an adverse life event to be prepared to face subsequent life adverse events while individuals with a non-adaptive process show trajectories where they do not regain their initial level of reserves. In this context, the lack of reserves is interpreted as a vulnerability when decreasing reserves meet a threshold where individuals are unable to restore a normal state, e.g., individuals face a loss of autonomy, which in many cases accumulates and leads to further significant social exclusion. A lack of reserves makes it difficult to deal with external stressors and overcome the negative stress associated with health hazards (Cullati et al., 2018).

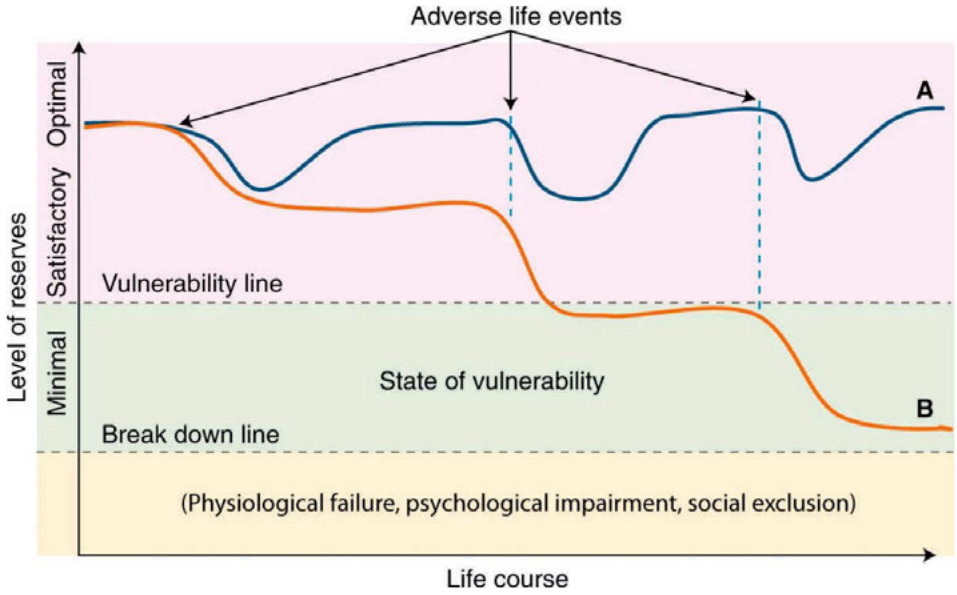

Figure 5 Schematic representation of the concept of reserves and vulnerability through the life course. Line A: trajectory of individuals who ideally regain their initial level of reserves, to be prepared to face subsequent life adverse events (adaptive process). Line B: trajectories of individuals who do not regain their initial level of reserves (non-adaptive process). Reproduced with permission from Spinger Nature from Cullati et al. (2018)

According to Cullati et al. (2018), reserves can be understood as a sub-dimension, or a special type, of resources. Reserves are potential means, i.e., a latent capability that can be used (or not) to overcome adverse life events or that are involved in delaying or modifying the decline in older age, e.g., bank savings. On the other hand, resources are means with an immediate or direct purpose, e.g., income. While, the primary function of resources is to ensure daily functioning, reserves have a protective function against the negative effects of ageing or decline of functional mobility. Thus, studying reserves may help to understand why some individuals are more affected than others as they help overcome shocks and delay or modify the processes of decline in well-being, health, wealth and social life during ageing. Moreover, such reserves help to recover from adverse events, stressors or nonnormative transitory periods during the life course, e.g., people with PD showing age-adequate normal and independent everyday mobility despite the PD diagnosis. Somehow their reserves offered protection (Cullati et al., 2018). Bouca-Machado et al. (2018) and Tosserams et al. (2020) described the contextual (World Health Organisation, 2002) reserves associated with functional mobility in people with PD. Thus, next to personal factors like genetics and sex/gender environmental factors (e.g., family support or a high educational attainment) might also play a role.

Cognitive and socioeconomic reserves

Stimulating activities or experiences over the life course (indirectly measured by proxies such as educational achievement) contribute to maintaining or improving cognitive reserve protecting against neurodegeneration (Stern, 2009). Although the model was first established in Alzheimer's disease, the relationship between motor symptoms and educational attainment attracted attention as people with PD with higher educational attainment showed significantly fewer motor deficits than those with low educational attainment (Sunwoo et al., 2016) despite greater reductions in dopamine levels. Specifically, educational attainment may lead to an increased ability to compensate disturbances in basal ganglia circuits affecting not only cognitive, but also motor aspects of PD. Consequently, educational attainment may play an important role in the concept of motor reserve (Blume et al., 2017). Also, the knowledge and skills attained through education may affect a person's cognitive functioning and health literacy, make them more receptive to health education messages, or more able to communicate with and access appropriate health services (Berkman et al., 2011, Fleisher et al., 2014). However, research needs to take into account that the meaning of educational attainment varies for different birth cohorts and there have been considerable changes in educational opportunities for women over recent decades (Galobardes et al., 2006). In addition to the cognitive reserve, the educational attainment can also act as a socioeconomic reserve. According to Beebe-Dimmer et al. (2004), formal education is normally completed in young adulthood and is strongly determined by parental characteristics, it can be conceptualised within a life course framework as an indicator that in part measures early life socioeconomic status, a strong determinant of future employment and income.

In addition to educational attainment, the place of residence might play a role as a socioeconomic reserve, especially in Luxembourg. Between 2010 and 2021, house prices increased by 135% (compared to 42% in the European Union) and most habitants of Luxembourg (72.4%) own a house or a flat. The housing situation varies, depending on the place of residence. Specifically, while in rural areas 79.3% live in a house, in cities this is only the case for 26.5% (Eurostat, 2023). The housing prices in Luxembourg indicate twice as high property values in the central areas (Strassen) compared to the more rural communities (Wiltz) (Ministère du Logement, 2023). Moreover, the overburden rate is higher in the rural compared to the central areas. Specifically, in 17.0% of the rural and 13.1% of the central households the total housing costs represented more than 40% of disposable income (Eurostat, 2023). This suggests a higher socioeconomic status of the inhabitants living in the central compared to a rural area in Luxembourg.

In addition to the housing alone, the health of the community and the local geographical neighbourhood plays a role in health promotion (Howden-Chapman, 2004). Green and active means of transport (e.g., carpooling, public transport, and active trips) may lead

to environmental benefits, on the one hand and health benefits—via increased physical activity—on the other (Giménez-Nadal et al., 2022). Also, environmental factors influence activity and participation in the International Classification of Functioning, Disability, and Health (ICF) (World Health Organisation, 2001). Due to their additional functional limitations, people with PD living at home experienced more accessibility[1] problems and less usability[2] of their home than people without PD (Nilsson et al., 2013). Also trips that are not work-related were their main source of daily mobility and thus especially important for people with PD. Furthermore, the reduction of transportation resources in rural and suburban areas may hit older people with PD the hardest (Giménez-Nadal et al., 2022, Smith and Sylvestre, 2002). Specifically, self-reported physical function has been found to be poorer among older people living in deprived urban neighbourhoods among others due to limited access to public transportation interfering with self-care tasks, physical activity and community participation (Balfour and Kaplan, 2002, Bowling et al., 2006). Moreover, the availability of transport infrastructure is linked to decreased time spent in housework trips and increased time spent in leisure trips, suggesting that this may help older adults to do their necessary daily activities faster. At the same time transport infrastructure helps them to access a greater range of leisure facilities including their social contacts.

Relational reserves

Relational reserves build on friendships, leisure time activities, educational attainment, marital and/or family life establishment and career development (Cullati et al., 2018). They tend to increase with age, then level off in older age (McDonald and Mair, 2010). The active acquisition of relations reserves is completed by a pool of relatives, passively inherited with a few members from each generation with an increasing importance of multigenerational bonds (Bengtson, 2004). Resources from members of one's personal network could be activated when needed (Cullati et al., 2018). According to Dykstra and Hagestad (2016), the partner and children might have a different effect on men compared to women. Also, life transitions, such as divorce or widowhood, have an impact on one's reserve of significant others (Kalmijn and van Groenou, 2016, Webber et al., 2010). Entering a partnership was identified as an advantageous factor improving trajectories of self-rated health (Cullati et al., 2014) and high levels of social support may represent a protective factor in reducing the vulnerability of older people (Melchiorre et al., 2013). Older adults with trajectories of high or even increasing social engagement experience lower levels of physical limitations over time (Thomas, 2011). Moreover, without relational reserves, individuals may be at risk of unmet healthcare needs (Fiorillo, 2020) and at risk of being unable to cope effectively with critical events (Cullati et al., 2018). Family caregivers were described as the most valued

1 Accessibility: Encounter between the functional capacity of the individual (personal component) and the design and demands of the physical environment (environmental component) (Nilsson et al. 2013).

2 Usability: To enable participation in life situations, the concept of usability implies that a person should be able to use (to move around, be in, and use) the environment on equal terms with other citizens (Iwarsson et al. 2003).

environmental positive factor, once people with PD rely on them for most of their ADL needs (Bouca-Machado et al., 2018, Raggi et al., 2015).

Finally, in case of unsuffient reserves, an adaption to an adverse life event may be achieved by raising the starting level of a declining trajectory, levelling off the slope of the decline and/or adjusting the individual definition of the threshold level (Cullati et al., 2018). Using this analogy in the context of PD, the progressive nature of PD suggests that higher reserve would lead to slower decline of functional mobility. The present work thus focuses the levelling off the slope of functional mobility decline, seeking to identify why determinants differ. Section 1.5 describes the cohorts used to assess trajectories of functional mobility.

1.5 COHORTS TO ASSESS TRAJECTORIES

Due to the heterogeneity and complexity of PD, its fluctuating nature and unpredictable medication response, assessment of disease progression in people with PD is challenging and requires continuous prolonged periods of evaluation to reach an accurate picture of symptoms and their fluctuations (Del Din et al., 2016, Bouca-Machado et al., 2018). In research, this requires intensive longitudinal studies of individual-level data, with several repeated measurements over time in the same individuals (Cullati et al., 2018). The Luxembourg Parkinson's study cohort (Hipp et al., 2018) and the data analysed in the dissertation are described in the next section.

The Luxembourg Parkinson's study cohort

The Luxembourg Parkinson's cohort is a nation-wide, monocentric, observational, longitudinal-prospective and dynamic cohort aiming at stratification and differential diagnosis of PD (Hipp et al., 2018). Among the participants are people with typical PD or PDD, living mostly at home in Luxembourg and the Greater Region (geographically close areas of the surrounding countries Belgium, France, and Germany). Over 800 participants with typical PD or PDD were recruited since 2015 with yearly follow-ups varying by a maximum of three months to minimize seasonal influences. In 2015, the estimated prevalence of PD in Luxembourg was 565 – 1356 people (Hipp et al., 2018). As 514 of the participants live in Luxembourg, we might have captured 37.9 to 91.0% of the people with PD living in Luxembourg. In addition to the referral by medical doctors, a communication campaign (advertisement on radio and television, dedicated webpage, social media campaign, multilingual flyers and posters, fact sheets and bi-annual print newsletter, collaboration with the associations of people with PD) informed the population about the option to enrol themselves. All participants underwent diagnostic evaluation and were assigned a clinical diagnosis of typical PD or PDD by a neurologist based on established United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992).

Participants of the Luxembourg Parkinson's study completed the questionnaires on paper at home prior to their baseline assessment while the MDS-UPDRS, BDI, and Hoehn and Yahr staging were completed during the baseline assessment onsite at the Parkinson's Research Clinic. The COVID-19 pandemic led to cancellations and delays in annual assessment and thus impacted data missingness. Similarly, deaths since baseline assessment in the analysed dataset may have contributed to attrition.

We enhanced the generalisability of our findings by analysing data of all participants with typical PD or PDD of the Luxembourg Parkinson's study from Luxembourg and the Greater Region, who are treated and live in varying settings and environments. More specifically, the participants covered a broad demographic range, including men and women from 22 to 93 years with 1 to 30 years of education, living from 0 to 32 years with the disease and speaking different languages. 69% of the participants were in disease stages H&Y 1-2 and the disease stages ranged from H&Y 1 to 5. We provide the full details in the individual chapters. Family members helped to complete the questionnaires if required. Standardised data collection was enabled by applying standardised operation procedures (SOP). Additionally, study nurses completed missing items in the patient-reported questionnaires during the baseline assessment together with the participants. Finally, samples of all participants providing their consent underwent genotyping allowing analysis including the association of genetic variants with progression of functional mobility. Tables in all chapters detail the characteristics of the outcomes, sources of data, measurement instruments and date of data export. Due to the dynamic design, numbers in the included chapter vary slightly as described in Table 1.

Table 1 Dates of data export and number of individuals per chapter

Chapter	Dates of data export	Number of individuals with typical PD or PDD
Chapter 2	2021-12-31	736
Chapter 4 & 5	2023-06-22	802
Chapter 6 & 7	2024-01-31	829

Causal inference in Epidemiology

The scientific contribution of epidemiology can be organised into three classes of tasks: 1) description (What happened, who was affected, people x had y), 2) prediction (What will happen, who will be affected, people x are more likely to get Y), and 3) counterfactual prediction (What will happen if..., why were they affected?, If we change X, how would it change Y?) also described as causal inference or explanation (Shmueli, 2010). While a good predictor may have no causal effect on the outcomes (e.g., taller people have larger feet), counterfactual prediction predicts certain features of the world, as if the world had been

different (e.g. progression of functional mobility that would have been observed if individuals with a rural place of residence were instead living in an urban place of residence or vice versa). Importantly, causal inference requires expert knowledge to specify the question, to identify relevant data sources, and to describe the causal structure of the system under study. Thus the validity of causal inferences depends on this structural knowledge (Hernán et al., 2019). Directed acyclic graphs (DAGs) are based on the structural knowledge and are an increasingly popular approach for identifying confounding variables that require conditioning when estimating causal effects (Tennant et al., 2021). Thus, a sufficient adjustment set closing all biasing paths and leaving all causal paths open to identify the total effect of our reserves will be identified. To be able to interpret the total effect of the reserves on the progression of functional mobility, we will not adjust for mediators or events occurring after the exposure. Also, we will not adjust a common consequence (Hernan and Monge, 2023, Digitale et al., 2023). Moreover, as the confounder effect estimates may be confounded themselves, we interpreted only the effect moderation (Westreich and Greenland, 2013).

Several challenges arise in the analysis of observational longitudinal data. Specifically, collider-bias can be induced by recruitment (in-selection) or loss to follow-up or mortality (out-selection) processes, as well as missing data or analytic choices about which variables are included as covariates (Digitale et al., 2023). Thus, collider bias is equivalent to observing this association in a sub-population where all individuals share the same value of participation (Munafo et al., 2018). Moreover, selection bias or the statistical adjustment for the collider (subsequent participation) can induce spurious associations (Munafo et al., 2018). Our discussion addresses the potential impact of those bias. Also, in general, evidence-based medicine discourages causal inferences from observational studies (Guyatt et al., 2000). However, particularly regarding the explanation of contextual factors and reserves build up over time, the explanatory factors, e.g. reserves, cannot be implemented as an intervention. Consequently, RCTs are not feasible (Shmueli, 2010). A list of considerations, e.g., the Bradford Hill criteria, can help to distinguish causal and noncausal association. One criterion among others is the inarguable criterion of temporality referring to the necessity that the cause precedes the effect in time (Rothmann et al., 2008), made possible in longitudinal data analysis. While the dissertation focusses on the statistical effect moderation and does not aim to make definite causal conclusions, the research questions have been visualised with directed acyclic graphs and statistical analyses adjusted accordingly.

Longitudinal data analysis

In this dissertation we investigate the moderation of the trajectory of patient-reported functional mobility by sex/gender, *GBA1*-variants and cognitive, relational and socio-economic reserves. Repeated measurements of longitudinal exposure are usually correlated with each other, also known as autocorrelation. Consequently, they do not satisfy

the independence of observations requirement of many common statistical analyses (Long, 2012). Analyses interested in the trajectories of a longitudinal exposure require advanced modelling (Gadd et al., 2019). We use longitudinal data from the Luxembourg Parkinson's study collected between the 4th March 2015 to the 29th January 2024 (mean number of follow-ups 3.2, range from 1 to 8). We analysed data from more than 800 people with typical PD or PDD with at least a baseline assessment. Data analysed in this dissertation was collected yearly, e.g. with an interval of one year. As time elapses during this one year interval, individuals with PD can have significant life events, such as changes in health status precipitating dropout from the study. The mixed effects models can accommodate missing data at random and adequately account for the typical pattern of variances and correlations among the repeated measures. Specifically, when missing data occurs only in the outcome, a subject will be included in the linear mixed effects models analysis as long as there is at least one non-missing time point. When missing data occurs for a static predictor, then the subject is omitted from the analysis. This can lead to changing sample size based on which predictors are included in the linear mixed effects models (Long, 2012). The predictors can be quantitative, categorical, or a combination. Any predictor that changes over time, e.g. a time-varying predictor time since diagnosis, accounts for within-subjects variability, and any predictor that is constant over time – but not constant among subjects –, e.g., static predictor sex/gender, accounts for between-subjects variability. When a static predictor is categorical like sex/gender, then the change curves in question are mean trends for the groups. In the present work, the time-variant predictor is a time predictor like years since diagnosis (disease duration). Thus, the analysis involves the fitting of a curve for the outcome over time. The regression line consists of the fitted values of the outcomes, which can be interpreted as predicted mean values for the fixed values of time since diagnosis. Therefore, the analysis of a longitudinal outcome on a time predictor focuses on the trend of the means over time (Long, 2012). Section 1.6 introduces the explanatory sequential mixed methods study design applied in the present dissertation and provides context to the statistical analyses.

1.6 EXPLANATORY SEQUENTIAL MIXED METHODS STUDY DESIGN

Due to PD heterogeneity, the people with Parkinson's experience of mobility impairment and respective coping strategies are very individual (Bouca-Machado et al., 2018). The complexity calls for answers beyond simple numbers in a quantitative sense or words in a qualitative sense. A combination of both forms of data provides the most complete analysis of complex problems (Creswell and Plano Clark, 2018).

As mentioned previously, this dissertation retrospectively analysed data collected since 2015 in the frame of the Luxembourg Parkinson's study cohort. Thus, we applied an explanatory

sequential mixed methods design. The name of the design, i.e., explanatory, rather than referring to causation, reflects how the qualitative data help to understand and explain the quantitative results (Shmueli, 2010). Our explanatory sequential mixed methods study started by analysing the progression of motor- and non-motor symptoms across sex/gender and *GBA1*-variants. Also, we analysed the statistical effect moderation of the patient-reported functional mobility trajectory by relational, cognitive or socioeconomic reserves. Specific results identified in this step were followed up with the subsequent qualitative phase exploring the experience of the roles the reserves may play in the decline of patient-reported functional mobility in people with PD to help explain the quantitative results. The flowchart (Figure 6) provides an overview of the different phases and procedures. During the first step, we designed and implemented a quantitative phase, i.e., the retrospective analysis of the Luxembourg Parkinson's study (Hipp et al., 2018). In the second step, we connected the quantitative part to the qualitative part by identifying specific quantitative results requiring additional explanation and using these results to guide the development of the qualitative strand. Integration involved connecting the results from the initial quantitative phase to help plan the follow-up qualitative data collection phase. Once the quantitative phase was completed, we integrated the two sets of connected results to draw conclusions. This design allowed us to form groups, e.g., people with PD with unexpectedly high functional mobility (positive-performing exemplars) based on our longitudinal quantitative data which were followed up through subsequent qualitative research. Thus, we intended to explain the quantitative positive-performing examples with subsequent qualitative research. Moreover, this design allowed the use of the quantitative results about participant characteristics to guide purposeful sampling for the qualitative phase (Creswell and Plano Clark, 2018).

Creswell and Plano Clark (2018) encourage researchers to use different philosophical worldviews in mixed methods research and to be explicit about when each is used. In the quantitative part we used the postpositivist worldview, assuming the one and only truth is out there waiting to be discovered by objective and value-free inquiry (Yvonne Feilzer, 2009) to select instruments, measure variables, and assess statistical results. However, for the measurement of the main outcome patient-reported functional mobility and in the subsequent qualitative phase, we valued multiple subjective experiences and in-depth descriptions by shifting to the constructivist worldview made up of the understanding or meaning of the phenomena formed through participants. This approach respected the fact that the subjective views of people with PD were shaped by social interaction and by their own personal histories (Yvonne Feilzer, 2009). The problem centred pragmatism, a research philosophy most commonly used in mixed methods research, guided the integration of quantitative and qualitative research strategies as an overarching philosophical worldview by valuing objective and subjective knowledge (Creswell and Plano Clark, 2018). Thus, the pragmatic approach helped to focus on the primary importance of the question by applying multiple methods of data collection to provide multiple perspectives of the

factors modersting the progression of functional mobility (Creswell and Plano Clark, 2018). Moreover, pragmatism sidesteps the controversial issues of truth and reality, philosophically accepts that there are singular and multiple realities that are open to empirical inquiry and orient itself toward solving practical problems in daily life, a valuable orientation in research aiming for an impact in practice. In that sense, pragmatism allows the researcher to be free of mental and practical constraints imposed by the forced dichotomy between postpositivism and constructivism (Creswell and Plano Clark, 2018). According to pragmatists, research should no longer aim to most accurately represent reality but to be useful (Yvonne Feilzer, 2009) and promoting research relevant for the endusers of research, e.g., people with PD, health professionals and politics (Creswell and Plano Clark, 2018). Section 1.7 will discuss how this dissertation involved people with PD and the public in the research project.

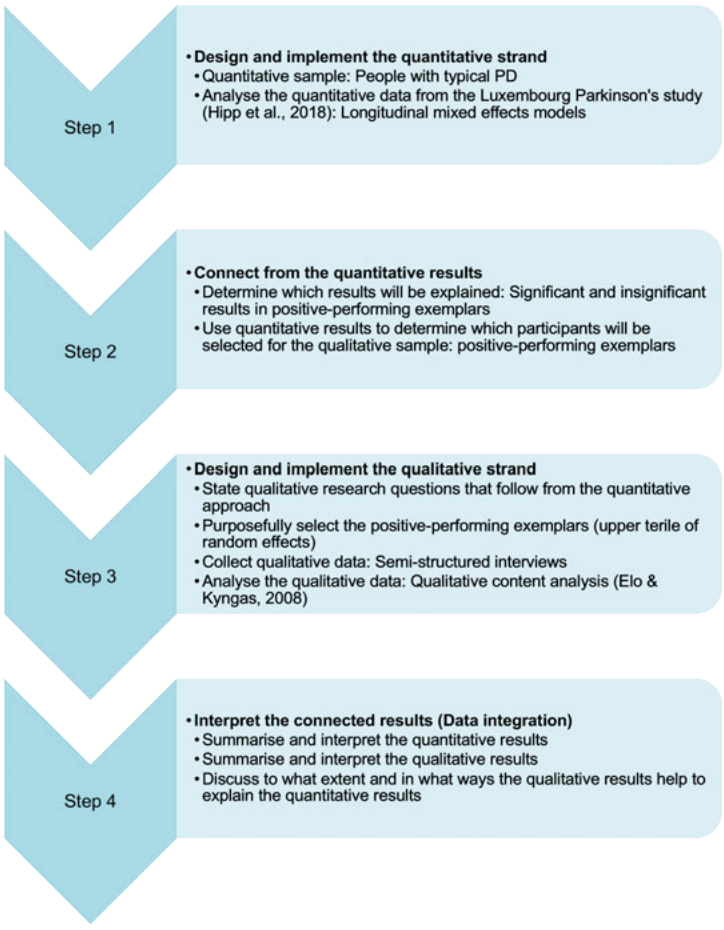

Figure 6 Flowchart of different phases and procedures (Adapted from Creswell & Plano Clark (2018))

1.7 PATIENT-PUBLIC INVOLVEMENT

Useful (clinical) research should, among other things, be aligned with the priorities of individuals living with the disease, the utilities they assign to different problems and different outcomes and how acceptable they find interventions over the period for which they are indicated (Ioannidis, 2016). There is a growing recognition that patient and public involvement (PPI) is important throughout the research process to avoid waste in the production and reporting of research evidence. Consequently, people living with the disease and health professionals must be involved in setting the research agendas and the development of interventions (Chalmers et al., 2014, Chalmers and Glasziou, 2009, Skivington et al., 2021).

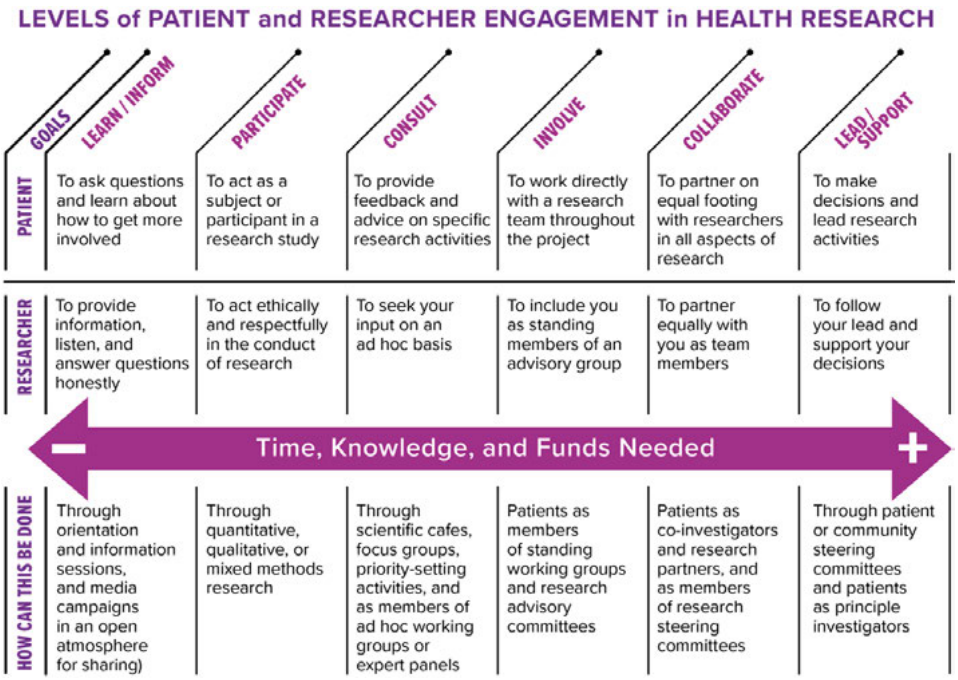

Figure 7 Levels of patient and researcher engagement in health research. Reproduced from "Patient and public engagement in priority setting: A systematic rapid review of the literature" (Manafo et al., 2018)

As illustrated in Figure 7, different levels of patient and researcher engagement in health research exist (Manafo et al., 2018). The higher the engagement the more time, knowledge and funds are needed. While participants learn/inform themselves by asking questions and participate as a participant in a research study, researchers can also consult them by seeking their input on different topics. To ensure the research in this dissertation is relevant

and valuable for the end users, we involved them in the setting of the research priorities. Specifically, in the preconception of the present dissertation, we consulted people with PD, their family and friends and health professionals by asking them about their top 10 research priorities. Mobility and independence, the topic of this dissertation, emerged as one of the top three priorities (Bowring et al., 2022). Thus, patient and public involvement forms the foundation of this dissertation further introduced in the next section. At the same time, the dissertation also concludes with patient public involvement, as the preliminary results of the mixed-methods study were presented and their implications were discussed with the members of the Luxembourg Parkinson Association (APL). At the same time, possible explanations were noted which people with PD or their family members considered important in relation to the understanding of unexpectedly high functional mobility. No new theme emerged that had not already been addressed by people with PD during the interviews presented in Chapter 7.

1.8 AIMS AND OUTLINE OF THE DISSERTATION

Functional mobility is one of the disease-related features most relevant to people with PD (Bowring et al., 2022), worsens as the disease progresses (Lindh-Rengifo et al., 2021, Mirelman et al., 2019) and has important consequences as loss of independence (Shulman et al., 2008), activity limitation (Tan et al., 2012, Tan et al., 2011), falls (Creaby and Cole, 2018), decreased social participation (Hammarlund et al., 2014), increased self-stigma (Hanff et al., 2021), and decreased quality of life (Perez-Lloret et al., 2014). As the resulting professional care and nursing home costs increase (Chaudhuri et al., 2024), a promotion of mobility and functionality could delay institutionalisation and respect the desire of people with PD to remain in their homes (Habermann and Shin, 2017).

Previous research on PD mainly asked the question: “Why does functional mobility in people with PD decrease?”. However, around one third of individuals with PD show unexpectedly high functional mobility (Hanff et al., 2022a). Therefore, a salutogenic research question (Antonovsky, 1979), “Why do some individuals show an unexpectedly stable trajectory of functional mobility despite Parkinson’s disease?” could help to gain a better understanding of this phenomenon and the factors involved. This dissertation aimed to understand factors moderating the progression of patient-reported functional mobility, the phenomenon of unexpectedly stable trajectories for functional mobility and how they are experienced by individuals with PD.

As we want to understand the phenomenon of functionality (functional mobility) despite disability (years since diagnosis), a key aspect of the International Classification of Functioning, disability and health (ICF), this classification helped to examine the phenomenon

on different levels as illustrated in Figure 8. The contextual factors include environmental and personal factors. While the external environmental factors facilitate or hinder the impact of other factors on functionality and disability, the personal factors, e.g., the attributes of a person, are described as internal influences (World Health Organisation, 2001).

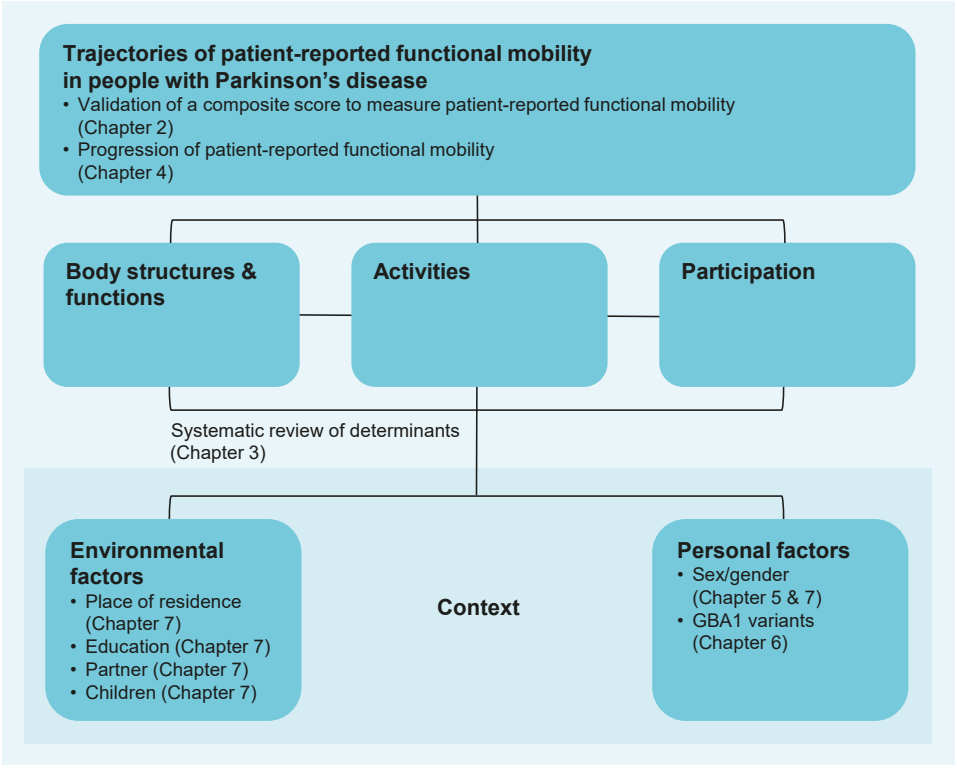

Figure 8 International Classification of Functioning, disability and health (ICF) (World Health Organisation, 2001) adapted to illustrate potential factors moderating the progression of patient-reported functional mobility

Using data from the Luxembourg Parkinson's study, a nationwide, observational, longitudinal-prospective and dynamic cohort, **Chapter two** of this dissertation reports the assessment of convergent and discriminative validity of the Functional Mobility Composite Score (FMCS). The FMCS is an algorithm based on the Parkinson's Disease Questionnaire-39 (PDQ-39) to assess patient-reported functional mobility in a multilingual context of Luxembourg. Moreover, the sub-scores by various subgroups provided in the supplement will help clinicians and other health professionals in the field to apply the FMCS in clinical practice.
To get an overview of the actual state of research, **Chapter three** deals with the current scientific knowledge on determinants of patient-reported functional mobility (Hanff et al.,

2024b). Specifically, this chapter reports a systematic review which identified disease duration, the ability to drive, caregiving, sex, age, cognitive impairment, postural instability and social participation as determinants of patient-reported functional mobility.

In preparation for the longitudinal analyses, **Chapter four** deals with the methodological aspects of statistical analysis of longitudinal data (Hanff et al., 2024a) by taking another important symptom (e.g. apathy that has been linked to the progressive loss of dopaminergic neurons) as an example. By comparing three statistical methods, we illustrated how the choice of statistical method may influence research outcomes, (e.g., progression in apathy), specifically the size of longitudinal effect estimates, in a cohort like the Luxembourg Parkinson's study (Hipp et al., 2018).

Using the methodology established and validated in Chapter two, **Chapter five** applies linear mixed effects models to deal with the differential trajectories of patient-reported functional mobility as the motor- and non-motor symptoms in men and women with PD (Hanff et al., 2023a). Compared to men, overall a slower disease progression was observed in women highlighting the need for stratified analyses for men and women.

While the previous chapter investigated the role of the personal factor sex/gender, **Chapter six** of this dissertation explores the role of body structures and –function. By applying linear mixed effects models, this chapter analyses the progression of patient-reported functional mobility and other symptoms in individuals with different genetic *GBA1* variants (Gaucher-related or PD-risk *GBA1* variants) compared to non-carriers. Although the *GBA1*-variants were not associated with a slower decline of patient-reported functional mobility, if the more rapid progression of non-motor symptoms are confirmed in an independent cohort, a re-evaluation of their pathologic relevance would be warranted.

To better understand the phenomenon of unexpectedly stable trajectories of functional mobility and the factors involved, **Chapter seven** deals with the environmental factors (World Health Organisation, 2001), i.e., the reserves moderating the progression of patient-reported functional mobility across sex/gender. This chapter reports linear mixed effects models investigating the moderation of the patient-reported functional mobility trajectory by relational, cognitive, and socioeconomic reserves. The statistical analyses were followed-up by qualitative interviews with participants experiencing an unexpectedly stable trajectory of functional mobility to explore their perceptions of barriers and facilitators related to those reserves. Finally, results of both parts are integrated in a sequential explanatory mixed-methods study (Creswell and Plano Clark, 2018) Among others psychosocial factors similar to self-efficacy, chronic inflammatory diseases and self-care activities promoting an active lifestyle emerged from the inductive analysis as characteristics of individuals with unexpectedly stable trajectories of functional mobility.

Finally, **Chapter eight** of this dissertation synthesises and discusses the results of all chapters in this dissertation, discusses methodological considerations and future directions and presents the overall conclusions of this dissertation.

CHAPTER 2

Validation of a Parkinson's Disease Questionnaire-39-based Functional Mobility Composite Score (FMCS) in people with Parkinson's disease.

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ABSTRACT

INTRODUCTION

Functional mobility is an important outcome for people with Parkinson's disease (PwP). Despite this, there is no established patient-reported outcome measure that serves as a gold standard for assessing patient-reported functional mobility in PwP. We aimed to validate the algorithm calculating the Parkinson's Disease Questionnaire-39 (PDQ-39) based Functional Mobility Composite Score (FMCS).

METHODS

We designed a count-based algorithm to measure patient-reported functional mobility in PwP from items of the PDQ-39 subscales mobility and activities of daily living. Convergent validity of the algorithm calculating the PDQ-39-based FMCS was assessed using the objective Timed Up and Go (n=253) and discriminative validity was assessed by comparing the FMCS with patient-reported (MDS-UPDRS II) and clinician-assessed (MDS-UPDRS III) motor symptoms as well as between disease stages (H&Y) and PIGD phenotypes (n=736). Participants were between 22 to 92 years old, with a disease duration from 0 to 32 years and 64.9% in a H&Y 1–2 ranging from 1 to 5.

RESULTS

Spearman correlation coefficients (rs) ranging from -0.45 to -0.77 ($p < 0.001$) indicated convergent validity. Hence, a t-test suggested sufficient ability of the FMCS to discriminate ($p < 0.001$) between patient-reported and clinician-assessed motor symptoms. More specifically, FMCS was more strongly associated with patient-reported MDS-UPDRS II (rs=-0.77) than clinician-reported MDS-UPDRS III (rs=-0.45) and can discriminate between disease stages as between PIGD phenotypes ($p < 0.001$).

CONCLUSION

The FMCS is a valid composite score to assess functional mobility through patient reports in PwP for studying functional mobility in studies using the PDQ-39.

INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative disorder resulting in a wide variety of motor and non-motor symptoms. The development of postural instability is considered an important hallmark of clinical progression in PD (Goetz et al., 2004). Tosserams et al. (2020) illustrated detrimental consequences for the participation of affected individuals in activities of daily living (ADLs). These consequences are due to impairments in functional mobility (FM), i.e. to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in ADLs at home, work and in the community (Bouca-Machado et al., 2018). This so-called "functional mobility" of people with PD (PwP) worsens as the disease progresses (Lindh-Rengifo et al., 2021, Mirelman et al., 2019) and impacts daily life. In particular, impaired functional mobility is associated with a loss of independence (Shulman et al., 2008), activity limitation (Tan et al., 2012, Tan et al., 2011), falls (Creaby and Cole, 2018), decreased social participation (Hammarlund et al., 2014), increased self-stigma (Hanff et al., 2021), and lower quality of life (Perez-Lloret et al., 2014). According to a recent update of the top 10 research priorities for the management of Parkinson's disease (Bowring et al., 2022), improvement of function and reduction of balance problems remain important research priorities for PwD, their significant others and health professionals.

No established instrument specifically assesses functional mobility through patient reports (Bouca-Machado et al., 2020a) although a patient-reported instrument would be feasible in different settings (clinic, home care, research), and would be less costly and invasive compared to objective physical performance tests. Notably, Patient-Reported Outcome Measures (PROMs) provide patients' perspectives and are often the outcomes of most importance to patients (Johnston et al., 2022). The "Mobility" and the "Activities of Daily Living" subscales of the PDQ-39 Health-related Quality of Life Questionnaire (Peto et al., 1995) have been applied individually to measure functional mobility through patient reports in previous research (Vervoort et al., 2016, Jaywant et al., 2016, PD MED Collaborative Group et al., 2014, Stocchi et al., 2014) but neither were originally developed nor validated to assess functional mobility. Their use for this purpose however implies a need for such scales and indicates that these established subscales may be worth investigating in terms of their validity for assessing functional mobility, until a new instrument could be developed, validated and translated. To this end, we combined these two subscales in an algorithm calculating the PDQ-39-based functional mobility composite score (FMCS) to measure patient-reported functional mobility. A further advantage of the algorithm calculating the PDQ-39-based FMCS is that there is no need for PwP to complete an additional questionnaire, reducing their burden. As detailed in the supplement section 1.1, content validity, structural validity, test-retest-reliability, internal consistency and construct validity have previously been confirmed separately for the individual subscales included in our

composite score. However, the convergent validity with an instrument assessing functional mobility has never been studied.

In this study, we aimed to validate the algorithm calculating the PDQ-39-based FMCS. As no gold standard for a PROM of functional mobility exists, we assessed the construct validity of the composite score. Consequently, we did not focus on the correlation with one gold standard but with several similar concepts.

METHODS

Study design, setting and participants

The COSMIN guidelines (de Vet et al., 2011) were used as methodological guideline for this study. This retrospective analysis is part of the Luxembourg Parkinson's study, a nation-wide, monocentric, observational, longitudinal-prospective study (Hipp et al., 2018). Among the participants are people with typical PD and Parkinson's disease dementia (PDD), living mostly at home in Luxembourg and the Greater Region (geographically close areas of the surrounding countries Belgium, France, and Germany). While the first patient was recruited in 2015, the systematic assessment of the Timed Up and Go (TUG) was added in November 2020.

As further described in supplement 1.1., after summing up the sixteen items of the PDQ-39 subscales mobility and activities of daily living (Peto et al., 1995), we transformed the FMCS score to a 0 – 100 scale according to the "User Manual" of the "The Parkinson's Disease Questionnaire" and inverted it by subtracting the individual score from the maximum score to enhance the interpretation of the results, i.e., a high score corresponds to good functional mobility.

$$FMCS\ Score = 100 - \left(\frac{Sum\ of\ 16\ items}{(4\ levels * 16\ items)} * 100\right)$$

We formulated hypotheses about the relationships between the algorithm calculating the PDQ-39-based FMCS and other instruments measuring similar constructs. Additionally, hypotheses about differences in the FMCS between subgroups of patients were defined. Specifically, we evaluated the convergent validity by analyzing the association between the FMCS and similar constructs like the TUG (Podsiadlo and Richardson, 1991), MDS-UPDRS-based Postural Instability and Gait Difficulty Score (Stebbins et al., 2013) and patient-reported and clinician-assessed motor symptoms (MDS-UPDRS II and III) (Goetz et al., 2008b). We also compared the association between the FMCS and the MDS-UPDRS II and MDS-UPDRS III (Goetz et al., 2008b). Additionally, we compared the association of the patient-reported symptoms of depression (BDI-I) with an objective measure of functional mobility (TUG)

to the patient-reported FMCS to assess discriminant validity, as the FMCS should better reflect the emotional state of PwP than an instrument with objective measures. Finally, we compared the FMCS between the subgroups to assess for discriminant validity since the FMCS should be able to differentiate between people with early and moderate-advanced disease stages as well as between people with and without a Postural Instabilities and Gait Difficulty (PIGD)-dominant phenotype (Stebbins et al., 2013). Detailed hypotheses can be found in the supplement. For the hypothesis-testing requiring TUG data, we included all 253 participants with typical PD or PDD (PwP) who performed a TUG in the Luxembourg Parkinson's study from November 2020 to December 2021. For the other analyses, we included all 736 PwP with a baseline assessment in the Luxembourg Parkinson's study. Participants with atypical PD were excluded from the analyses. Family members helped to complete the questionnaires if participants were having difficulties due to physical or cognitive impairments.

Variables and data collection procedure

PROM administration and comparison instruments

Participants of the Luxembourg Parkinson's study completed the PDQ-39 on paper at home prior to their baseline assessment while the TUG, MDS-UPDRS, BDI, and Hoehn and Yahr staging were completed during the baseline assessment onsite at the Parkinson's Research Clinic. We enabled standardized data collection by applying standardized operation procedures (SOP). Additionally, study nurses completed missing items in the patient-reported questionnaires during the baseline assessment together with the participants. Supplement Table S1 details the measurement instruments with which the FMCS is compared while supplement Table S2 lists all other variables.

Quantitative variables

The variables analyzed in the convergent validation (i.e. MDS-UPDRS-based PIGD score, MDS-UPDRS II and III, TUG and BDI-I scores), were treated as numerical variables to retain all information. The grouping for the discriminative validation was organized as follows: early disease stages (H&Y stages 1, 1.5 and 2) and moderate-advanced disease stages (H&Y stages of 2.5 – 5). This grouping was chosen as H&Y stage 2.5 is marked by the appearance of postural impairment (Goetz et al., 2004). Participants with an MDS-UPDRS TD/PIGD ratio of ≤ 0.90 were classified as a PIGD-dominant phenotype while ratios of > 0.90, i.e., tremor-dominant and intermediate phenotypes were classified as non-PIGD dominant phenotypes (Stebbins et al., 2013).

Statistical methods

Data analysis was carried out in R, version 3.6.3 (R Core Team, 2021). We identified skewed data distribution by visual inspection of histograms and Q-Q-Plots (using the "ggplot2" package by Wickham (2016)) combined with a significant Shapiro Test (using the "stats"

package by R Core Team (2021)) rejecting normality of the FMCS. However, we identified no departures from linearity in scatter plots (Fig. 1). Convergent validity was assessed by two-tailed Spearman correlation test (r_s). In addition, two t-tests tested for differences between correlation of FMCS with patient-reported and objective measures (using the "lavaan" package by Rosseel (2012)). The two-sided Wilcoxon rank-sum tests (WRS) tested group differences to assess discriminative validity (using the "stats" package by R Core Team (2021)). The hypotheses in the supplement provide more details. We defined a Bonferroni-adjusted 5% significance level of 0.05 / 8 to counteract the problem of multiple testing. We performed sensitivity power analyses in jamovi 2.2.5.0 (The jamovi project, 2021) to calculate the minimum hypothetical effect size for which the chosen design will have the specified sensitivity. During the analysis, we handled missing data as a complete-case analysis.

RESULTS

Participants characteristics

While 690 of 736 (93.8%) eligible participants with PD or PDD completed the items included in the composite score at home, we experienced challenges performing the TUG onsite during the COVID-19 pandemic, with many PwP preferring a telephone questionnaire. Consequently, data related to the TUG was missing in 60% (363/610) of all PwP recruited since the start of the systematic assessment of the TUG (which started in November 2020). Characteristics of study participants and the number of participants with missing data for each variable of interest are summarized in Table 1 and supplemental Table S3. To enhance interpretation and give a clinical connotation to the scores, scores of the FMCS by various subgroups can be found in the supplement.

Table 1 Sociodemographic and health-related characteristics of the participants (N = 736) included at baseline assessment

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (IQR)	Missing N (%)
Sociodemographic characteristics				
Age (y.)	67.3 (10.9)	22.0 – 92.9	68.3 (60.2 - 74.7)	0 (0%)
Children (n)	1.9 (1.2)	0.0 – 7.0	2.0 (1.0 - 2.0)	2 (0.3%)
Years of Education	12.9 (4.1)	1.0 – 30.0	12.0 (10.0 - 16.0)	5 (0.7%)
Language most fluent				0 (0%)
French	212 (28.8%)			
German	118 (16.0%)			
Luxembourgish	316 (42.9%)			
Other	90 (12.2%)			
Male sex	489 (66.4%)			0 (0%)
Marital status				3 (0.4%)
Single	39 (5.3%)			
Married / Partnered	562 (76.4%)			
Divorced / Widowed	132 (17.9%)			
Retired	531 (72.1%)			9 (1.2%)
Health-related characteristics				
Hoehn and Yahr (H&Y) Disease Stages				8 (1.1%)
H&Y 1	73 (9.9%)			
H&Y 1.5	51 (6.9%)			
H&Y 2	380 (51.6%)			
H&Y 2.5	99 (13.5%)			
H&Y 3	71 (9.7%)			
H&Y 4	38 (5.2%)			
H&Y 5	16 (2.2%)			
Disease duration (y.)	5.2 (5.1)	0.0 – 32.3	3.5 (1.2 - 7.7)	46 (6.3%)
MoCA (0 – 30)[b]	24.6 (4.3)	5.0 – 30.0	25.0 (22.0 - 28.0)	19 (2.6%)
BDI-I (0 – 63)[a]	9.8 (7.2)	0.0 – 51.0	8.0 (5.0 - 14.0)	42 (5.7%)
MDS-UPDRS I (0 – 52)[a]	10.4 (6.9)	0.0 – 39.0	9.0 (5.8 - 14.0)	28 (3.8%)
MDS-UPDRS II (0 – 52)[a]	11.3 (8.3)	0.0 – 46.0	10.0 (5.0 - 15.0)	22 (3.0%)
MDS-UPDRS III (0 – 132)[a]	34.7 (16.4)	1.0 – 100.0	33.0 (23.0 - 45.0)	17 (2.3%)
MDS-UPDRS IV (0 – 24)[a]	1.6 (3.3)	0.0 – 16.0	0.0 (0.0 - 1.8)	10 (1.4%)
MDS-UPDRS-based PIGD Score (0 – 20)[a]	3.6 (3.8)	0.0 – 20.0	2.0 (1.0 - 5.0)	23 (3.1%)
PDQ-39 (0 – 100)[a]	25.2 (17.3)	0.0 – 82.1	21.8 (11.4 - 35.3)	68 (9.2%)
FMCS (0 – 100)[b]	73.8 (23.0)	1.6 – 100.0	79.7 (59.4 - 93.8)	46 (6.3%)

Note a higher scores indicating more severe impairment, b higher scores indicating less severe impairment.

Convergent validity

As indicated in Figure 1, the analyses of convergent validity to address the hypotheses 1 – 4 showed the FMCS correlates as expected with similar constructs, i.e. patient-reported and clinician-assessed postural instabilities and gait difficulties (A), observed functional mobility (B), patient-reported motor symptoms in daily living (C), and clinician-assessed motor symptoms (D). According to our sensitivity power analyses, our Spearman correlation tests with sample sizes of 253 and 736 will detect effect sizes of 0.16 and 0.09, respectively, with a probability greater than 0.8, assuming a two-sided criterion for detection that allows for a maximum Type I error rate of α=0.05.

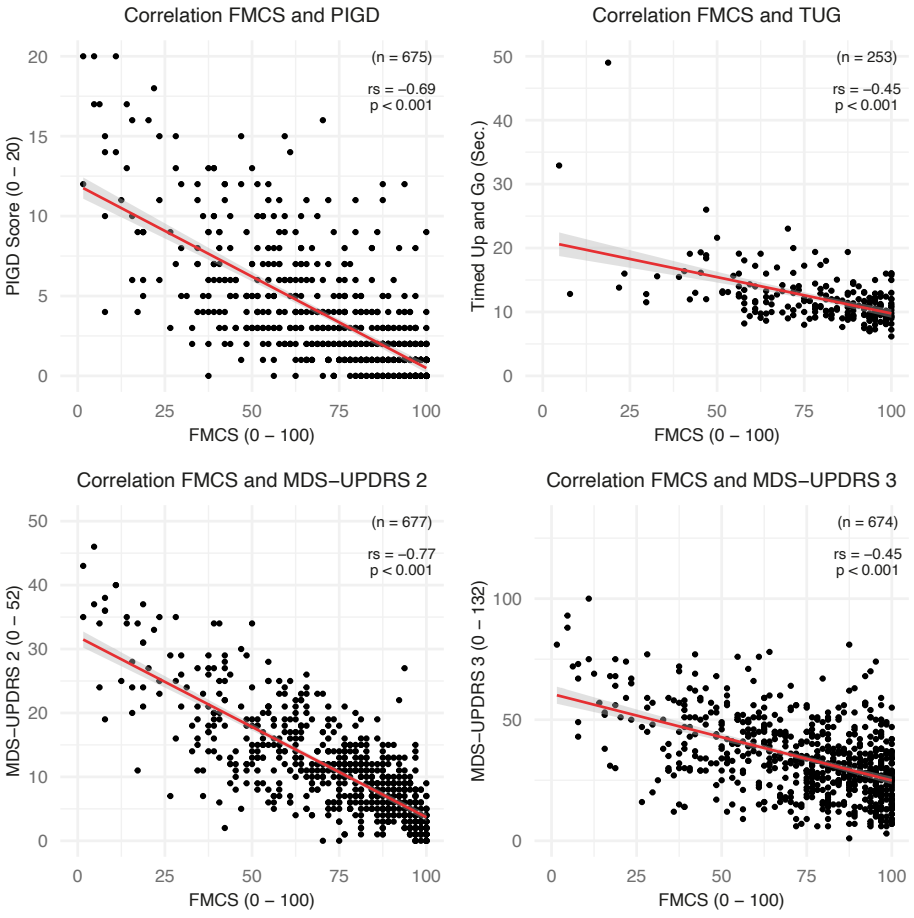

Figure 1 Scatterplots illustrating hypothesis-testing for convergent validity

Discriminative validity

Supplementary Tables S4 and S5 describe characteristics of the subgroups. As indicated in Figure 2, Wilcoxon rank-sum tests to address the hypotheses 5 and 6 confirm statistically significant mean ranks differences, i.e. lower FMCS in participants in an moderate-advanced disease stage compared to those in early disease stages (A) corresponding to a higher difference than the mean change in score (3.65) that is subjectively meaningful to PwP according to the clinical significance threshold described in the supplement 1.1. An illustration of FMCS per disease stage can be found in the supplement Table S6. Our analyses revealed the same for participants with a PIGD-phenotype compared to those without (B). Consequently, the FMCS discriminates between participants of both sets of groups. According to our sensitivity power analyses, the sample sizes of both comparator groups can detect minimum hypothetical effect sizes of 0.195 for the PIGD- and of 0.204 for the H&Y-comparator group with a probability greater than 0.80, assuming a two-sided criterion for detection that allows for a maximum Type I error rate of alpha = 0.05. Consequently, the effect sizes identified correspond to a detectable absolute r_s of 0.43 and 0.48, respectively.

As expected, the FMCS had a significantly stronger association with the subjective MDS-UPDRS II compared to the objective MDS-UPDRS III (Table 2). Notably, we identified a stronger association between the FMCS and the patient-reported BDI-I compared to between the objective TUG and the BDI-I, indicating that our instrument can differentiate between patient-reported and objective outcomes.

Table 2 Hypothesis-testing for discriminative validity – PROM versus objective measures

H0 - Hypotheses	Absolute correlations (r_s)	Difference (CI)	Sample size	Rejected
The absolute correlation of the FMCS with the MDS-UPDRS II = the absolute correlatioan of the FMCS with the MDS-UPDRS III.	0.77 vs 0.50	β : 0.27 (0.20 – 0.33)	663 / 736	✓
The absolute correlation of the BDI with the FMCS = the absolute correlation of the BDI with the TUG.	0.55 vs 0.21	β : 0.34 (0.21 – 0.47)	220 / 253	✓
Total amount of H0 – Hypotheses that were rejected				(2 / 2) 100%

Note $p < 0.001$

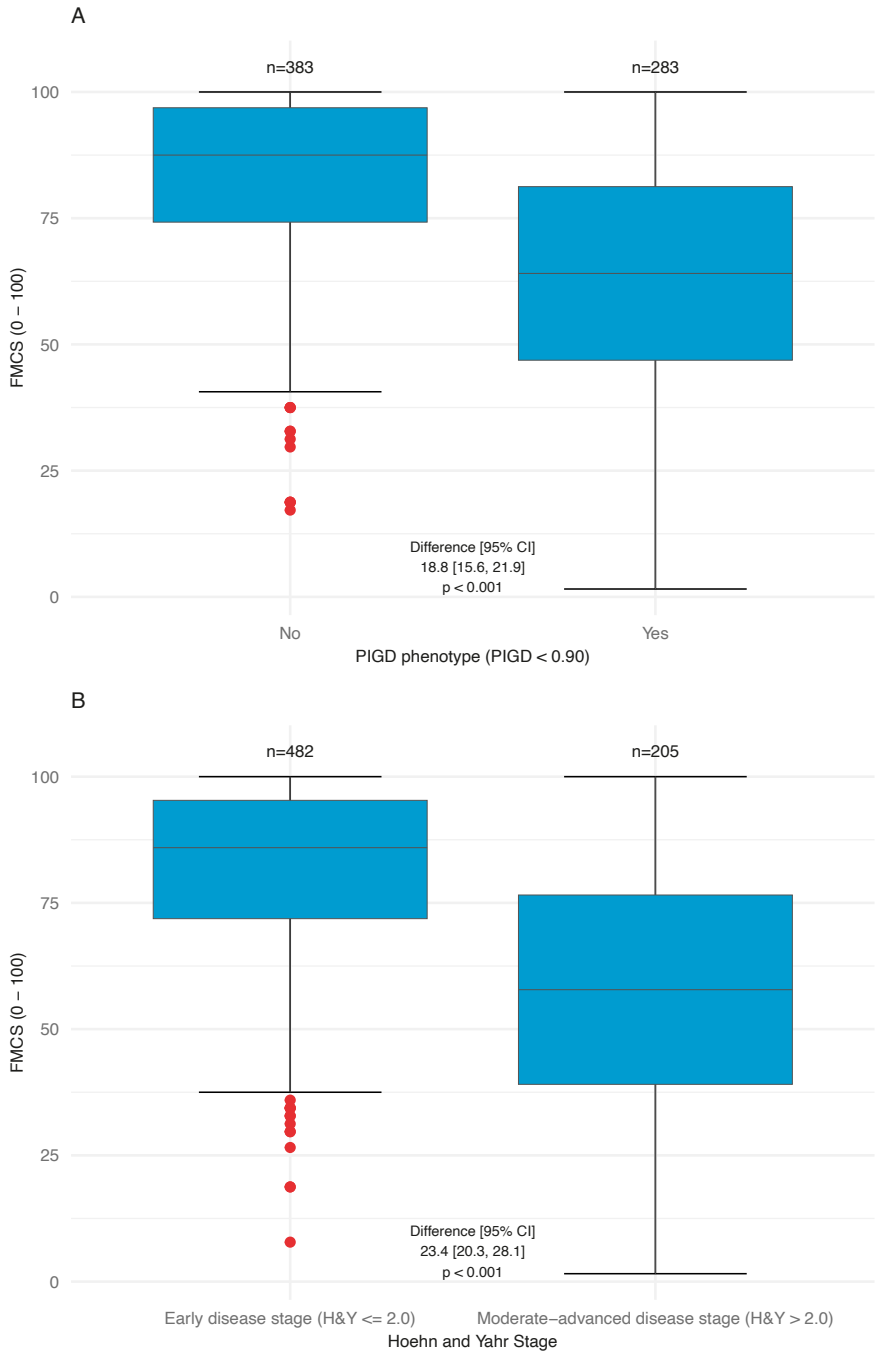

Figure 2 Wilcoxon rank-sum tests (WRS) show statistically significant mean ranks differences for disease stages (A) and PIGD phenotype (B) (hypothesis-testing for discriminative validity – comparator groups)

DISCUSSION

While no current established instrument specifically assesses functional mobility through patient reports (Bouca-Machado et al., 2020a), multiple studies have measured patient-reported functional mobility using the subscale mobility of the PDQ-39 (Jaywant et al., 2016, Stocchi et al., 2014, Vervoort et al., 2016) without establishing construct validation of the subscale for this purpose. Our results in the current analyses provide support for the convergent and discriminative validity of a PDQ-39-based patient-reported functional mobility composite score (FMCS), integrating items of the frequently used and well-validated PDQ-39, which is available in several languages.

This study has some strengths and limitations. For instance, we assessed construct validity by hypothesis-testing focussing on the correlation with several similar concepts since no gold standard for patient-reported functional mobility exists. Until such a gold standard measure is developed, validated and translated the current FMCS provides a valid measure based on existing questionnaires. In this study, family members helped to complete the questionnaires if required. Our results confirm previous findings by Fleming et al. (2005) stating that proxies scores differed from those of PwP. Consequently, the interpretation of proxy ratings needs to take this into account. Future research could investigate the feasibility of our score in patients with PDD and the time required for completion. While the COVID-19 pandemic may have led to missing data and sampling bias for the analyses involving the TUG, our sensitivity power analyses indicated the sample sizes allow us to detect the expected effect sizes. These adequate sample sizes were enabled by the well characterized Luxembourg Parkinson's study. Accordingly, all H0-hypotheses stated in the supplement were rejected in favor of the alternative hypotheses indicating a high validity of the FMCS according to Prinsen et al. (2018). Moreover, we enhanced the generalizability of our findings by analyzing data of all participants of the Luxembourg Parkinson's study including people with PD or PDD from Luxembourg and the Greater Region, who are treated and live in varying settings and environments. More specifically, the range of participants was broad, including men and women from 22 to 92 years with 1 to 8 children and 1 to 26 years of education, living from 0 to 32 years with the disease and speaking different languages. 64.9% of the participants were in disease stages H&Y 1 – 2, the disease stages ranged from H&Y 1 to H&Y 5. Our work provides a composite score that is available now in several languages and that allows a retrospective analysis of functional mobility in any study where PDQ-39 data have been collected (Vervoort et al., 2016, Jaywant et al., 2016, PD MED Collaborative Group et al., 2014, Stocchi et al., 2014). Questionnaire completion with pencil and paper should be feasible in different settings (clinic, home care, research), and should be less costly and invasive compared to objective physical performance tests. A further advantage of the PDQ-39-based algorithm is that there is no need for PwP to complete an additional questionnaire, reducing their burden.

In conclusion, this study has obtained comprehensive results supporting the cross-sectional construct validity of the Functional Mobility Composite Score (FMCS), an instrument assessing functional mobility through patient reports. The spreadsheet calculator in form of an R-Shiny app (Chang et al., 2022) (https://tq9t3h-ahanff.shinyapps.io/FMCS_calculator/) and sub scores by various subgroups provided in the supplement will help clinicians and other health professionals in the field to apply the FMCS in clinical practice. As the components of the FMCS have been and are widely applied, our composite score could be calculated from available data in the literature to gain insight into patient reported functional mobility in single or meta-analyses. Future work will examine the longitudinal construct validity, which, if demonstrated, will allow the FMCS to be applied in the monitoring of new treatment options addressing functional mobility.

SUPPLEMENTAL MATERIAL

Supplementary information

Theoretical construct of the FMCS and validity of the two subscales

The theoretical construct provided by Bouca-Machado et al. (2020a), i.e., to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living at home, work and in the community guided the development. Consequently, the composite score combines the items of the subscale mobility with the items of the subscale ADL of the Parkinson's Disease Questionnaire (PDQ-39) (Peto et al., 1995). To ensure that all key concepts according to the definition of Bouca-Machado et al. (2018) were included, we compared the items of the subscales Mobility and Activities of Daily Living to the different characteristics of functional mobility according to their definition (Bouca-Machado et al., 2018). Consequently, we can confirm that the items of both subscales cover all relevant characteristics of functional mobility. As a previous factor analysis confirmed unidimensionality (Hagell and Nygren, 2007, Fitzpatrick et al., 1997) except for two items, we concluded that the items are mainly measuring one construct, i.e., the construct of functional mobility. Consequently, after summing up the items, we transformed the FMCS score to a 0 – 100 scale according to the "User Manual" of the "The Parkinson's Disease Questionnaire" (Jenkinson et al., 2022) and inverted it by subtracting the individual score from the maximum score to enhance the interpretation of the results, i.e., a high score corresponds to good functional mobility.

$$FMCS\ Score = 100 - \left(\frac{Sum\ of\ 16\ items}{(4\ levels * 16\ items)} * 100\right)$$

A spreadsheet calculator in form of an R-Shiny app (Chang et al., 2022) can be found under the following osf-webpage: https://tq9t3h-ahanff.shinyapps.io/FMCS_calculator/. According to Peto et al. (2001) mean change in the PDQ-39 subscore mobility of +3.2/100 (SD 13.26) and of +4.4/100 (SD 16.56) for the PDQ-39 subscore ADL corresponds to patients indicating feeling a little worse. The subscore mobility weights 62.5% (10/16) of the count based algorithm calculating the PDQ-39-based FMCS while the subscore ADL weights for 37.5% (6/16) of the score. Consequently, we weighted the change accordingly[3] resulting in a change of -3.65/100 indicating the patients experience worse functionally mobility.

The PDQ-39 is a thoroughly tested, translated, widely applied patient-reported quality of life assessment with adequate clinimetric characteristics. In particular, regarding content validity, questionnaire items were originally generated from in-depth interviews with PwP (Peto et al., 1995). Consequently, the included items are also relevant for the target population, i.e., PwP. Both subscales show internal consistency according to the criteria

3 (3.2 x 10) + (4.4 x 6) = 32 + 26.4 = 58.4/16 = 3.65

of Prinsen et al. (2018), i.e. a Cronbach's α ≥ 0.70 and ≤ 0.95 in almost all studies (Peto et al., 1995, Hagell and Nilsson, 2009, Martinez-Martin et al., 2007, Brown et al., 2009, Bushnell and Martin, 1999, Carod-Artal et al., 2007, Damiano et al., 2000, Hagell et al., 2003, Jenkinson et al., 1995). In addition, Hagell and Nygren (2007) reported corrected item-total correlations above the recommended criteria of 0.4 for all items. Regarding reliability, previous research showed test-retest-reliability, i.e. intraclass correlation coefficient (ICC) values above 0.70 for both subscales with test-retest periods between three days and two weeks (Peto et al., 1995, Hagell and Nilsson, 2009, Martinez-Martin et al., 2007, Luo et al., 2005). While construct validity of each subscale was previously assessed by correlations with patient-reported motor symptoms (MDS-UPDRS II) (Martinez-Martin et al., 2007) (r > 0.70), disease stage Hoehn and Yahr (H&Y) (r > 0.60) (Martinez-Martin et al., 2007, Jenkinson et al., 1995, Jenkinson et al., 1997, Schrag et al., 2000), disability scores (Columbia University Rating Scales (Jenkinson et al., 1995, Luo et al., 2005), Barthel index (Harrison et al., 2000), and Schwab and England Disability Score (Jenkinson et al., 1995, Schrag et al., 2000) (r > 0.55)), clinician-assessed motor symptoms (MDS-UPDRS III) (Jenkinson et al., 1995, Schrag et al., 2000) (r > 0.50), depression (Beck Depression Inventory (Schrag et al., 2000) and Hospital Depression Scale (Martinez-Martin et al., 2007)) (r > 0.50) and Levodopa duration (Martinez-Martin et al., 2007) (r > 0.40), a construct validation with an instrument measuring functional mobility was never performed. Although, correlations are less clear regarding disease duration in years (Martinez-Martin et al., 2007, Schrag et al., 2000) (r: 0.18 – 0.50) and cognition (Mini-mental score (Schrag et al., 2000) or Short Portable Mental Status Questionnaire (Martinez-Martin et al., 2007) (r: 0.23 – 0.39), both subscales discriminate PwP according to their disease stage (Carod-Artal et al., 2007, Damiano et al., 2000, Jenkinson et al., 1995, Jenkinson et al., 1997), perceived PD (Hagell et al., 2003) and symptoms severity (Peto et al., 1995).

Hypotheses

We tested the following four directed hypotheses to assess convergent validity:
H0: Correlation of FMCS and TUG = 0
HA: Correlation of FMCS and TUG < 0

We expected an absolute correlation of > 0.40 as the objective TUG does not consider the subjective point of view of PwP. Recent research by Leavy et al. (2018) supports our assumption as they detected a similar absolute correlation (r_s = 0.46) between patient-reported mobility and spatiotemporal domain step velocity.

H0: Correlation of FMCS and PIGD Score = 0
HA: Correlation of FMCS and PIGD Score < 0

We expected an absolute correlation (r_s) of > 0.60 as the PIGD is a combination of clinician-assessed and patient-reported items about balance and gait. Consequently, it does consider the subjective point of view of PwP.

H0: Correlation of FMCS and MDS-UPDRS II = 0
HA: Correlation of FMCS and MDS-UPDRS II < 0

We expected an absolute correlation (r_s) of > 0.60 as the MDS-UPDRS II is a patient-reported outcome of motor symptoms. Consequently, it does consider the subjective point of view of PwP and measures symptoms that are associated with functional mobility.

H0: Correlation of FMCS and MDS-UPDRS III = 0
HA: Correlation of FMCS and MDS-UPDRS III < 0

We expected an absolute correlation (r_s) of only > 0.40 as the MDS-UPDRS III is a clinician-assessed measure of motor symptoms compared to the PROM FMCS. Recent research by Zolfaghari et al. (2021) supports our expectation as they detected a correlation of the MDS-UPDRS III with the MDS-UPDRS II in two different datasets (r_s = 0.38 and r_s = 0.28).
Also, we tested the following four directed hypotheses to assess discriminative validity:

H0: FMCS in early disease stages = FMCS in advanced disease stages
HA: FMCS in early disease stages > FMCS in advanced disease stages

We expected people in early disease stages having at least a 3.65 pts higher FMCS compared to people in advanced disease stages according the minimally important difference experienced by people with PD.

H0: FMCS in people with PIGD-dominant phenotype = FMCS in people without PIGD-dominant phenotype
HA: FMCS in people with PIGD-dominant phenotype < FMCS in people without PIGD-dominant phenotype

We expected people with a PIGD-dominant phenotype having at least a 3.65 pts lower FMCS compared to people without according the minimally important difference experienced by people with PD.

H0: Absolute correlation (r_s) of the FMCS with the MDS-UPDRS II = Absolute correlation (r_s) of the FMCS with the MDS-UPDRS III
HA: Absolute correlation (r_s) of the FMCS with the MDS-UPDRS II > Absolute correlation (r_s) of the FMCS with the MDS-UPDRS III

We expected the absolute correlation (r_s) of the FMCS with the MDS-UPDRS II to be significantly stronger than the absolute correlation (r_s) of the FMCS with the MDS-UPDRS III, as the clinician-assessed motor symptoms do not consider the subjective point of view of PwP compared to the PROM of functional mobility.

H0: Absolute correlation (r_s) of the FMCS with the BDI-I = Absolute correlation (r_s) of the TUG with the BDI-I.
HA: Absolute correlation (r_s) of the FMCS with the BDI-I > Absolute correlation (r_s) of the TUG with the BDI-I.

We expected the absolute correlation (r_s) of the FMCS with the BDI-I to be significantly stronger than the absolute correlation (r_s) of the TUG and the BDI-I as the BDI-I and the FMCS are both patient-reported outcomes compared to the objective TUG. Consequently, the FCMS should reflect the emotional state of the PwP better than a physical performance test of functional mobility like the TUG.

Table S1 Characteristics of comparator instruments

Comparator instruments	Construct it intends to measure	Assessment type	Details	Measurement properties	Recomm-ended by MDS	Original Scale
Timed Up and Go (TUG)	Functional Mobility	Assessor Observation	Measures a similar construct, but not a patient-reported outcome measure. The participant is required to get up from a standard chair, walk at a comfortable and safe speed to a line 3 m away, then turn at the line and walk back to the chair to sit down (Bloem et al., 2016).	Adequate test-retest and inter-rater reliability in PD, with ICCs above 0.70. Known-group validity in PD is demonstrated by the test's ability to discriminate between early and middle disease stages, postural instability–gait difficulty dominant, and tremor-dominant types of PD. Construct validity in PD is demonstrated by correlations with walking speed, stride length, and turning ability (Bloem et al., 2016).	✓ Bloem et al. (2016)	Podsiadlo and Richardson (1991)
MDS-UPDRS-based PIGD Score	Postural Instabilities and Gait Difficulty	Patient-Reported and Clinician-Assessed Outcome Measure	Based on five MDS-UPDRS items relevant to gait and postural instability (items 13-15, 29, and 30) (Bloem et al., 2016). Combination of patient-reported and clinician-assessed outcome measures.	Good internal consistency, and moderate to good interrater reliability. Adequate face- and construct validity (Bloem et al., 2016).	✓Bloem et al. (2016)	Stebbins et al. (2013)
MDS-UPDRS II	Motor Symptoms in Daily Living	Patient-Reported Outcome Measure	Five of the 13 items assess impairments, not a disability (speech, salivation/drooling, chewing/swallowing, tremor, and freezing). The eight disability items assess eating, dressing, hygiene, handwriting, doing hobbies/activities (new), turning in bed, getting out of bed/car/chair (new), walking, and balance (Shulman et al., 2016).	Good internal consistency and validity with high correlation with the UPDRS-ADL. Cut-off values were determined as: 0 to 2 points, no disability; 3 to 16, mild; 17 to 31, moderate; and ≥32, severe (Bloem et al., 2016).	✓Bloem et al. (2016)	Rodriguez-Blazquez et al. (2013)

Table S1 Continued.

Comparator instruments	Construct it intends to measure	Assessment type	Details	Measurement properties	Recommended by MDS	Original Scale
MDS-UPDRS III	Motor Symptoms	Clinician-Assessed Outcome Measure	Motor examination (33 scores based on 18 questions with several right, left or other body distributions scores). Instructions for the rater to give or demonstrate to the patient and is completed by the rater.	Good internal consistency and validity with high correlation with the older version, UPDRS part III.	NA	Goetz et al. (2008b)
Beck Depression Inventory (BDI-I)	Symptoms of Depression	Patient-Reported Outcome Measure	One of the most used self-rated instruments for major depression in clinical practice. Weighted toward psychological symptoms of depression. Used to measure the severity of depression and as a screening instrument (Schrag et al., 2007).	High test-retest reliability and internal consistency. Good concurrent and discriminant validity. Correlates with biological markers of depression and appears to be valid in patients with significant cognitive impairment. Valid across cultures (Bloem et al., 2016).	✓Bloem et al. (2016)	Beck et al. (1988)

Note MDS: Movement Disorders Society, UPDRS: Unified Parkinson's Disease Rating Scale, PIGD: Postural Instabilities and Gait Difficulty

Table S2 Sociodemographic and disease-related variables

Variables	Instruments	Recommended by MDS	Original Scale
Age (y.)	NA		
Male sex			
Children (n)			
Years of education			
Disease duration (y.)			
Disease stage	Hoehn and Yahr (H&Y)	✓Goetz et al. (2004)	Hoehn and Yahr (1967)
Cognition	Montreal Cognitive Assessment (MoCA)	✓Skorvanek et al. (2018)	Nasreddine et al. (2005)
Patient-Reported Non-Motor Symptoms	MDS-UPDRS I Score	NA	Goetz et al. (2008a)
Clinician-Assessed Motor Complication	MDS-UPDRS IV Score	NA	Goetz et al. (2008a)
Health-Related Quality of Life Score	PDQ-39	✓Martinez-Martin et al. (2011)	Peto et al. (1995)

Table S3 Sociodemographic and health-related characteristics of the participants (N = 253) included in cross-sectional analysis involving the TUG

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (IQR)	Missing N (%)
Sociodemographic characteristics				
Age (y.)	67.3 (10.2)	22.9 - 92.7	68.6 (59.9 – 74.4)	0 (0.0%)
Children (n)	1.8 (1.1)	0.0 - 6.0	2.0 (1.0 - 2.0)	1 (0.04%)
Years of Education	13.5 (4.0)	5.0 - 25.0	13.0 (11.0 – 16.0)	0 (0.0%)
Language most fluent				0 (0.0%)
French	65 (26.3%)			
German	33 (13.4%)			
Luxembourgish	113 (45.7%)			
Other	36 (14.6%)			
Male sex	177 (71.7%)			0 (0.0%)
Marital status				1 (0.04%)
Single	7 (2.8%)			
Married / Partnered	193 (78.1%)			
Divorced / Widowed	44 (17.8%)			
Retired	162 (65.6%)			3 (0.1%)
Health-related characteristics				
Hoehn and Yahr (H&Y) Disease Stages				0 (0.0%)
H&Y 1	11 (4.5%)			
H&Y 1.5	21 (8.5%)			
H&Y 2	132 (53.4%)			
H&Y 2.5	55 (22.3%)			
H&Y 3	22 (8.9%)			
H&Y 4	6 (2.4%)			
H&Y 5	0 (0.0%)			
Disease duration (y.)	6.6 (5.0)	0.0 - 24.8	5.4 (2.8 – 8.6)	5 (2.0 %)
MoCA (0 – 30)[b]	25.4 (3.8)	10.0 - 30.0	26.0 (424.0 – 28.0)	7 (2.8%)
BDI-I (0 – 63)[a]	9.0 (7.4)	0.0 - 51.0	7.5 (4.0 – 12.0)	27 (10.7%)
MDS-UPDRS I (0 – 52)[a]	10.2 (6.1)	0.0 - 33.0	8.5 (6.0 - 14.0)	25 (9.9%)
MDS-UPDRS II (0 – 52)[a]	10.9 (7.8)	0.0 - 34.0	9.0 (5.0 - 16.0)	21 (8.3%)
MDS-UPDRS III (0 – 132)[a]	34.5 (13.8)	5.0 - 75.0	34.0 (25.0 - 45.0)	7 (2.8%)
MDS-UPDRS IV (0 – 24)[a]	1.3 (2.8)	0.0 - 15.0	0.0 (0.0 – 0.8)	3 (1.2%)
MDS-UPDRS-based PIGD Score (0 – 20)[a]	3.2 (3.1)	0.0 - 20.0	2.0 (1.0 - 5.0)	21 (8.3%)
PDQ-39 (0 – 100)[a]	20.6 (15.4)	0.0 - 82.1	18.6 (7.7 - 28.2)	26 (10.3%)
FMCS (0 – 100)[b]	79.4 (19.4)	4.7 - 100.0	84.4 (67.2 - 95.3)	24 (9.5 %)
TUG[b]	12.5 (5.0)	6.2 – 51.4	11.4 (9.8 – 13.3)	0 (0.0%)

Note [a] higher scores indicating more severe impairment, [b] higher scores indicating less severe impairment.

Table S4 Characteristics of PIGD comparator groups

Variables	Not PIGD dominant (N = 399)	PIGD dominant (N = 305)
Age (y)	67.3 (14.7)	69.9 (13.3)
Male sex	286 (71.7%)	186 (70.0%)
Children (n)	2 (1)	2 (2)
Years of education	13 (6)	12 (6)
Disease duration (y)	2.6 (4.4)	5.2 (8.2)
MoCA	26 (5)	25 (5)
BDI-I	7.0 (7.5)	10.0 (8.0)
MDS-UPDRS I	8.0 (8.0)	10.0 (10.0)
MDS-UPDRS II	7.0 (8.8)	13.5 (13.0)
MDS-UPDRS III	31.0 (19.0)	37.5 (23.3)
MDS-UPDRS IV	0 (0)	0 (5)
FMCS Score	87.5 (22.7)	64.1 (34.4)

Note categorical variables: counts (%), numerical variables: median (IQR)

Table S5 Characteristics of disease stages comparator groups

Variables	Early disease stage (N = 508)	Moderate-advanced disease stage (N = 225)
Age (y)	67.0 (14.2)	73.1 (13.2)
Male sex	350 (68.9%)	137 (60.9%)
Children (n)	2 (1)	2 (2)
Years of education	13 (6)	12 (4)
Disease duration (y)	2.7 (4.8)	6.0 (7.7)
MoCA	26 (5)	24 (6)
BDI-I	7 (8)	11 (8)
MDS-UPDRS I	8 (7)	13 (11)
MDS-UPDRS II	8 (8)	16 (13)
MDS-UPDRS III	29 (18)	45 (22)
MDS-UPDRS IV	0.0 (0.0)	0.0 (4.3)
FMCS Score	86.0 (23.4)	57.8 (37.5)

Note categorical variables: counts (%), numerical variables: median (IQR)

Table S6 FMCS by various subgroups

Characteristics	Categories	Mean (SD)
Sociodemographic characteristics		
Years of Education	< 13 y.	73 (24)
	≥ 13 y.	76 (21)
Retired	No	78 (19)
	Yes	72 (24)
Health-related characteristics		
Phenotype	Tremor (≥ 1.15)	84 (16)
	Intermediate (<1.15 & >0.90)	74 (21)
	PIGD (≤ 0.90)	62 (24)
Hoehn and Yahr (H&Y)	H&Y 1	89 (12.9)
Disease Stages	H&Y 1.5	86 (16.5)
	H&Y 2	79 (18.4)
	H&Y 2.5	66 (19.8)
	H&Y 3	59 (23.3)
	H&Y 4	34 (19.2)
	H&Y 5	36 (34.0)
Depression (BDI-I)	None or minimal depression (< 10)	84 (16)
	Mild depression (10 - 18)	65 (23)
	Moderate depression (19 - 29)	54 (23)
	Severe depression (≥ 30)	38 (23)
Levodopa Equivalent	Below median	79 (21)
Daily Dose	Above median	64 (23)
Completion by a proxy	No	76 (21)
	Yes	51 (31)

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2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.
A-MH: 1A-C, 2A-B, 3A; CMC: 1A-C, 2C, 3A-B; AR: 1A, 2A-C, 3B; GA: 3B; MZ, AKL: 1A, 2A, 2C, 3B; RK: 1A-B, 2A, 2C, 3B

CHAPTER 3

Determinants of patient-reported functional mobility in people with Parkinson's disease: A systematic review.

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ABSTRACT

BACKGROUND

Information on determinants of patient-reported functional mobility is lacking but would inform the planning of healthcare, resources and strategies to promote functional mobility in people with Parkinson's disease (PD).

RESEARCH QUESTION

To identify the determinants of patient-reported functional mobility of people with PD.

METHODS

Eligible: Randomized Controlled Trials, cohort, case-control, or cross-sectional analyses in people PD without date or setting restrictions, published in English, German, or French. Excluded: instruments with under 50% of items measuring mobility. On August 9th 2023 we last searched Medline, CINAHL and PsychInfo. We assessed risk of bias using the mixed-methods appraisal tool. Results were synthesized by tabulating the determinants by outcomes and study designs.

RESULTS

Eleven studies published 2012-2023 were included (most in Swedish outpatient settings). Samples ranged from 9-255 participants. Follow-up varied from 1.5-36 months with attrition of 15 to 42%. Heterogenic study designs complicated results synthesis. However, determinants related to environment seem to associate the strongest with patient-reported functional mobility, although determinants related to body structures and functions were most investigated. We identified disease duration, the ability to drive, caregiving, sex, age, cognitive impairment, postural instability and social participation as determinants of patient-reported functional mobility.

DISCUSSION

Methodological quality of the studies was limited. No study reported an a priori power calculation. Three studies controlled for confounders. The included studies lack representativeness of the population of people living with PD. Standardized sets of outcomes could enable more systematic research synthesis.

CONCLUSIONS

Future research should focus on activities, participation and environmental factors and improve methodological quality. OSF Open-Ended Registration on 25.01.2022, Registration DOI: 10.17605/OSF.IO/8UGB7

INTRODUCTION

Parkinson's disease (PD) is a highly complex neurodegenerative disorder, resulting in a wide variety of motor and non-motor symptoms, negatively impacting physical function and quality of life (Tosserams et al., 2020, Muslimovic et al., 2008, Global Parkinson's Disease Survey (GPDS) Steering Committee, 2002). In their narrative reviews, Tosserams et al. (2020), Bouca-Machado et al. (2018) illustrated that reduced functional mobility has important consequences for the participation of people with PD at home, at work, or within the community. Functional mobility is defined as moving independently and safely in different environments in order to accomplish functional activities or tasks and to participate in activities of daily living (ADL) at home, work and in the community (Bouca-Machado et al., 2018). To measure functional mobility in these different settings, a patient-reported measure (i.e., a report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else" (FDA, 2009)) is a practical, less costly and invasive measurement approach than the administration of objective, physical performance tests. Notably, such Patient-Reported Outcome Measures (PROMs) provide patients' perspectives and are often the outcomes of most importance to patients (Johnston et al., 2022). Moreover, patient-reported functional mobility takes into account subjective and underlying factors that might not be captured by objective measurements alone. Thus, it provides insight into functional mobility in daily life and acknowledges that each patient's experience of mobility is unique. Finally, understanding determinants associated with functional mobility from the perspective of people with PD enables healthcare providers to tailor interventions to the needs of people with PD by addressing the aspects that matter most to them. While recent longitudinal analyses by Lindh-Rengifo et al. (2021) indicated perceived balance while dual-tasking and global cognitive functioning could predict patient-reported functional mobility, comprehensive overviews of the determinants of patient-reported functional mobility are unfortunately lacking. Such analyses could help direct future research and lend insight into the determinants associated with functional mobility as experienced and reported by the people living with the disease. Consequently, our objective was to systematically review the literature to answer the following question: What are the determinants of patient-reported functional mobility of people with typical PD? We intentionally refrained from distinguishing a priori between exposures (determinants with a causal role for functional mobility) and factors co-occurring or associated with functional mobility to allow for a broad overview.

METHODS

The review was carried out according to the Joanna Briggs Institute reviewers' manual (Aromataris and Munn, 2020). In writing this review we adhered to the PRISMA 2020 reporting

guideline (Page et al., 2021). A completed PRISMA checklist is included as supplement 1. The review protocol is publicly available in the OSF-registry (https://osf.io/8ugb7) (Hanff et al., 2022b). A table in the supplement documents five deviations from the protocol.

Eligibility criteria

We included studies assessing determinants of patient-reported functional mobility in randomized controlled trials (RCTs), cohort, case-control, or analytical cross-sectional study designs in people with typical PD or Parkinson's disease dementia (PDD) without date, setting or culture restrictions, published in English, German, or French language. Studies with less than 50% of items measuring mobility as an activity or function, according to the ICF definitions, were excluded. In- and exclusion criteria are presented in Table 1. Further definitions and information regarding these criteria can be found in the protocol (Hanff et al., 2022b).

Information sources and search strategy and selection process

We developed literature search strategies using medical subject headings (MeSH) and text words related to functional mobility. The full search strategies for all databases can be found in the supplement. On 3rd of December 2021 we searched Medline (PubMed interface, 1946 onwards), CINAHL (EBSCO host interface, 1976 onwards), and PsycINFO (EBSCO host interface, 1894 onwards). We applied the Joanna Briggs Institute (JBI) three-step search strategy in consultation with an information specialist and Health Sciences Librarian with expertise in systematic review searching to locate etiology and risk data (Moola et al., 2020, Peters et al., 2020, Stephenson et al., 2020). We performed a manual backward citation search (using reference lists) and a forward citation search on 31st of May 2022 in the Web of Science database (Clarivate interface, 1900 onwards). We repeated the search on August 9th 2023 to ensure a current representation of the literature. We included papers regardless of the peer review practice of the journal. Title / abstract screening and full-text screening were independently performed by two reviewers. Any disagreements were solved by discussion and consensus. The software CADIMA (Kohl et al., 2018) and EndNote (version 9.3.3, Clarivate, UK) were used for the management and documentation of the results.

Data collection process and items

Data was collected by one reviewer according to an excel template of the standardized data extraction instrument provided by Moola et al. (2020), supplemented by the STROBE reporting guideline checklist. A second reviewer checked the completed data extraction forms. Regarding the outcome of patient-reported functional mobility, data of instruments were included if at least 50% of the items assessed the component of patient-reported mobility in the form of activity (e.g., an execution of a task or action by an individual). The protocol (Hanff et al., 2022b) provides definitions and examples of included items according

to the ICF (World Health Organisation, 2002). In addition, data was sought for relevant study details (i.e., sample size, study inclusion and exclusion criteria, years of follow-up, information related to missing data, recruitment procedures, statistical technique(s), study outcome and determinant measurements, as well as effect sizes, p-values, and confidence intervals). In case of missing information for this relevant study details reviewers contacted authors of primary sources or reviews for further information.

Study risk and reporting bias assessment

Due to the heterogeneity of study designs, we used the mixed-methods appraisal tool (MMAT) for risk of bias assessment (Hong et al., 2018) instead of the Joanna Briggs Institute critical appraisal tools (Moola et al., 2020) mentioned in our preregistration. Neither assessments of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies), nor of the strength of the body of evidence (e.g., Grading of Recommendations, Assessment, Development and Evaluations (GRADE)) were performed.

Effect measures and synthesis methods

In the absence of the authors reply, numbers were extracted using the WebPlotDigitizer (Rohatgi, 2021). To calculate Cohen's d and their 95% CIs with the meta-analysis effect size calculator (Wilson), we used the reported pre- and post-intervention mean values for Harrison et al. (2020), while for Leavy et al. (2020) we used the reported between-group differences of changes from baseline and standard deviation. Finally, from Olsson et al. (2020), we used the pre- / post-intervention mean values and standard error values. As confidence intervals were not reported for almost all studies reporting standardized regression coefficients (Lindh-Rengifo et al., 2021, Rantakokko et al., 2019, Ryder-Burbidge et al., 2022), the missing 95% CIs in the studies of Lindh-Rengifo et al. (2021) and Rantakokko et al. (2019) were calculated by the equation: $upper\ or\ lower\ CI * standardised\ beta\ /\ beta$, while for the study of Ryder-Burbidge et al. (2022) we applied the equation

$$\boldsymbol{standardised\ beta + or - (1.96 * standard\ error)}$$

No calculations for Dutra et al. (2022) were possible due to missing information. Due to obvious variation in outcomes, study designs and determinants, no heterogeneity and subgroup analyses were performed. However, we tabulated the determinants by outcomes and study designs to promote comparability.

Table 1 In- and exclusion criteria

	Components		Inclusion	Exclusion
Content	P	Population	People with typical PD or PDD	People with atypical PD or other diseases
	E	Exposure	Modifiable and non-modifiable determinants	-
	O	Outcome	**Patient-reported mobility measured as with at least 50% of the items as an activity** Activity is defined as "The execution of a task or action by an individual" (World Health Organisation, 2002): • Changing basic body position (D410) • Transferring oneself (D420) • Lifting and carrying objects (D430) • Walking (D450) • Going up and down stairs (D451) • Moving around in different locations (D460), using equipment (D465) using transportation (D470) • Driving (D475) **Instruments assessing mobility as an activity** • Life Space Assessment (LSA) • Walk-12G	**Mobility measured as body function** Function Is defined as "The physiological functions of body systems (including psychological functions)" (World Health Organisation, 2002): • Clinically based tests, physiological tests • Performance measure • Gait quantification methods (Bloem et al., 2016) **No patient-reported instruments** • Clinician or caregiver reported instruments, observations **Instruments measuring following activities** • Maintaining body position (D415) • Moving objects with lower extremities (D435) • Hand and arm use (D445) • Fine hand use (D430), fine foot use (D446) • Moving around by means other than walking (D455) • Riding animals for transportation (D480)
Form	**Types of evidence sources**		**Studies assessing the statistical association of one or several factors with the defined outcome** • Randomized controlled trials • Prospective and retrospective cohort studies • Case-control studies • Analytical cross-sectional studies	• Commentaries • Conference abstracts • Descriptive study designs (case reports, case series) • Editorials, letters • Study protocols • Instrument validation studies
	Publication		No restrictions	No restrictions
	Timeframe		No restrictions	No restrictions
	Language		English, German, French	Other languages
	Setting		No restrictions	No restrictions
	Culture		No restrictions	No restrictions

Note Codes, e.g., D410, according to the ICF-classification included

RESULTS

Study selection

After searching three databases, a total of 2390 records were identified, with one additional article identified through forward citation searching. After removing 510 duplicates and examining 1881 titles and abstracts, 181 potentially relevant articles were retained. We assessed the full text of 181 articles and 10 were finally included in the systematic review (Daneault et al., 2014, Harrison et al., 2020, Leavy et al., 2020, Leavy et al., 2018, Lindh-Rengifo et al., 2021, Nilsson et al., 2012, Olsson et al., 2020, Rantakokko et al., 2019, Ryder-Burbidge et al., 2022, Zajac et al., 2021). While most articles (165 / 171) did not examine patient-reported outcome measures (PROMs) and/or less than 50% of their items assessed mobility, some articles (13 / 171) were excluded due to multiple reasons. Finally, data for only two outcome measures fulfilling the in- and exclusion criteria were included: Walk-12G (Bladh et al., 2012) and the UAB Life-Space Assessment (Kammerlind et al., 2014, Baker et al., 2003). While the higher the Walk-12G, the worse the functional mobility, the opposite is true for the UAB Life-Space Assessment. The repeated literature search in August 2023 identified one additional study published since December 1st 2021 (Dutra et al., 2022). The PRISMA flowchart in Figure 1 illustrates the process of source selection and the reasons for exclusion. We excluded the cross-sectional study by Kader et al. (2017) as they analyzed the baseline data of the longitudinal study by Lindh-Rengifo et al. (2021).

Study characteristics

Tables 2, 3 and 4 provide an overview of the included studies and their characteristics. Details of the excluded full text sources as well as their exclusion criteria can be found on the project page (https://osf.io/jcqzr/).

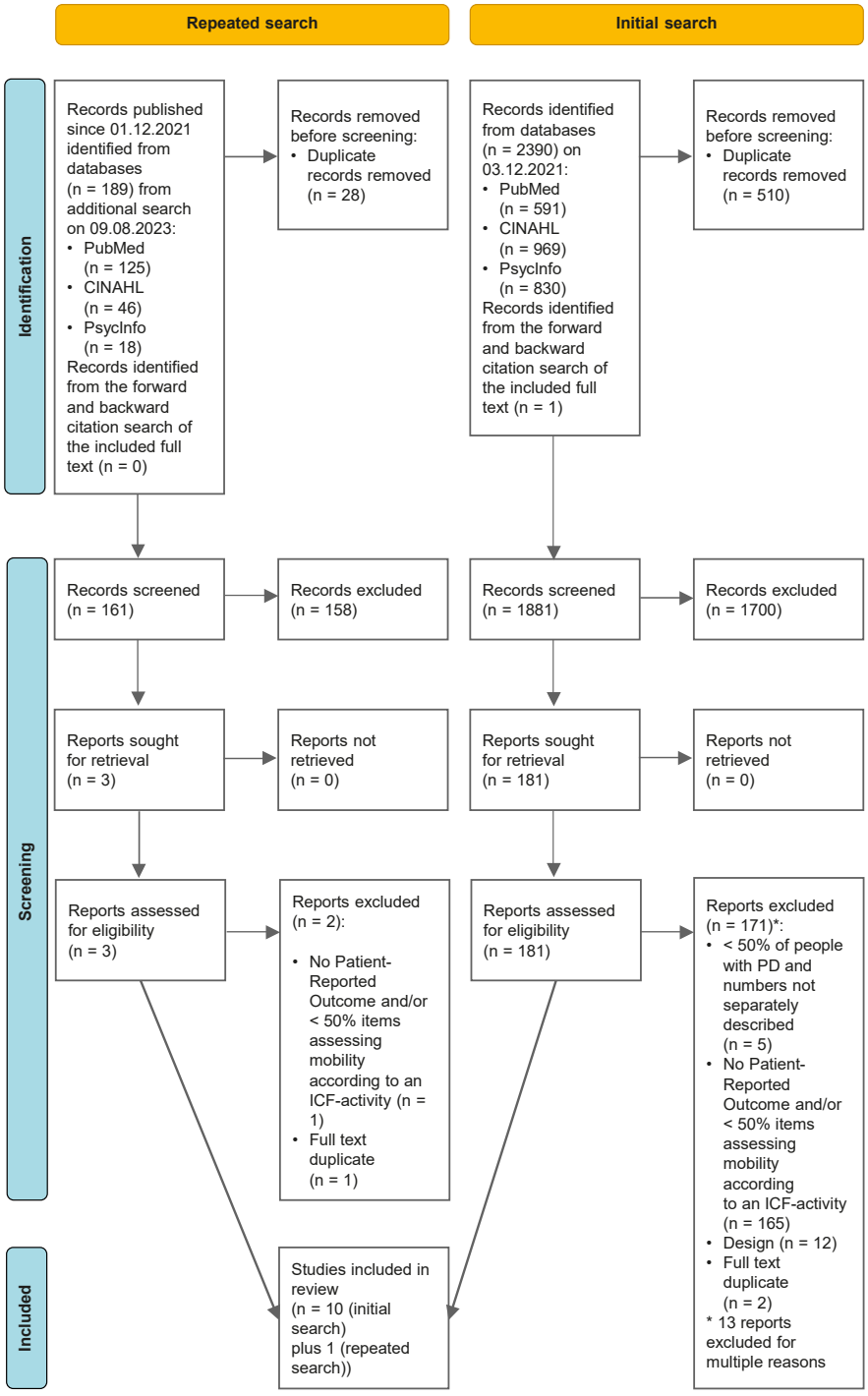

Figure 1 PRISMA Flowchart

Table 2 Study characteristics – Cohort study

Citation (Year)	**Objectives**	**Country Setting**	**Baseline sample size** N **Female** n (%)	**Follow-up sample size** n (%)	**Follow-up** (months) **Attrition** n (%)	**Age** mean (SD)	**Disease Stage (H&Y)** median (q1 - q4)	**Years since diagnosis** median (q1 - q4)	**(MDS) UPDRS III** median (q1 - q4)	**Cognition** mean (SD)	**Functional mobility** mean (SD)	**Functional mobility as primary outcome**	**Functional mobility** mean (SD)	**Determinants included in the study**
Lindh-Rengifo et al. (2021)	To investigate how perceived walking difficulties evolve over a 3-year period in people with PD To identify predictive factors of perceived walking difficulties.	Sweden Outpatient	255 49 (19%)	148 (58%)	36 107 (42%)	67.9 (8.92)	2 (2-3)	8 (5-11)	UPDRS: 28 (NR)	MoCA: 25.7 (3.1)	Walk-12G 14.8 (10.8)	✔	Walk-12G 14.8 (10.8)	Body structures and functions: Perceived balance problem while dual tasking, Global Cognition (MoCA), Pain, Postural instability, Fatigue (NHP Energy), Worse lower extremity function, Personal: Age, Activities and participation: Walk-12G Baseline

Abbreviations NR = Not reported; Hoehn and Yahr (H&Y) range: 0 - 5, higher = worse; Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) range: 0 - 132, higher = worse; Unified Parkinson's Disease Rating Scale part III (UPDRS III) range: 0 - 108, higher = worse; Montreal Cognitive Assessment (MoCA) range: 0 - 30, higher = better; Mini Mental State Examination (MMSE) range: 0 - 30, higher = better; Walk-12G range: 0 - 42, higher = worse; University of Alabama at Birmingham Life Space Assessment (UAB LSA) range: 0 - 120, higher = better

Table 3 Study characteristics – Controlled trial and pre-post study design

Citation (Year)	**Objectives**	**Country Setting**	**Baseline sample size** N **Female** n (%)	**Follow-up sample size** n/N (%)	**Follow-up** (months) **Attrition** n/N (%)	**Age** mean (SD)	**Disease stage (H&Y)** n (%) per stage	**Years since diagnosis** mean (SD)	**(MDS) UPDRS III** mean (SD)	**Cognition** Median (Range)	**Functional mobility** mean (SD)	**Functional mobility as primary outcome**	**Determinants included in the study**
Controlled trial study design													
Leavy et al. (2020)	To assess the clinical effectiveness of the adapted HiBalance program on balance control and gait among people with PD.	Sweden Reha-bilitation	117 I: 33/61 (54%) C: 22/56 (39%)	99 (85%)	10 19 (16%)	I: 70 (8.5) C: 70 (6.5)	I: H&Y 2: 28/61 (46%) I: H&Y 3: 33/61 (54%) C: H&Y 2: 20/56 (36%) C: H&Y 3: 36/56 (64%)	I: 6.6 (5.1) C: 8.0 (5.8)	NRt	NA	Walk-12G: I: 15.5 (7.5) C: 12 (7.3)	✕	Activities and participation: HiBalance program Body structures and functions: TMT-B
Pre-post study design													
Daneault et al. (2014)	To assess the impact of STN DBS on life-space mobility and Quality of Life	Canada Hospital	20 7 (35%)	20 (100%)	NA 0 (0%)	57.2 (7.7)	NR	11.3 (3.7)	UPDRS: 18.5 (11)	NR	UAB LSA: NR	✔	Environment: Subthalamic Stimulation
Harrison et al. (2020)	To determine the effectiveness of a targeted dance intervention to improve walking speed for people with PD by increasing motor motivation.	USA Out-patient	10[a] 3 (30%)	11/14 (79%)	1.5 3/14 (21%)	69 (8)	H&Y 2: 6 (60%) H&Y 2.5: 3 (30%) H&Y 3: 1 (10%)	6 (3)	MDS-UPDRS: 29 (12)	MMSE: 28 (26 - 29)	UAB LSA: 68 (35)	✕	Activities and participation: Contemporary dance
Olsson et al. (2020)	To investigate feasibility and effect of table tennis training on balance control and physical function in people with PD.	Sweden Out-patient	9 4 (44%)	8 (89%)	2.5 2 (22%)	66.9 (5.5)	H&Y 2: 8 (89%) H&Y 2.5: 1 (11%)	8.6 (4.9)	UPDRS: 23 (11)	NR	Walk-12G: 10.9 (2.3)	✕	Activities and participation: Table Tennis

Note NR = Not reported, NA = Not applicable, I = Intervention, C = Control, Hoehn and Yahr (H&Y) range: 0 - 5, higher = worse; Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) range: 0 - 132, higher = worse; Unified Parkinson's Disease Rating Scale part III (UPDRS III) range: 0 - 108, higher = worse; Montreal Cognitive Assessment (MoCA) range: 0 - 30, higher = better; Mini Mental State Examination (MMSE) range: 0 - 30, higher = better; Walk-12G range: 0 - 42, higher = worse; University of Alabama at Birmingham Life Space Assessment (UAB LSA) range: 0 - 120, higher = better; [a] = participants included in final analyses

Table 4 Study characteristics – Cross-sectional study design

Citation (Year)	**Objectives**	**Country Setting**	**Sample size** N **Female** n (%)	**Age** mean (SD)	**Disease Stage (H&Y)** n (%) per stage	**Years since diagnosis** mean (SD) or median (q1 - q4)	**(MDS) UPDRS III** mean (SD)	**Cognition** mean (SD) or median (q1 - q4)	**Functional mobility (FM)** mean (SD) or median (q1 - q4)	**Functional mobility as primary outcome**	**Determinants included in the study**
Leavy et al. (2018)	To investigate the relationship between patient-reported walking difficulties (Walk- 12G) and performance-based walking in laboratory and free-living conditions.	Sweden Outpatient	49 28 (57%)	75 (5.9)	HY 2: 22 (45%) HY 3: 27 (55%)	6 (3-9)	UPDRS: 40 (10.9)	MMSE: 28 (27-29)	Walk-12G: 12 (7-20)	✕	Activities and participation: Habitual walking - Steps per day in free-living conditions
Nilsson et al. (2012)	To explore the potential contributions of motor, non-motor, and demographic factors, as well as complications of drug therapy, on fear of falling among people with PD.	Sweden Hospital	154 62 (40%)	70 (9.1)	NR	6 (5.4)	NR	NR	Walk-12G: 13 (6-23)	✕	Body structures and functions: Fear of falling (FES)
Rantakokko et al. (2019)	To describe life-space mobility and explore associations of motor and non-motor symptoms with life-space mobility in people with people with PD.	Sweden Outpatient	164 58 (35%)	71.6 (8.9)	H&Y 1: 10 (6%) H&Y 2: 69 (42%) H&Y 3: 37 (23%) H&Y 4: 39 (24%) H&Y 5: 10 (7%)	NR	UPDRS: 31.4 (16.7)	MoCA: 25.1 (4.0)	UAB LSA: 72.3 (28.8)	✔	Activities and participation: Walk-12G, Timed Up and Go Body structures and functions: UPDRS III, Freezing of Gait (FOGQ), Depression (GDS-15), Pain, Fatigue (NHP Energy), Global cognition (MoCA)

Table 4 Continued.

Citation (Year)	**Objectives**	**Country Setting**	**Sample size** N **Female** n (%)	**Age** mean (SD)	**Disease Stage (H&Y)** n (%) per stage	**Years since diagnosis** mean (SD) or median (q1 - q4)	**(MDS) UPDRS III** mean (SD)	**Cognition** mean (SD) or median (q1 - q4)	**Functional mobility (FM)** mean (SD) or median (q1 - q4)	**Functional mobility as primary outcome**	**Determinants included in the study**
Ryder-Burbidge et al. (2022)	To explore individual, social and environmental factors that impact life-space mobility in PD.	Canada Outpatient	113 45 (40%)	71.2 (9.0)	NR	NR	NR	NR	UAB LSA: 64.2 (25.8)	✔	Personal: Age, Sex Environmental: No driver's license, Receiving caregiving, No extra money in the house, Activities and participation: Social participation index Health Conditions: Respiratory condition
Zajac et al. (2021)	To determine the extent to which walking activity might contribute to total life-space mobility.	NR	69 29 (42%)	67.5 (8.7)	H&Y 2: 27 (39%) H&Y 2.5: 30 (43%) H&Y 3: 12 (17%)	NR	NR	NA	UAB LSA: Mean: 92 IQR: 42.25	✔	Activities and participation: Daily walking activity (StepWatch 4 Activity Monitor)
Dutra et al. (2022)	To explore the relationship between life space mobility, self-efficacy, and balance.	Brasil Hospital	88 40 (45.5%)	63.2 (10.5)	H&Y 1: 15 (17.0%) H&Y 2: 42 (47.7%) H&Y 3: 21 (23.9%) H&Y 4: 10 (11.9%)	9.0 (6.0)	MDS-UPDRS: 85.1 (31.2%)	MoCA: 26.0 (23.0-35.0)	UAB LSA: 65.2 (22.8)	✔	Personal: Age, Sex Body structures and functions: MDS-UPDRS, Global cognition (MoCA), Depression (BDI-II) Health Conditions: Disease duration, Motor subtypes

Note NR = Not reported, NA = Not applicable, Hoehn and Yahr (H&Y) range: 0 - 5, higher = worse; Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) range: 0 - 132, higher = worse; Unified Parkinson's Disease Rating Scale part III (UPDRS III) range: 0 - 108, higher = worse; Montreal Cognitive Assessment (MoCA) range: 0 - 30, higher = better; Mini Mental State Examination (MMSE) range: 0 - 30, higher = better; Walk-12G range: 0 - 42, higher = worse; University of Alabama at Birmingham Life Space Assessment (UAB LSA) range: 0 - 120, higher = better

Study design, outcomes, and determinants assessment

A total of eleven studies, including one controlled trial (Leavy et al., 2020), three pre-post studies (Olsson et al., 2020, Harrison et al., 2020, Daneault et al., 2014), one prospective cohort study (Lindh-Rengifo et al., 2021) and five cross-sectional studies (Zajac et al., 2021, Rantakokko et al., 2019, Nilsson et al., 2012, Leavy et al., 2018, Ryder-Burbidge et al., 2022, Dutra et al., 2022) published between 2012 and 2022, were included in this review. Most (6/11) were conducted in Sweden (Lindh-Rengifo et al., 2021, Leavy et al., 2020, Rantakokko et al., 2019, Olsson et al., 2020, Nilsson et al., 2012, Leavy et al., 2018) and / or in the outpatient (6/11) (Ryder-Burbidge et al., 2022, Rantakokko et al., 2019, Leavy et al., 2018, Olsson et al., 2020, Harrison et al., 2020, Lindh-Rengifo et al., 2021) setting. Sample size ranged from 9 (Olsson et al., 2020) to 255 people with PD (Lindh-Rengifo et al., 2021). The follow-up of participants of longitudinal and pre-post-study designs varied between 1.5 (Harrison et al., 2020) and 36 months (Lindh-Rengifo et al., 2021) with an attrition rate of minimum 15% (Leavy et al., 2020) and maximum 42% in the study with the longest follow-up (Lindh-Rengifo et al., 2021). The detailed risk of bias assessment can be found in the supplement 4.

Most studies using the Walk-12G (Kammerlind et al., 2014, Bladh et al., 2012) to measure patient-reported functional mobility were from Sweden (Lindh-Rengifo et al., 2021, Leavy et al., 2020, Olsson et al., 2020, Nilsson et al., 2012, Leavy et al., 2018). Compared to the definition of functional mobility by Bouca-Machado et al. (2018), the Walk-12G (Bladh et al., 2012) assesses the mobility and functionality and the UAB LSA (Baker et al., 2003) additionally measures the environment. Neither of the two instruments assess the other components of functional mobility (i.e., move safely in order to participate in ADL at home, work and in the community). The Walk-12G mean values ranged from 11 (Olsson et al., 2020) to 15 (Lindh-Rengifo et al., 2021) while the UAB LSA mean values ranged from 64 (Ryder-Burbidge et al., 2022) to 92 (Zajac et al., 2021). Table 5 illustrates potential determinants of patient-reported functional mobility investigated by the included studies. According to the frequency, less attention has been paid to health conditions, activities and participation as environmental and personal factors, while determinants related to body structures and functions have received most attention.

Table 5 Overview of investigated potential determinants of patient-reported functional mobility

ICF categories (World Health Organisation, 2001)	**Investigated determinant**	**Sources**
Health condition		
	Respiratory condition	Ryder-Burbidge et al. (2022)
	Disease duration	Dutra et al. (2022)
	Motor subtype	Dutra et al. (2022)
Body functions and structures		
Body functions are the physiological functions of body systems (including psychological functions). **Body structures** are anatomical parts of the body such as organs, limbs and their components.	MDS-UPDRS	Dutra et al. (2022)
	Motor symptoms	
	Clinician-assessed motor symptoms (MDS-UPDRS III)	Rantakokko et al. (2019)
	Freezing of Gait	Rantakokko et al. (2019)
	Perceived balance problem while dual tasking	Lindh-Rengifo et al. (2021)
	Postural instability	Lindh-Rengifo et al. (2021)
	Worse lower extremity function	Lindh-Rengifo et al. (2021)
	Non-motor symptoms	
	Depression	Rantakokko et al. (2019), Dutra et al. (2022)
	Fatigue	Rantakokko et al. (2019), Lindh-Rengifo et al. (2021)
	Fear of falling	Nilsson et al. (2012)
	Global cognitive cognition	Rantakokko et al. (2019), Lindh-Rengifo et al. (2021), Dutra et al. (2022)
	Pain	Rantakokko et al. (2019), Lindh-Rengifo et al. (2021)
	TMT-B	Leavy et al. (2020)
Activities and participation		
Activity is the execution of a task or action by an individual. **Participation** is involvement in a life situation	Contemporary dance	Harrison et al. (2020)
	HiBalance program	Leavy et al. (2020)
	Social participation	Ryder-Burbidge et al. (2022)
	Steps per day in free-living conditions	Leavy et al. (2018), Zajac et al. (2021)
	Table tennis	Olsson et al. (2020)
	Timed up and Go	Rantakokko et al. (2019)
Environmental factors		
Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives.	No driver's license	Ryder-Burbidge et al. (2022)
	No extra money in the house	Ryder-Burbidge et al. (2022)
	Receiving caregiving	Ryder-Burbidge et al. (2022)
	Subthalamic stimulation	Daneault et al. (2014)

Table 5 Continued.

ICF categories (World Health Organisation, 2001)	Investigated determinant	Sources
Personal factors		
Personal factors are the particular background of an individual's life and living, and comprise features of the individual that are not part of a health condition or health states. These factors may include gender, race, age, other health conditions, fitness, lifestyle, habits, upbringing, coping styles, social background, education, profession, past and current experience (past life events and concurrent events), overall behavior pattern and character style, individual psychological assets and other characteristics, all or any of which may play a role in disability at any level.	Age	Lindh-Rengifo et al. (2021), Ryder-Burbidge
	Sex	Ryder-Burbidge et al. (2022), Dutra et al. (2022)

Characteristics of study participants

Mean age of the participants was between 57.2 (Daneault et al., 2014) and 75.0 years (Leavy et al., 2018) with a minimum of 30% (Harrison et al., 2020) and a maximum of 51% (Leavy et al., 2018) female participants. While the Hoehn and Yahr (H&Y) disease stage was not reported in 3/11 studies (Nilsson et al., 2012, Daneault et al., 2014, Ryder-Burbidge et al., 2022), most of the participants in the remaining studies were in a H&Y stage II (i.e., without impaired balance). As the original and the modified H&Y scale were both applied, between study comparison was limited to four determinants. The studies of Harrison et al. (2020) and Nilsson et al. (2012) had the patients with the lowest disease duration (mean of six years) while the participants of Daneault et al. (2014) had the highest disease duration (eleven years). Although the MDS-UPDRS is the gold standard clinical research assessment tool for PD motor impairment, four out of eleven studies did not report the (MDS) UPDRS (Leavy et al., 2020, Nilsson et al., 2012, Ryder-Burbidge et al., 2022, Zajac et al., 2021). Similarly, only three of the eleven included studies (Rantakokko et al., 2019, Dutra et al., 2022, Lindh-Rengifo et al., 2021) applied the MoCA, a scale recommended by the Movement Disorders Society to assess cognition in people with PD (Skorvanek et al., 2018), while two (Harrison et al., 2020, Leavy et al., 2018) applied the Mini Mental State Examination (MMSE) (Horton and Alana, 1990). While most studies reported mean cognition scores below the cut-off score (Hoops et al., 2009) for presence of mild cognitive impairment in people with PD (Rantakokko et al., 2019, Lindh-Rengifo et al., 2021, Harrison et al., 2020, Leavy et al., 2018), this was not the case for one study (Dutra et al., 2022). The remaining six studies did not perform any cognitive assessment to detect mild cognitive impairment (Daneault et al., 2014, Leavy et al., 2020, Nilsson et al., 2012, Olsson et al., 2020, Ryder-Burbidge et al., 2022, Zajac et al., 2021).

Results of individual studies

Tables 6, 7 and 8 present summary statistics, effect estimates and their precision for controlled trials and pre-post study designs, as well as for cross-sectional and prospective cohort study designs. While most determinants were addressed only by single studies (Rantakokko et al., 2019, Leavy et al., 2020, Nilsson et al., 2012, Ryder-Burbidge et al., 2022, Leavy et al., 2018, Zajac et al., 2021, Lindh-Rengifo et al., 2021), Table 9 synthesizes the association with patient-reported functional mobility of the six determinants included in more than one study. In these studies, higher age was significantly associated with worse patient-reported functional mobility. Results for global cognition and depression were not so conclusive, as negative and positive associations were found by previous research, while results were less heterogenic for pain. Results of studies assessing fatigue tend to show that fatigue is associated with worse patient-reported functional mobility. One study reported significant association of male sex with a worse outcome. Finally, by examining the standardized regression coefficients in the three studies using multiple regression (Rantakokko et al., 2019, Ryder-Burbidge et al., 2022, Lindh-Rengifo et al., 2021) from high to low effect size in comparison with the ICF-categories (Table 7 and 8), it seems that environmental factors, i.e., having a driver's license, had a stronger association (β from 0.22 to 0.40) with patient-reported functional mobility than body structures and function (β from 0.02 to 0.18). Unfortunately, only one study (Ryder-Burbidge et al., 2022) assessed environmental factors.

Table 6 Summary of the methods and results of the included controlled trials and pre-post study designs

Citation (Year)	**Examined intervention**	**Functional mobility** mean (SD)	**Statistical analysis**	**Effect measure**	**Effect size** (Confidence interval (95%)	**p-value**	**Sample size**	**Power calculation reported**
UAB LSA								
Daneault et al. (2014)	Subthalamic Stimulation	Pre-Post change: 9.8	Paired t-tests	d	NR	> 0.05	20	✕
Harrison et al. (2020)	Contemporary dance	Pre-Post change: 3	Paired t-tests	d	0.09 (-0.9269, 0.7454)	0.66	11	✕
Walk-12G								
Leavy et al. (2020)	HiBalance program	C: Change : 1.72 (8.38) I: Change : 2.75 (6.78)	ANOVA	d	0.112 (-0.251, 0.475)	0.887	99	✕
Olsson et al. (2020)	Table tennis	Pre-Post change: -2.6	Wilcoxon rank-sum test	d	0.373 (-0.684, 1.430)	0.462	8	✕

Abbreviations NR = Not reported, I = Intervention, C = Control

Table 7 Summary of the methods and results of the included prospective cohorts and cross-sectional study designs – Outcome: Walk-12G

Citation (Year)	ICF-category	Examined determinants	Instruments	Patient Reported Determinant	Discrete determinant	Statistical analysis	Effect	Effect size (Confidence interval (95%))	p-value	Sample size	Power calculation reported
Nilsson et al. (2012)	S&F	Fear of falling[2]	FES	✔	✔	Spearman's rank correlation	ρ	0.82 (NA)	<0.001	154	✕
Leavy et al. (2018)	A&P	Objective daily habitual walking - Steps per day in free-living conditions[1]	Actigraph GT3X+ accelerometer	✕ Gait quantification methods	✔	Spearman's rank correlation	ρ	0.46 (NA)	0.001	49	✕
Leavy et al. (2020)	S&F	Cognitive flexibility in shifting attention between 2 competing tasks[2]	TMT-B	✕ Performance test	✔	Multiple Regression	NR	NR	NR	99	✕
Lindh-Rengifo et al. (2021)[a]	S&F	Perceived balance problem while dual tasking	One question	✔	✕	Multiple Regression	β	0.18 (0.063, 0.297)	0.003	148	✕
	P	Age	Years	✕ Interview	✔			0.172 (0.066, 0.277)	0.002		
	S&F	Cognition[1]	MoCA	✕ Performance test	✔			-0.107 (-0.209, -0.004)	0.041		
	S&F	Fatigue	1 of 3 questions of the NHP Energy subscale	✔	✔[d]			0.101 (-0.011, 0.213)	0.076		
	S&F	Pain	One question	✕ Interview	✕			0.100 (-0.003, 0.204)	0.058		
	S&F	Postural instability	One item	✕ Clinician assessed	✕			0.091 (-0.007, 0.189)	0.070		
	S&F	Objective worse lower extremity function[2]	Five chair stands test ≥16.0 s	✕ Observation	✔[d]			-0.088 (-0.192, 0.017)	0.099		

Abbreviations A&P = Activities and Participation, E = Environmental, HC = Health Conditions, P = Personal, S&F = Body structures and functions, B = regression coefficient, β = standardized regression coefficient, [a]95% Stand. CI = upper or lower CI x standard. beta / beta, NA = Not applicable, NR = Not reported, [d] = dichotomized, [1]: Higher = Better, [2]: Higher = worse

Table 8 Summary and results of the included prospective cohorts and cross-sectional study designs – Outcome: UAB LSA

First author and citation (Year)	ICF-category	Examined determinants	Instruments	Patient Reported Determinant	Discrete determinant	Statistical analysis	Effect	Effect size (Confidence interval (95%)	p-value	Sample size	Power calculation reported
Rantakokko et al. (2019)[a]	A&P	Patient-reported walking difficulties	Walk-12G[2]	✔	✔	Multiple Regression	β	-0.19 (-0.582, 0.202)	0.036	122	✔
	S&F	Pain	"Are you bothered by pain?"	✖ Interview	✖			-0.13 (-6.951, 6.691)	0.054		
	A&P	Objective functional mobility	TUG[2]	✖ Observation	✔			-0.12 (-0.375, 0.135)	0.139		
	S&F	Depression	GDS-15[2]	✖ Interview	✔			-0.10 (-1.256, 1.056)	0.161		
	S&F	Motor symptoms	MDS-UPDRS III[2]	✖ Clinician assessed	✔			0.08 -0.292, 0.452	0.409		
	S&F	Cognition	MoCA[1]	✖ Performance test	✔			-0.06 (-1.020, 0.900)	0.45		
	S&F	Fatigue	1 of 3 questions of the NHP Energy subscale	✔	✔ [d]			-0.04 (-7.468, 7.388)	0.631		
	S&F	Freezing of Gait	FOGQsa item 3. Score ≥1 = yes	✔	✔ [d]			0.02 (-6.644, 6.684)	0.784		

Table 8 Continued.

First author and citation (Year)	ICF-category	Examined determinants	Instruments	Patient Reported Determinant	Discrete determinant	Statistical analysis	Effect	Effect size (Confidence interval (95%)	p-value	Sample size	Power calculation reported
Ryder-Burbidge et al. (2022)[b]	E	No driver's license	NR	✕ Interview	✕	Multiple Regression	β	-0.40 (-0.547, -0.071)	≤0.05	113	NR
	A&P	Social participation	Social participation index[1]	✔	✔			0.36 (0.225, 0.495)	≤0.05		
	E	Receiving caregiving	NR	✕ Interview	✕			-0.24 (-0.372, -0.102)	≤0.05		
	E	No extra money in the house	NR	NR	✕			-0.22 (-0.358, -0.084)	≤0.05		
	P	Sex	NR	NR	✕			-0.17 (-0.479, 0.134)	≤0.05		
	P	Age	Years	NR	✕			-0.10 (-0.180, -0.020)	≤0.05		
	HC	Respiratory condition	NR	✔	✕			NR	NR		
Zajac et al. (2021)	A&P	Objective daily walking activity	StepWatch 4 Activity Monitor	✕ Gait quantification methods	✔	Simple regression	B	0.002 (0.000, 0.003)	0.07	69	NR

Table 8 Continued.

First author and citation (Year)	ICF-category	Examined determinants	Instruments	Patient Reported Determinant	Discrete determinant	Statistical analysis	Effect	Effect size (Confidence interval (95%)	p-value	Sample size	Power calculation reported
Dutra et al. (2022)	S & F	Balance confidence	ABC Scale1	✔	✔ d	Pearson's or Spearman's rank correlation	r / ρ	0.51 (NR)	NR	88	✔
	S & F	Balance	Mini-BESTest1	✖ Performance test	✔ d	Pearson's correlation	r	0.42 (NR)	NR		
	P	Age	Years	✖ Interview	✖	Pearson's or Spearman's rank correlation	r / ρ	-0.27 (NR)	NR		
	S & F	Cognition	MoCA2	✖ Performance test	✔ d	Pearson's or Spearman's rank correlation	r / ρ	0.29 (NR)	NR		
	S & F	Motor- and non-motor symptoms	MDS-UPDRS2	✖ Clinician assessed	✔ d	Pearson's or Spearman's rank correlation	r / ρ	0.28 (NR)	NR		
	S & F	Depression	BDI-II2	✔	✔ d	Pearson's or Spearman's rank correlation	r / ρ	0.34 (NR)	NR		
	HC	Disease duration	NR	✖ Interview	✖	Pearson's or Spearman's rank correlation	r / ρ	0.02 (NR)	NR		
	P	Male sex	NR	✖ Interview	✖	Chi-square test	x2	NR	0.51		
	HC	Motor subtype	NR	✖ Interview	✖	Chi-square test	x2	7.54 (NR)	0.006		

Abbreviations NA = Not applicable, NR = Not reported, A&P = Activities and Participation, E = Environmental, HC = Health Conditions, P = Personal, S&F = Body structures and functions, ABC scale = Activities-Specific Balance Confidence Scale, B = regression coefficient, β = standardized regression coefficient, [a]95% Stand. CI = upper or lower CI x standard. beta / beta, [b] Stand. Beta = beta +/- (1.96*standard error), [d] = dichotomized, ρ= Spearman's rho, x^2 = Chi-square, [1]: Higher = Better, [2]: Higher = worse

Table 9 Associations between various types of factors and functional mobility

Determinant	Interpretation	Author	β	CI	p-value
Age	NA	Lindh-Rengifo et al. (2021) [2]	0.172	0.066, 0.277	0.002
	NA	Dutra et al. (2022)[1]	-0.27	NR	NR
	NA	Ryder-Burbidge et al. (2022) [1]	-0.1	-0.180, -0,020	<0.05
Cognition	MoCA[2]	Lindh-Rengifo et al. (2021) [2]	-0.107	-0.209, -0.004	0.041
	MoCA[2]	Dutra et al. (2022)[1]	0.29	NR	NR
	MoCA[2]	Rantakokko et al. (2019) [1]	-0.06	-1.020, 0.900	0.45
Depression	GDS-15[2]	Rantakokko et al. (2019) [1]	-0.10	-1.256, 1.056	0.161
	BDI-II[2]	Dutra et al. (2022)[1]	0.340	NR	0.009
Fatigue	Fatigue = Yes	Lindh-Rengifo et al. (2021) [2]	0.101	-0.011, 0.213	0.076
	Fatigue = Yes	Rantakokko et al. (2019) [1]	-0.04	-7.468, 7.388	0.631
Pain	Pain = Yes	Lindh-Rengifo et al. (2021) [2]	0.1	-0.003, 0.204	0.058
	Pain = Yes	Rantakokko et al. (2019) [1]	-0.13	-6.951, 6.691	0.054
Sex	Male sex	Ryder-Burbidge et al. (2022)[1]	-0.17	-0.479, 0.134	≤0.05
	Male sex	Dutra et al. (2022)[1]	NR	NR	0.510

Abbreviations [1]: Higher = Better, [2]: Higher = worse

DISCUSSION

We systematically reviewed the literature assessing determinants of functional mobility in community-dwelling people with PD to answer the question: What are the determinants of patient-reported functional mobility of people with typical PD? Although we need to interpret these findings with caution due to the heterogeneity and the small number of studies, determinants related to environment seem to have the strongest association with patient-reported functional mobility, while determinants related to body structures and functions were most frequently investigated.

Across studies we noted a large heterogeneity of used methods and reported results. Three studies applied multiple regression and reported standardized regression coefficients (Lindh-Rengifo et al., 2021, Rantakokko et al., 2019, Ryder-Burbidge et al., 2022). Rantakokko et al. (2019), Ryder-Burbidge et al. (2022), Dutra et al. (2022) assessed the same primary outcome: the University of Alabama Birmingham Life-Space Assessment (UAB LSA). Most studies did not find statistical support for an association. However, environmental factors, i.e., having a driving license might have a stronger association with patient-reported functional mobility than the frequently studied body structures and function. These findings are in line with the previous results by Tosserams et al. (2020), Bouca-Machado et al. (2018), stating we need to pay more attention to the assessment of environmental and personal factors. Moreover, our results strengthen their hypothesis that the environmental factors (ability to drive (Ryder-Burbidge et al., 2022), caregiving (Ryder-Burbidge et al., 2022)), the personal factors (sex (Ryder-Burbidge et al., 2022), age (Ryder-Burbidge et al., 2022, Lindh-Rengifo

et al., 2021)), the body function (cognitive impairment (Lindh-Rengifo et al., 2021), postural instability (Lindh-Rengifo et al., 2021)), and "social participation" (Ryder-Burbidge et al., 2022) are determinants of patient-reported functional mobility. Furthermore, according to the recent review of Ramos et al. (2020), architecture and design (e.g., housing adaptations/ accessibility/usability, floor surface/lights/signaled pedestrian crossings or reaching/ space between objects) are associated with functional mobility. However, the included studies of that review applied qualitative study designs (Pretzer-Aboff et al., 2009, Lamont et al., 2012) or did not assess patient-reported functional mobility (Slaug et al., 2013). In comparison, while Ryder-Burbidge et al. (2022) investigated the role of social participation and environmental determinants (e.g., having a driver's license, money, or caregiving) none of the included studies assessed environmental factors like architecture and design. In summary, determinants related to environment seem to have the strongest association with patient-reported functional mobility however based on few studies, while determinants related to body structures and functions were most frequently investigated.

The reporting of those results was not always complete. Namely, eleven risk of bias elements could not be answered due to missing information. While reporting guidelines were available (Vandenbroucke et al., 2007) and are recommended by the International Committee of Medical Journal Editors (2010), the more recent studies did not have a higher reporting quality than the older studies. Moreover, the methodological quality of the included studies was limited. For instance, most of the determinants were assessed by single items instead of validated questionnaires. Half of the studies had patient-reported functional mobility as the primary outcome, while this was not the case for Leavy et al. (2020), Nilsson et al. (2012), Daneault et al. (2014), Harrison et al. (2020), Olsson et al. (2020). No study reported an a priori power calculation (for one, a sample size calculation was mentioned but not with sufficient detail to determine when it was conducted (Dutra et al., 2022)) and only one study reported a post-data collection sensitivity power analysis (Rantakokko et al., 2019). Rantakokko et al. (2019), Lindh-Rengifo et al. (2021), Ryder-Burbidge et al. (2022) were the only studies reporting controlling of confounders. Despite Leavy et al. (2020) not providing effect sizes and confidence intervals, we did not exclude the study from our review. The included studies lack representativeness of the population of people living with PD as either interventional and pre-post studies selected participants based on a defined set of rather narrow inclusion or exclusion criteria. Further, possibly biased study enrolment was not tested in the observational studies, which did not report reasons why certain eligible individuals chose not to participate. The present review process had some minor limitations. For instance, we did no grey literature search and did not include clinical trial registries for ongoing studies. Additionally, we performed no assessments of meta-bias(es) or the strength of the body evidence. Finally, due to the limited geographical distribution of the studies, our findings may not be representative of a broader global population.

Despite the limited evidence, our work shows that determinants related to participation and environment seem to have the strongest association with functional mobility, while determinants related to body structures and functions were most frequently investigated. Consequently, we recommend future research focuses less on body structures and functions and more on participation and environmental factors. Future research projects investigating patient-reported functional mobility should improve methodological quality, for example by conducting and including sample size calculations, controlling for confounders, and avoiding selective participant recruitment or convenience sampling without reporting reasons of non-participation. As we intentionally refrained from distinguishing *a priori* between exposures (determinants with a causal role for functional mobility) and factors co-occurring or associated with functional mobility, this could be investigated by future research. More consensus-derived standardized sets of outcomes (Gargon et al., 2017) that should be measured and reported could reduce study heterogeneity and enable more systematic research synthesis in the future. Finally, our findings suggest health professionals can tailor interventions to the context of people with PD, i.e., their ability to drive (Ryder-Burbidge et al., 2022), caregiving (Ryder-Burbidge et al., 2022), to their personal factors, i.e., sex (Ryder-Burbidge et al., 2022) and age (Ryder-Burbidge et al., 2022, Lindh-Rengifo et al., 2021) as to their cognition (Lindh-Rengifo et al., 2021), postural stability (Lindh-Rengifo et al., 2021) and social participation (Ryder-Burbidge et al., 2022).

SUPPLEMENTAL MATERIAL

Deviations from the protocol

Table S1 Deviations from the protocol

Protocol method	Deviation
"For quality reasons, included only papers published in peer-reviewed journals."	We included papers regardless of the peer review practice of the journal.
"(...) we will examine the reference lists of the sources that have been selected from full-text and / or included in the review and conduct forward and backward citation searches in the Web of Science database (Clarivate interface, 1900 onwards)."	We did a manual backward citation search in the reference lists.
"The reviewers intend to contact authors of primary sources or reviews for further information if this is relevant."	In the absence of the authors reply, numbers were extracted using the WebPlotDigitizer (Rohatgi, 2021). To calculate Cohen's d and their 95% CIs with the meta-analysis effect size calculator (Wilson), we used the reported pre- and post-intervention mean values for Harrison et al. (2020), while for Leavy et al. (2020) we used the reported between-group differences of changes from baseline and standard deviation. Finally, from Olsson et al. (2020), we used the pre- / post-intervention mean values and standard error values. As confidence intervals were not reported for almost all studies reporting standardized regression coefficients (Lindh-Rengifo et al., 2021, Rantakokko et al., 2019, Ryder-Burbidge et al., 2022), the missing 95% CIs in the studies of Lindh-Rengifo et al. (2021) and Rantakokko et al. (2019) were calculated by the equation: $upper\ or\ lower\ CI * standardised\ beta\ /\ beta$, while for the study of Ryder-Burbidge et al. (2022) we applied the equation $standardised\ beta + or - (1.96 * standard\ error)$.
„In a table, associations of determinants with functional mobility will be described. Determinants will be organized according to the ICF-classification (e.g. a characteristic of an determinant) (Moola et al., 2020)."	We tabulated the determinants by outcomes and study designs to promote comparability. Finally, we ordered the determinants from high to low effect sizes independently of the statistical significance.
"The JBI critical appraisal tools (Moola et al., 2020) will be used to determine the methodological quality of the studies to include in the review."	Due to the heterogeneity of study designs, we performed the mixed-methods appraisal tool (MMAT) for risk of bias assessment (Hong et al., 2018)

Search strategies

PubMed

("parkinson disease"[MeSH Terms] OR "parkinson*"[Text Word]) **AND** ("dependent ambulation"[MeSH Terms] OR "mobility limitation"[MeSH Terms] OR "walking"[MeSH Terms] OR ("ambulat*"[All Fields] AND "difficult*"[Text Word]) OR "mobilit*"[Text Word] OR "walk*"[Text Word]) **AND** (((((("assessed"[Text Word] OR "assessment"[Text Word] OR "assessments"[Text Word] OR "based"[Text Word] OR ("rated"[Text Word] OR "rating"[Text Word] OR "ratings"[Text Word]) OR ("report"[Text Word] OR "reported"[Text Word] OR "reporting"[Text Word])) AND ("patient"[Text Word] OR "self"[Text Word])) OR ("patient reported outcome measures"[MeSH Terms] OR "self report"[MeSH Terms])) AND ("index"[Text Word] OR "indices"[Text Word] OR "instrument"[Text Word] OR "instruments"[Text Word] OR "measure"[Text Word] OR

"measures"[Text Word] OR "questionnaire"[Text Word] OR "questionnaires"[Text Word] OR "profile"[Text Word] OR "profiles"[Text Word] OR "scale"[Text Word] OR "scales"[Text Word] OR "score"[Text Word] OR "scores"[Text Word] OR "status"[Text Word] OR "survey"[Text Word] OR "surveys"[Text Word])) OR ("Walk-12G"[Text Word] OR "life space assessment"[Text Word] OR "life space mobility"[Text Word] OR "human activity profile"[Text Word]))

CINAHL

(MH "parkinson disease" OR TX "parkinson*") **AND** (MH "Physical Mobility" OR MH "walking" OR TX "ambulat* difficult*" OR TX "mobilit*" OR TX "walk*") **AND** (((((TX "assessed" OR TX "assessment" OR TX "assessments" OR TX "based" OR (TX "rated" OR TX "rating" OR TX "ratings") OR (TX "report" OR TX "reported" OR TX "reporting")) AND (TX "patient" OR TX "self")) OR (MH "patient-reported outcomes")) AND (TX "index" OR TX "indices" OR TX "instrument" OR TX "instruments" OR TX "measure" OR TX "measures" OR TX "questionnaire" OR TX "questionnaires" OR TX "profile" OR TX "profiles" OR TX "scale" OR TX "scales" OR TX "score" OR TX "scores" OR TX "status" OR TX "survey" OR TX "surveys")) OR (TX "Walk-12G" OR TX "life space assessment" OR TX "life space mobility" OR TX "human activity profile"))

PsycInfo

(DE "parkinson disease" OR TX "parkinson*") **AND** (DE "Locomotion" OR DE "Physical Activity" OR DE "walking" OR TX "ambulat* difficult*" OR TX "mobilit*" OR TX "walk*") **AND** (((((TX "assessed" OR TX "assessment" OR TX "assessments" OR TX "based" OR (TX "rated" OR TX "rating" OR TX "ratings") OR (TX "report" OR TX "reported" OR TX "reporting")) AND (TX "patient" OR TX "self")) OR (DE "self-report")) AND (TX "index" OR TX "indices" OR TX "instrument" OR TX "instruments" OR TX "measure" OR TX "measures" OR TX "questionnaire" OR TX "questionnaires" OR TX "profile" OR TX "profiles" OR TX "scale" OR TX "scales" OR TX "score" OR TX "scores" OR TX "status" OR TX "survey" OR TX "surveys")) OR (TX "Walk-12G" OR TX "life space assessment" OR TX "life space mobility" OR TX "human activity profile"))

Results of the Risk of Bias Assessment

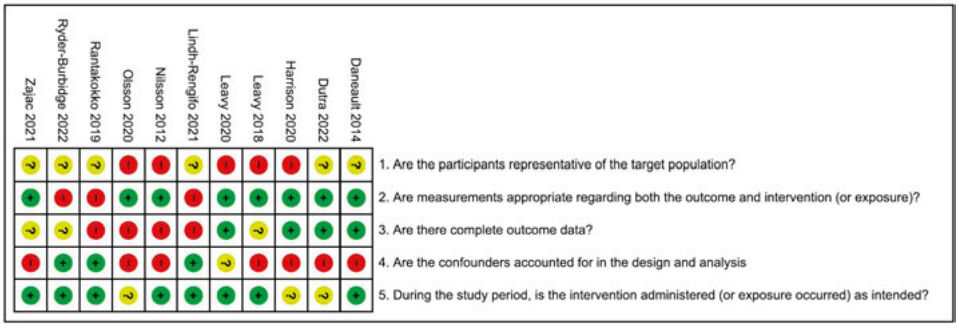

Figure S1 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Registration and protocol

OSF Open-Ended Registration on 25.01.2022, Registration DOI: 10.17605/OSF.IO/8UGB7
The registered protocol can be accessed at the following link: https://osf.io/8ugb7.

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CHAPTER 4

Mixed effects models but not t-tests or linear regression detect progression of apathy in Parkinson's disease over seven years: A comparative analysis.

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Christophe Ley

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ABSTRACT

INTRODUCTION

While there is an interest in defining longitudinal change in people with chronic illness like Parkinson's disease (PD), statistical analysis of longitudinal data is not straightforward for clinical researchers. Here, we aim to demonstrate how the choice of statistical method may influence research outcomes, (e.g., progression in apathy), specifically the size of longitudinal effect estimates, in a cohort.

METHODS

In this retrospective longitudinal analysis of 802 people with typical Parkinson's disease in the Luxembourg Parkinson's study, we compared the mean apathy scores at visit 1 and visit 8 by means of the paired two-sided t-test. Additionally, we analysed the relationship between the visit numbers and the apathy score using linear regression and longitudinal two-level mixed effects models.

RESULTS

Mixed effects models were the only method able to detect progression of apathy over time. While the effects estimated for the group comparison and the linear regression were smaller with high p-values (+1.016/ 7years, $p = 0.107$, -0.056/ 7years, $p = 0.897$, respectively), effect estimates for the mixed effects models were positive with a very small p-value, indicating a significant increase in apathy symptoms by +2.345/ 7years ($p < 0.001$).

CONCLUSION

The inappropriate use of paired t-tests and linear regression to analyse longitudinal data can lead to underpowered analyses and an underestimation of longitudinal change. While mixed effects models are not without limitations and need to be altered to model the time sequence between the exposure and the outcome, they are worth considering for longitudinal data analyses. In case this is not possible, limitations of the analytical approach need to be discussed and taken into account in the interpretation.

BACKGROUND

In longitudinal studies: "an outcome is repeatedly measured, i.e., the outcome variable is measured in the same subject on several occasions." (Twisk, 2013). When assessing the same individuals over time, the different data points are likely to be more similar to each other than measurements taken from other individuals. Consequently, the application of special statistical techniques is required, which take into account the fact that the repeated observations of each subject are correlated (Twisk, 2013). Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder resulting in a wide variety of motor and non-motor symptoms including apathy, defined as a disorder of motivation, characterised by reduced goal-directed behaviour and cognitive activity and blunted affect (Levy and Dubois, 2006). Apathy increases over time in people with PD (Poewe et al., 2017). Specifically, apathy has been associated with the progressive denervation of ascending dopaminergic pathways in PD (Pagonabarraga et al., 2015, Drui et al., 2014) leading to dysfunctions of circuits implicated in reward-related learning (Drui et al., 2014).

METHODS

T-tests are often misused to analyse changes over time (Liang et al., 2019). Consequently, we aim to demonstrate how the choice of statistical method may influence research outcomes, specifically the size and interpretation of longitudinal effect estimates in a cohort. Thus, the findings are intended for illustrative and educational purposes related to the statistical methodology. In a retrospective analysis of data from the Luxembourg Parkinson's study, a nation-wide, monocentric, observational, longitudinal-prospective dynamic cohort (Hipp et al., 2018, Pavelka et al., 2023), we assess change in apathy using three different statistical approaches (paired t-test, linear regression, mixed effects model). We defined the following target estimand: In people diagnosed with PD, what is the change in the apathy score from visit 1 to visit 8? To estimate this change, we formulated the statistical hypothesis as follows:

$$H0 : \text{Mean change from visit 1 to visit 8} = 0$$
$$HA : \text{Mean change from visit 1 to visit 8} \neq 0$$

While apathy was the dependent variable, we included the visit number as an independent variable (linear regression, mixed effects model) and as a grouping variable (paired t-test). The outcome apathy was measured by the discrete score from the Starkstein apathy scale (0 – 42, higher = worse) (Starkstein et al., 1992), a scale recommended by the Movement Disorders Society (Leentjens et al., 2008). This data was obtained from the National Centre of Excellence in Research on Parkinson's disease (NCER-PD). The establishment of data collection standards, completion of the questionnaires at home at the participants'

convenience, mobile recruitment team for follow-up visits or standardized telephone questionnaire with a reduced assessment were part of the efforts in the primary study to address potential sources of bias (Hipp et al., 2018, Pavelka et al., 2023). Ethical approval was provided by the National Ethics Board (CNER Ref: 201407/13). We used data from up to eight visits, which were performed annually between 2015 and 2023. Among the participants are people with typical PD or PD dementia (PDD), living mostly at home in Luxembourg and the Greater Region (geographically close areas of the surrounding countries Belgium, France, and Germany). People with atypical PD were excluded. The sample at the date of data export (2023-06-22) consisted of 802 individuals of which 269 (33.5%) were female. The average number of observations was 3.0. Fig. S1 reports the numbers of individuals at each visit while the characteristics of the participants are described in Table 1.

Table 1 Characteristics of the participants

Variables	Mean (SD) / n (%)	Min. – Max.	Median (Pct25-75)	Missing N (%)
Age (years)	67.1 (10.9)	22.0 – 92.9	68.2 (60.2 – 74.6)	1 (0.1%)
Female sex	270 (33.7%)			0 (0.0%)
Years of education	13.0 (4.1)	1.0 – 30.0	13.0 (10.0 – 16.0)	9 (1.1%)
Actual diagnosis				0 (0.0%)
Parkinson's disease	707 (88.2%)			
Parkinson's disease dementia	95 (11.9%)			
Age at diagnosis (years)	62.4 (11.7)	18.0 – 91.0	63.0 (54.0 – 71.0)	8 (1.0%)
Years since diagnosis	5.0 (5.1)	0.0 – 32.3	3.2 (1.1 – 7.4)	54 (6.7%)
Apathy score (0 – 42)	12.0 (5.9)	1 – 36	13.0 (10.0 – 17.0)	54 (6.7%)
MDS-UPDRS I (0 – 52)a	10.4 (6.9)	0.0 – 39.0	9.0 (5.0 - 14.0)	33 (4.1%)
MDS-UPDRS II (0 – 52)a	11.0 (8.4)	0.0 – 48.0	9.0 (5.0 - 15.0)	24 (3.0%)
MDS-UPDRS III (0 – 132)a	34.1 (16.7)	0.0 – 100.0	32.0 (22.0 - 44.0)	21 (2.6%)
MDS-UPDRS IV (0 – 24)a	1.6 (3.2)	0.0 – 16.0	0.0 (0.0 - 1.0)	17 (2.2%)

Note [a] Greater = Worse, [b] Greater = Better, MDS-UPDRS: Movement Disorders Society – Unified Parkinson's Disease Rating Scale, MDS-UPDRS I: non-motor symptoms, MDS-UPDRS II: patient-reported motor symptoms, MDS-UPDRS III : clinician assessed motor symptoms, MDS-UPDRS IV: motor complications

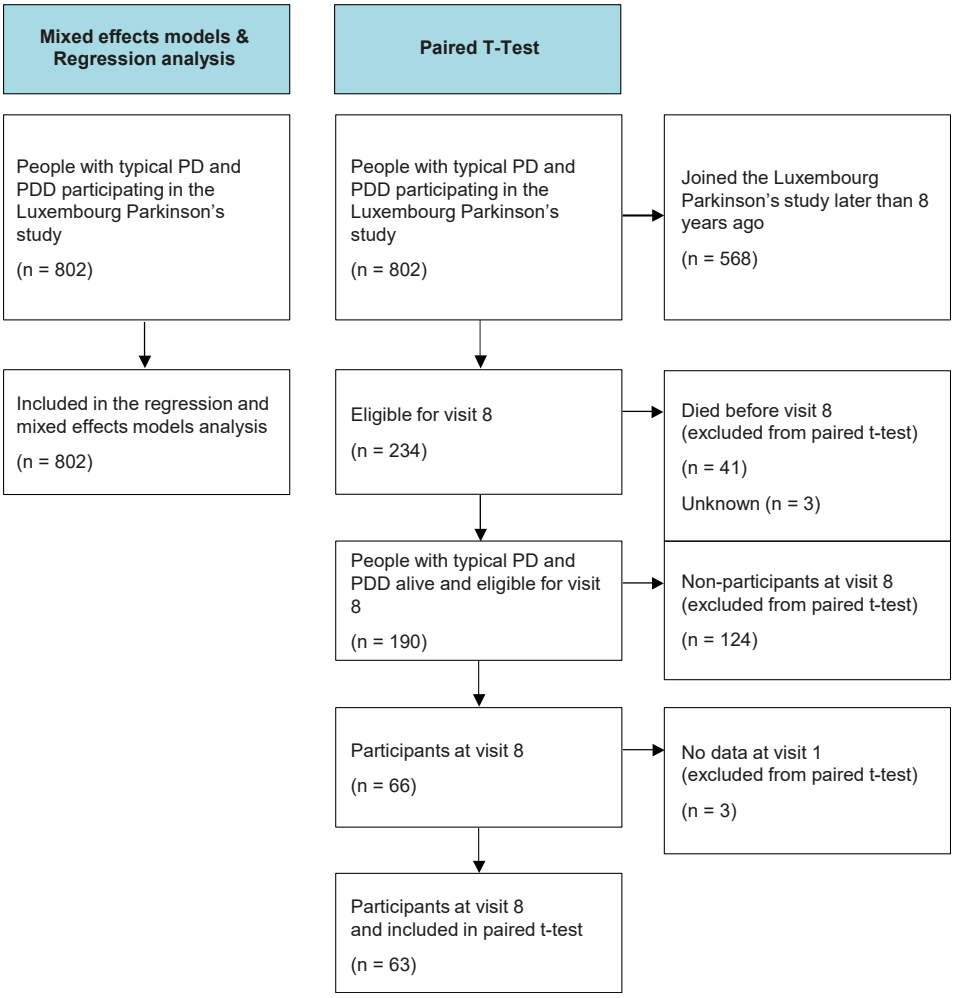

Figure 1 Flow diagram of patient recruitment

As illustrated in the flow diagram (Fig. 1), the sample analysed from the paired t-test is highly selective: from the 802 participants at visit 1, the t-test only included 63 participants with data from visit 8. This arises from the fact that, first, we analyse the dataset from a dynamic cohort, i.e., the data at visit 1 were not collected at the same time point. Thus, 568 of the 802 participants joined the study less than eight years before, leading to only 234 participants eligible for the eighth yearly visit. Second, after excluding non-participants at visit 8 due to death (n = 41) and other reasons (n = 130), only 63 participants at visit 8 were left. To discuss the selective study population of a paired t-test, we compared the characteristics (age, education, age at diagnosis, apathy at visit 1) of the remaining 63 participants at visit 8 (included in the paired t-test) and the 127 non-participants at visit 8 (excluded from the paired t-test) (Little, 1988).

The paired two-sided t-test compared the mean apathy score at visit 1 with the mean apathy score at the visit 8. We attract the reader's attention to the fact that this implies a rather small sample size as it includes only those people with data from the first and 8th visit. The linear regression analysed the relationship between the visit number and the apathy score (using the "stats" package (R Core Team, 2023)), while we performed longitudinal two-level mixed effects models analysis with a random intercept on subject level, a random slope for visit number and the visit number as fixed effect (using the "lmer"-function of the "lme4"-package (Bates et al., 2015)). The latter two approaches use all available data from all visits while the paired t-test does not. We illustrated the analyses in plots with the function "plot_model" of the R package sjPlot (Lüdecke, 2022). We conducted data analysis using R version 3.6.3 (R Core Team, 2023) and the R syntax for all analyses is provided on the OSF project page (https://doi.org/10.17605/OSF.IO/NF4YB).

RESULTS

Panel A in Fig. 2 illustrates the means and standard deviations of apathy for all participants at each visit, while the flow-chart (Fig. S1) illustrates the number of participants at each stage. On average, we see lower apathy scores at visit 8 compared to visit 1 (higher score = worse). By definition, the paired t-test analyses pairs, and in this case, only participants with complete apathy scores at visit 1 and visit 8 are included, reducing the total analysed sample to 63 pairs of observations. Consequently, the t-test compares mean apathy scores in a subgroup of participants with data at both visits leading to different observations from Panel A, as illustrated and described in Panel B: the apathy score has increased at visit 8, hence symptoms of apathy have worsened. The outcome of the t-test along with the code is given in Table 2. Interestingly, the effect estimates for the increase in apathy were not statistically significant (+1.016 points, 95%CI: -0.225, 2.257, p = 0.107). A possible reason for this non-significance is a loss of statistical power due to a small sample size included in the paired t-test. To visualise the loss of information between visit 1 and visit 8, we illustrated the complex individual trajectories of the participants in Fig. 3. Moreover, as described in Table S1 in the supplement, the participants at visit 8 (63/190) analysed in the t-test were inherently significantly different compared to the non-participants at visit 8 (127/190): they were younger, had better education, and most importantly their apathy scores at visit 1 were lower. Consequently, those with the better overall situation kept coming back while this was not the case for those with a worse outcome at visit 1, which explains the observed (non-significant) increase. This may result in a biased estimation of change in apathy when analysed by the compared statistical methods.

From the results in Table 2, we see that the linear regression coefficient, representing change in apathy symptoms per year, is not significantly different from zero, indicating

no change over time. One possible explanation is the violation of the assumption of independent observations for linear regressions. On the contrary, the effect estimates for the linear mixed effects models indicated a significant increase in apathy symptoms from visit 1 to visit 8 by +2.680 points (95%CI: 1.880, 3.472, $p < 0.001$). Consequently, mixed effects models were the only method able to detect an increase in apathy symptoms over time and choosing mixed effect models for the analysis of longitudinal data reduces the risk of false negative results. The differences in the effect sizes are also reflected in the regression lines in Panel A and B of Fig. 4.

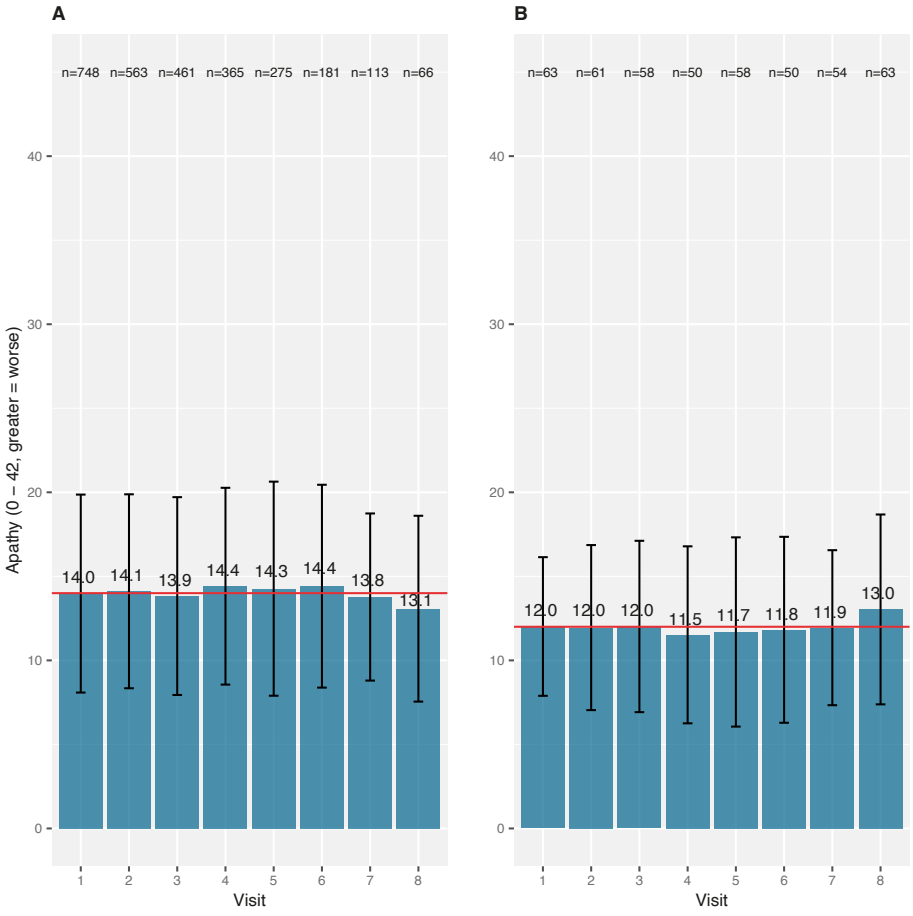

Figure 2 Bar charts illustrating apathy scores (means and standard deviations) per visit (Panel A: all participants, Panel B: subgroup analysed in the t-test). The red line indicates the mean apathy at visit 1

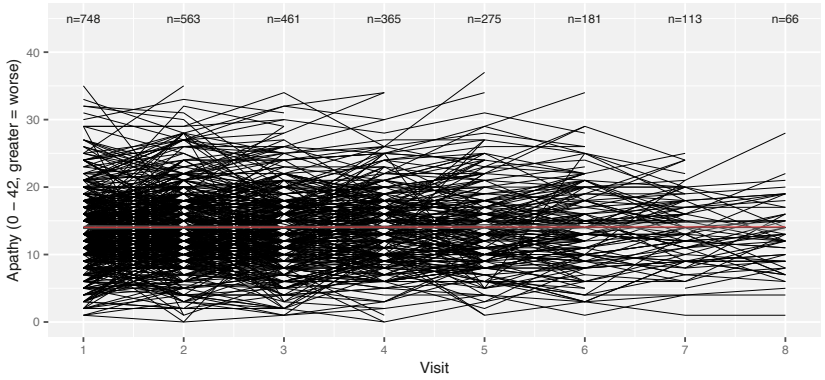

Figure 3 Scatterplot illustrating the individual trajectories. The red line indicates the regression line

Table 2 Results from the group comparison, the linear regression and the linear mixed models

Statistical test	Change from visit 1 to visit 8	95% CI	p-value
Paired t-test	+1.016	-0.225, 2.257	0.107
Linear regression	-0.064	-0.856, 0.979	0.897
Linear mixed effects models	+2.680	1.880, 3.472	< 0.001

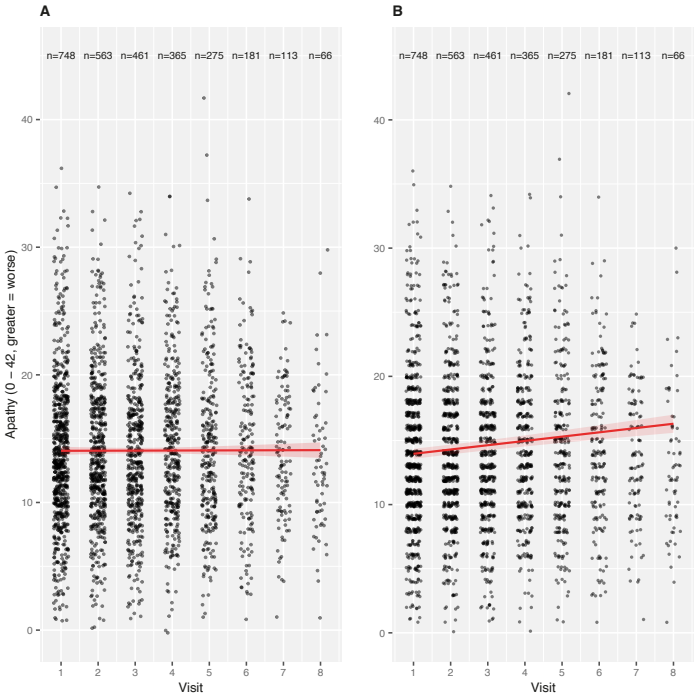

Figure 4 Scatterplot illustrating the relationship between visit number and apathy. Apathy measured by a whole number interval scale, jitter applied on x- and y-axis to illustrate the data points (Panel A: Linear regression, Panel B: Linear mixed effects model). The red line indicates the regression line.

DISCUSSION

The effect sizes differed depending on the choice of the statistical method. Thus, the paired t-test and the linear regression resulted in an output that would lead to different interpretations than the mixed effects models. More specifically, compared to the t-test and linear regression (which indicated non-significant changes in apathy of only +1.016, -0.064 points from visit 1 to visit 8, respectively), the linear mixed effects models found an increase of +2.680 points from visit 1 to visit 8 on the apathy scale. This increase is more than twice as high as indicated by the t-test and suggests linear mixed models is a more sensitive approach to detect meaningful changes perceived by people with PD over time.

Mixed effects models are a valuable tool in longitudinal data analysis as these models expand upon linear regression models by considering the correlation among repeated measurements within the same individuals through the estimation of a random intercept (Twisk, 2006, Twisk, 2013, Twisk, 2019). Specifically, to account for correlation between observations, linear mixed effects models use random effects to explicitly model the correlation structure, thus removing correlation from the error term. A random slope in addition to a random intercept allows both the rate of change and the mean value to vary by participant, capturing individual differences. This distinguishes them from group comparisons or standard linear regressions, in which such explicit modelling of correlation is not possible. Thus, the linear regression not considering correlation among the repeated observations leads to an underestimation of longitudinal change, explaining the smaller effect sizes and insignificant results of the regression. By including random effects, linear mixed effects models can better capture the variability within the data.

Another common challenge in longitudinal studies is missing data. Compared to the paired t-test and regression, the mixed effects models can also include participants with missing data at single visits and account for the individual trajectories of each participant as illustrated in Fig. 2 (Long, 2012). Although multiple imputation could increase the sample size, those results need to be interpreted with caution in case the data is not missing at random (Twisk et al., 2013, Long, 2012). Note that we do not further elaborate here on this topic since this is a separate issue to statistical method comparison. Finally, assumptions of the different statistical methods need to be respected. The paired t-test assumes a normal distribution, homogeneity of variance and pairs of the same individuals in both groups (Student, 1908, Polit, 2014). While mixed effects models don't rely on independent observations as it is the case for linear regression, all other assumptions for standard linear regression analysis (e.g., linearity, homoscedasticity, no multicollinearity) also hold for mixed effects model analyses. Thus, additional steps, e.g., check for linearity of the relationships or data transformations are required before the analysis of clinical research questions (Twisk, 2019).

CONCLUSION

While mixed effects models are not without limitations and need to be altered to model the time sequence between the exposure and the outcome (Twisk, 2013), they are worth considering for longitudinal data analyses. Thus, assuming an increase of apathy over time (Poewe et al., 2017), mixed effects models were the only method able to detect statistically significant changes in the defined estimand, i.e., the change in apathy from visit 1 to visit 8. Possible reasons are a loss of statistical power due to a small sample size included in the paired t-test and the violence of the assumption of independent observations for linear regressions. Specifically, the effects estimated for the group comparison and the linear regression were smaller with high p-values, indicating a statistically insignificant change in apathy over time. The effect estimates for the mixed effects models were positive with a very small p-value, indicating a statistically significant increase in apathy symptoms from visit 1 to visit 8 in line with clinical expectations. Mixed effects models can be used to estimate different types of longitudinal effects while an inappropriate use of paired t-tests and linear regression to analyse longitudinal data can lead to underpowered analyses and an underestimation of longitudinal change and thus clinical significance. Therefore, researchers should more often consider mixed effects models for longitudinal analyses. In case this is not possible, limitations of the analytical approach need to be discussed and taken into account in the interpretation.

SUPPLEMENTAL MATERIAL

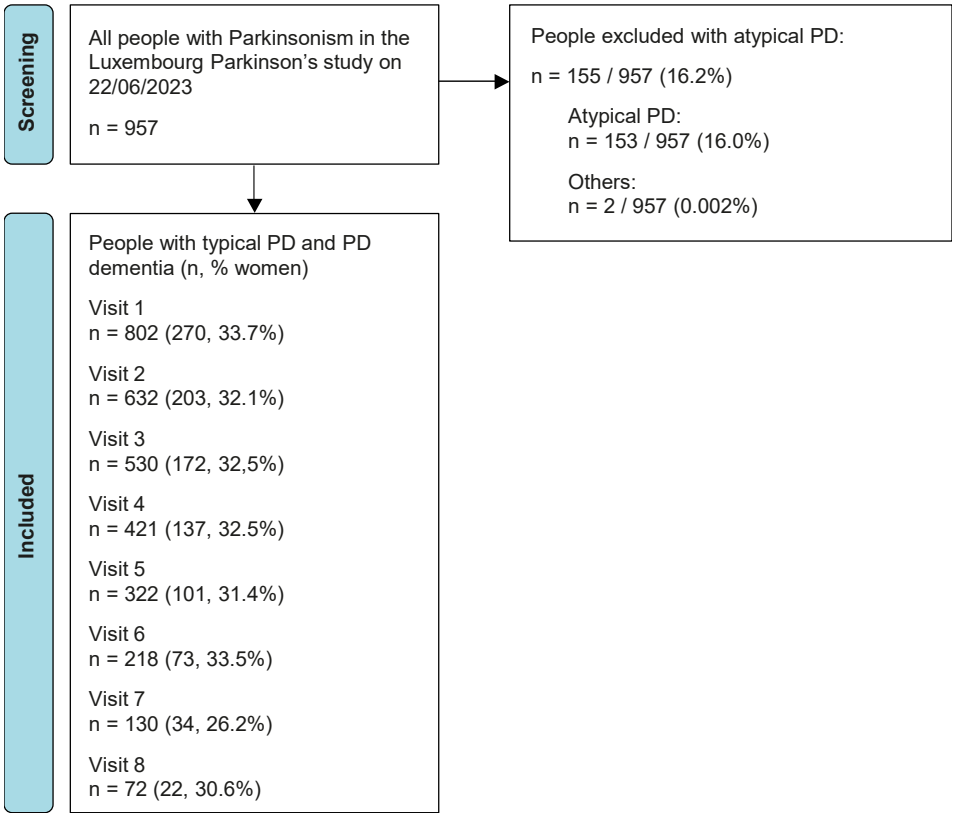

Figure S1 Flow-chart

Table S1 Comparison of characteristics between particpants at visit 8 (included in the paired t-test) and the non-participants at visit 8 (excluded from the paired t-test)

Values at baseline	Participants without visit 8 (N = 127)	Participants with visit 8 (N = 63)	p-value
Apathy Score	14.3 (6.0)	12.0 (4.1)	p = 0.003
Age (y.)	65.8 (11.7)	62.3 (9.6)	p = 0.029
Age at diagnosis (y.)	59.5 (12.8)	58.0 (10.3)	p = 0.367
Years of education	12.6 (3.6)	14.0 (3.5)	p = 0.009

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CHAPTER 5

Sex-specific progression of Parkinson's disease: A longitudinal mixed-models analysis.

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ABSTRACT

BACKGROUND

Despite its relevance, the clinical progression of motor- and non-motor symptoms associated with Parkinson's disease (PD) is poorly described and understood, particularly in relation to sex-specific differences in clinical progression.

OBJECTIVE

Identification of differential aspects in disease progression in men and women with PD.

METHODS

Linear mixed-model analyses of a total of 802 people with typical PD from the Luxembourg Parkinson's study's prospective cohort, including sex as a moderator. Marginal means of the outcomes for men and women were estimated and illustrated for the following outcomes: MDS-UPDRS I-IV, apathy, depression, global cognition, olfaction, bodily discomfort, rapid eye movement sleep behaviour disorder, quality of sleep, dysphagia, patient-reported functional mobility, postural instability and gait disturbances and tremor. Men and women had similar age and median time of follow-up was three years.

RESULTS

We observed an overall slower progression in women compared to men. Specifically, we detected a slower progression in women for global cognition (MoCA) (-0.159, 95%CI: -0.272, -0.046, p = 0.006), quality of sleep (PDSS) (-0.716, 95%CI: -1.229, -0.203, p = 0.006), Postural Instabilities and Gait Disturbances (PIGD) (0.133, 95%CI: 0.025 0.241, p = 0.016) and patient-reported motor symptoms (MDS-UPDRS II) (0.346, 95%CI: 0.120, 0.572, p = 0.003). The findings for patient-reported motor symptoms were significant after adjustment for FWER (Bonferroni-Holm).

CONCLUSIONS

Differential progression of symptoms in men and women with PD exists and needs to be explored further. To enhance well-being in PD, we recommend considering a sex-specific approach to managing PD symptoms.

BACKGROUND

In the 2016 Global Burden of Disease Study, the age-standardized prevalence of Parkinson's disease (PD) was 1.4 times higher in men than in women (Collaborators, 2019). Consequently, sex-specific factors in PD merit further study. However, most research has focused on biological differences between men and women, neglecting to place these in the psychosocial context that impacts clinical care and quality of life of men and women with PD (Subramanian et al., 2022, Post et al., 2007, Marras et al., 2002). Therefore, the effect of sex and/or gender should be considered in designing future studies in PD (Colombo et al., 2015).

Moreover, previous longitudinal studies addressed the sex-specific progression of some symptoms. Thus, the association of sex with patient-reported and clinician-assessed motor symptoms, the phenotype, activities of daily living and medication with progression was investigated (Picillo et al., 2022). Another study (Iwaki et al., 2021) explored the role of sex in the progression of patient-reported motor symptoms, cognition, dyskinesia, wearing off, depression, REM sleep behaviour disorder and some non-motor symptoms. However, most often single studies (Subramanian et al., 2022, Post et al., 2007, Marras et al., 2002) have mainly reported cross-sectional sex differences of selected symptoms in men and women with PD while a comprehensive empirical description and illustration of the motor- and non-motor symptoms associated with Parkinson's disease progression has not been reported in the literature. Aiming to provide an overview of symptom and general disease progression of PD in men and women that can be easily interpreted by health professionals, we describe the progression of motor- and non-motor symptoms in men and women and investigate the effect modification by sex in people with typical PD participating in a large monocentric longitudinal cohort.

METHODS

Study design, setting, participants and study size

This retrospective analysis is part of the Luxembourg Parkinson's study, a nationwide, monocentric, observational, longitudinal-prospective and dynamic cohort (Hipp et al., 2018, Pavelka et al., 2023). The completed STROBE reporting guideline checklist (Vandenbroucke et al., 2007) is included in Supplement 3.

All participants underwent diagnostic evaluation and were assigned a clinical diagnosis of typical PD or Parkinson's disease dementia (PDD) by a neurologist based on established United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992). The diagnosis was not required before participation as the

Luxembourg Parkinson's study also included converters. The participants were recruited from Luxembourg and the Greater Region (geographically close areas of the surrounding countries, namely Belgium, France, and Germany). In addition to the referral by medical doctors, a communication campaign (advertisement on radio and television, dedicated webpage, social media campaign, multilingual flyers and posters, fact sheets and bi-annual print newsletter, collaboration with patient associations) informed the population about the option to enrol themselves. Recruitment started in 2015 with annual follow-ups. The Luxembourg Parkinson's Study aims at stratification and differential diagnosis of Parkinson's disease (Hipp et al., 2018, Pavelka et al., 2023).

Variables, data sources and measurement

The outcomes of interest were progression (i.e., change per additional year since diagnosis) of motor and non-motor symptoms listed in Tab. 1. All outcomes were numerical and assessed during annual follow-ups varying by a maximum of three months to minimize seasonal influences. The progression could be distinguished from cohort or period effects as people with PD were included at different time points (Twisk, 2013) due to the dynamic cohort study design. People with PD with complete data for time since diagnosis were included in the longitudinal analysis. Tab. 1 describes the characteristics of the outcomes and provides sources of data and details of the assessment methods.

Statistical methods

Data analysis was carried out in R, version 4.3.1 (R Core Team, 2023). The two-sided Wilcoxon rank-sum test and the Kruskal-Wallis test for discrete variables and the chi-squared test for categorical variables compared baseline characteristics between men and women (using the "stats" package (R Core Team, 2023)). In addition to the Bonferroni-adjusted p-values (p-value * 29 variables ≤ 0.05) we provided the unadjusted p-values (p- value ≤ 0.05).

To describe the progression of different motor- and non-motor symptoms and the effect modification by sex, we created one model per outcome (using "lmer"-function of the "lme4"-package(Bates et al., 2015)). Consequently, we performed longitudinal two-level mixed models analyses with years since diagnosis and sex as fixed effects, a random intercept on participant level and a random slope for years since diagnosis. In addition to the linear effect we tested a quadratic and a cubic function. Thus, we evaluated whether a random slope for time (i.e., years since diagnosis) was necessary by performing a likelihood ratio test (using "anova"-function of the "lme4"-package (Bates et al., 2015), method = "lrt"). Then, after modelling the linear development over time, we first extended the fixed effects with a quadratic time component, i.e. square of time and compared the model with and without quadratic time component. Finally, if the model with a quadratic time component added to the linear component fitted significantly (p-value ≤ 0.05) better to the data, this model was then compared to the model with an additional cubic time component. We

controlled for time to diagnosis and modelled differences between the individuals with the random intercept. Difference in progression between men and women was described by a significant interaction effect for sex. We estimated the linear mixed models using the maximum likelihood method while statistical significance and confidence intervals for the mixed models were obtained with the Kenward-Roger approximation for degrees of freedom. We took multiple testing into account by indicating results significant after adjustment for a 5% Family-Wise Error Rate (FWER) (Bonferroni-Holm). To enhance clinical interpretation, we provided estimated marginal means, i.e., estimated means of motor- and non-motor symptoms given 0, 10, 20, 30 and 40 years since diagnosis. Thus, we examined the range of the years since diagnosis from its minimal observed value to its maximal observed value, then fixed the covariates (diagnosis duration) at their mean to finally look at the estimated values for the different symptoms for the whole range of values of years since diagnosis (using "ggpredict"-function of the "ggeffects"-package (Lüdecke, 2018)). Those estimated means for the different symptoms (y-axis) given years since diagnosis (x-axis) and the mean value for the covariates were illustrated as an interaction plot (using the "plot_model"-function of the "sjPlot"-package (Lüdecke, 2022)). As women's ratings of disability differed between self-reported and physician-reported (Abraham et al., 2023), we categorised the results in patient-reported or clinician-assessed outcomes / performance tests. Time, in this case modelled as years since diagnosis, was included in the mixed models to describe progression of the different outcomes (significance tested via t-test). Degree of disability as illustrated in Fig. 2 was calculated by the following formula:

$$Degree\ of\ disability = \left(\frac{Estimated\ marginal\ means}{Maximum\ score} \times 100\right).$$

For illustrative purposes in Fig. 2, the following scores were inverted to the higher, the worse: functional mobility (FMCS), quality of sleep (PDSS), global cognition (MoCA) and olfaction (Sniffin' Sticks). Finally the estimated marginal means were trimmed above the upper and below the lower limit.

Table 1 Instrument, assessment types and variable name of the included constructs

Construct intended to measure	Instrument	Assessment type	Variable name
Patient-reported outcomes			
Apathy	SAS (Starkstein et al., 1992)	Patient-Reported Outcome Measure	spark_score
Depression	BDI-I (Beck et al., 1988)	Patient-Reported Outcome Measure	bdi_score
Dysphagia	MDT-PD (Buhmann et al., 2019, Simons et al., 2019)	Clinician- Assessed Outcome Measure	mdt_score
Functional mobility	FMCS (Hanff et al., 2023b)	Patient-Reported Outcome Measure	FMCS_PDQ39
Non-motor symptoms	MDS-UPDRS I (Martinez-Martin et al., 2013)	Patient-Reported and Clinician Assessed Outcome Measure	UPDRS_1
Motor symptoms	MDS-UPDRS II (Martinez-Martin et al., 2013)	Patient-Reported Outcome Measure	UPDRS_2
Bodily discomfort	PDQ-39 subscale bodily discomfort (Peto et al., 1995)	Patient-Reported Outcome Measure	pdq39_q36_q39_ score
Quality of sleep	PDSS (Chaudhuri et al., 2002)	Patient-Reported Outcome Measure	pdss_score
Rem-sleep behavior disorder	RBDSQ (Stiasny-Kolster et al., 2007)	Patient-Reported Outcome Measure	rem_score
Clinician assessed outcomes or performance tests			
Cognition	MoCA Total Score (Nasreddine et al., 2005)	Performance test	MoCA_score
Motor symptoms	MDS-UPDRS III (Martinez-Martin et al., 2013)	Clinician-Assessed Outcome Measure	UPDRS_3
Motor fluctuations	MDS-UPDRS IV (Martinez-Martin et al., 2013)	Clinician-Assessed Outcome Measure	UPDRS_4
Olfaction	ODOFIN Sniffin' Sticks Identification Test 16	Performance test	sniff_score
Postural instability and gait disturbance	MDS-UPDRS based PIGD score (Stebbins et al., 2013, Jankovic et al., 1990),	Patient-Reported and Clinician Assessed Outcome Measure	PIGD_score
Tremor	MDS-UPDRS based tremor scale (Forjaz et al., 2015, Jankovic et al., 1990)	Patient-Reported and Clinician Assessed Outcome Measure	trem_trem_score
Exposure			
Time variant with baseline assessment and yearly follow-up	Disease duration (y.): Date of assessment – Date of diagnosis	Interview	disease_duration
Confounder			
Time variant with baseline assessment and yearly follow-up	Time to diagnosis (y.): Date of diagnosis – Date of first motor symptoms	Interview	diagnosis_ duration

Abbreviations BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disturbances, RDBSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

RESULTS

As illustrated in Fig. 1, 957 persons participated in the Luxembourg Parkinson's Study up to the date of data export (22.06.2023). After the exclusion of people with atypical PD, we included 802 people with typical PD with a baseline assessment between 04.03.2015 and 22.06.2023.

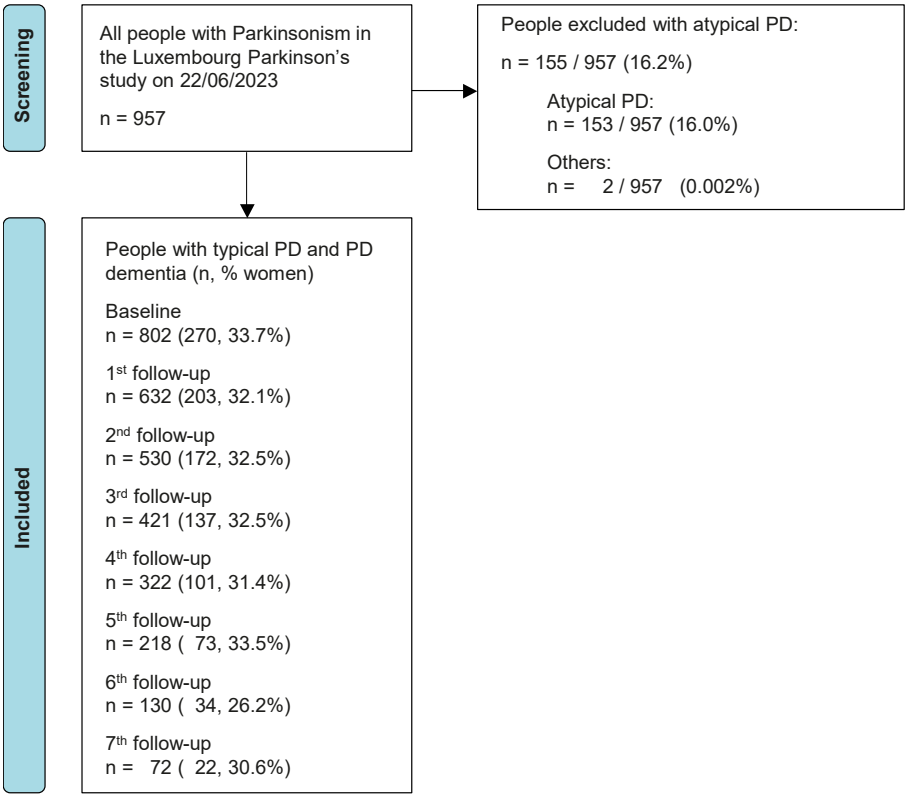

Figure 1 Flow diagram of recruitment

Table 2 Key characteristics

Sample size	802
Data collection period	04.03.2015 – 22.06.2023
Study design	Cohort
Average number of observations	3.0 (3.0)
Setting	People with typical PD living at home or in a nursing home in Luxembourg and the greater region
Inclusion criteria	People with typical PD
Gender	269 (33.6%) women
Age	68.2 (14.3)
Disease stage	2.0 (0.5)
Outcomes Concept (Measure)	Apathy (SAS), depression (BDI-I), functional mobility (FMCS), non-motor symptoms (MDS-UPDRS I), patient-reported motor symptoms (MDS-UPDRS II), clinician-assessed motor symptoms (MDS-UPDRS III), motor complications (MDS-UPDRS IV), dysphagia (MDT-PD), global cognition (MoCA), olfaction (Sniffin' Sticks), bodily discomfort (PDQ-39 subscale bodily discomfort), quality of sleep (PDSS), postural instabilities and gait disturbances (MDS-based PIGD), REM sleep behaviour disorder (RBDSQ), tremor (MDS-based tremor scale)
Determinants	Disease duration, time to diagnosis

Abbreviations Categorical variables: counts (%), numerical variables: Median (IQR), Abbreviations: PD: Parkinson's disease, BDI-I: Beck Depression Inventory, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disturbances, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Table 2 summarizes key study characteristics to understand the potential applicability, and thus generalizability of the findings, while Tab. S1 provides a detailed description of the study participants and missing data. The clinical and demographic characteristics of study participants at baseline by sex are presented in Tab. 3. Testing for differences at baseline in 29 characteristics at a Bonferroni-adjusted 5% significance level, women had significantly worse scores for depression (BDI-I) and bodily discomfort (PDQ-39 subscale bodily discomfort), while men had worse olfaction scores (Sniffin' sticks). In women, the Levodopa Equivalent Daily Dose (LEDD) per kg body weight (mg/ kg) was significantly higher compared to men. Women had significantly less years of education and experienced a bereavement significantly more often compared to men. We did not test for any differences in weight and height at baseline. We did not identify any statistically significant differences for age, years since diagnosis or time to diagnosis at baseline between men and women with typical PD. Missing data patterns were visually inspected for sociodemographic characteristics and the different outcomes; most variables had missing data for less than 5% of the male and female samples. Rates for missing data were higher for Munich Dysphagia Test-assessed dysphagia (51% and 55% for men and women, respectively).

While many outcomes showed a linear trajectory, this was not the case for apathy (SAS), global cognition (MoCA), depression (BDI-I), bodily discomfort (PDQ-39 subscale bodily discomfort), patient-reported motors symptoms (MDS-UPDRS II), motor complications (MDS-

UPDRS IV), postural instability and gait disturbances (MDS-UPDRS based PIGD score) where adding the quadratic effect significantly improved the fit of the model. We described the model statistics and the detailed fixed and random effects in Tab. 4 and 5 and illustrated the progression (estimated marginal means converted to % impairment) of men and women in Fig. 2. Fig. S1 - S3 detail the interaction plots for clinical interpretation.

Table 3 Characteristics of men and women

Variables	Men (N = 532)	Women (N = 270)	Unadjusted p-value	Adjusted p-value
Sociodemographic characteristics				
Age (y)	68.2 (14.5)	68.1 (14.3)	p = 0.3925	p = 1
Years of education	13.0 (4.0)	12.0 (4.8)	p = 0.0001	p = 0.0038
Most fluently spoken language			p = 0.2490	p = 1
Luxembourgish	234 (44.0%)	111 (41.1%)		
French	145 (27.3%)	82 (30.4%)		
German	84 (15.8%)	45 (16.7%)		
Other	69 (13.0%)	31 (11.5%)		
Children (n)	2.0 (2.0)	2.0 (1.0)	p = 0.0085	p = 0.2470
Marital status			p = 0.0002	P = 0.0058
Single	20 (3.8%)	24 (8.9%)		
Married / Partnered	442 (83.1%)	164 (60.7%)		
Divorced / Bereaved	67 (12.6%)	80 (29.6%)		
Health-related characteristics				
Diagnosis			p = 0.1668	p = 1
PD	463 (87.0%)	244 (90.4%)		
PDD	69 (13.0%)	26 (9.6%)		
Hoehn and Yahr (H&Y) Disease Stages			p = 0.3921	p = 1
H&Y 1	58 (10.9%)	30 (11.1%)		
H&Y 1.5	43 (8.1%)	26 (9.6%)		
H&Y 2	275 (51.7%)	119 (44.1%)		
H&Y 2.5	64 (12.0%)	41 (15.2%)		
H&Y 3	45 (8.5%)	31 (11.5%)		
H&Y 4	27 (5.1%)	13 (4.8%)		
H&Y 5	11 (2.1%)	5 (1.9%)		
Phenotype			p = 0.0366	p = 1
Tremor dominant	223 (41.2%)	84 (31.1%)		
Intermediate	58 (10.9%)	24 (8.9%)		
PIGD dominant	198 (37.2%)	129 (47.8%)		
Disease duration (y.)	3.1 (5.9)	3.5 (6.6)	p = 0.1079	p = 1
Age at diagnosis (y.)	63.0 (16.5)	63.0 (17.0)	p = 0.2974	p = 1
Age at onset of motor-symptoms (y.)	61.0 (18.0)	60.0 (17.2)	p = 0.2121	p = 1
Time to diagnosis (y.)	1.0 (3.0)	1.0 (3.0)	p = 0.5486	p = 1
LEDD (mg/kg)	5.5 (6.1)	6.6 (7.7)	p = 0.0008	p = 0.0228
PDQ-39 (0 – 100)[a]	19.9 (22.4)	25.0 (21.6)	p = 0.0042	p = 0.1229

Table 3 Continued.

Variables	Men (N = 532)	Women (N = 270)	Unadjusted p-value	Adjusted p-value
Non-motor symptoms				
MoCA (0 – 30)[b]	25.0 (5.0)	26.0 (5.0)	p = 0.0123	p = 0.3578
BDI-I (0 – 63)[a]	8.0 (9.0)	10.0 (9.0)	p = 0.0002	p = 0.0064
SAS (0 - 42)[a]	13.0 (7.0)	13.0 (7.0)	p = 0.3345	p = 1
Sniffin' Sticks (0 - 16)[b]	8.0 (5.0)	9.0 (4.0)	p < 0.0001	p < 0.0001
PDQ-39 subscale bodily discomfort (0 – 100)[a]	25.0 (33.3)	41.7 (41.7)	p = 0.0001	p = 0.0035
PDSS (0 - 150)[b]	110.0 (34.0)	106.5 (36.1)	p = 0.0198	p = 0.5726
RBDSQ (0 - 13)[a]	4.0 (5.0)	4.0 (4.0)	p = 0.1777	p = 1
MDS-UPDRS I (0 – 52)[a]	9.0 (8.0)	10.0 (9.0)	p = 0.0118	p = 0.3424
Motor symptoms				
MDS-UPDRS II (0 – 52)[a]	10.0 (10.0)	9.0 (10.0)	p = 0.7435	p = 1
MDS-UPDRS III (0 – 132)[a]	33.0 (21.0)	31.0 (23.8)	p = 0.1936	p = 1
MDS-UPDRS IV (0 – 24)[a]	0.0 (0.0)	0.0 (2.5)	p = 0.1724	p = 1
FMCS (0 – 100)b	81.2 (31.2)	76.6 (34.4)	p = 0.0378	p = 1
MDS-UPDRS based PIGD Score (0 – 20)[a]	2.0 (4.0)	3.0 (4.0)	p = 0.0617	p = 1
MDS-UPDRS based tremor Scale (0 - 4)[a]	0.5 (0.6)	0.5 (0.6)	p = 0.0294	p = 0.8526
MDT Score (3 - 103)[a]	6.0 (9.0)	6.0 (7.8)	p = 0.4668	p = 1

Abbreviations Categorical variables: counts (%), numerical variables: median (IQR), a : Greater = worse, b : Greater = better, numerical variables : two-sided Wilcoxon rank-sum test, categorical variables : chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disturbances, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

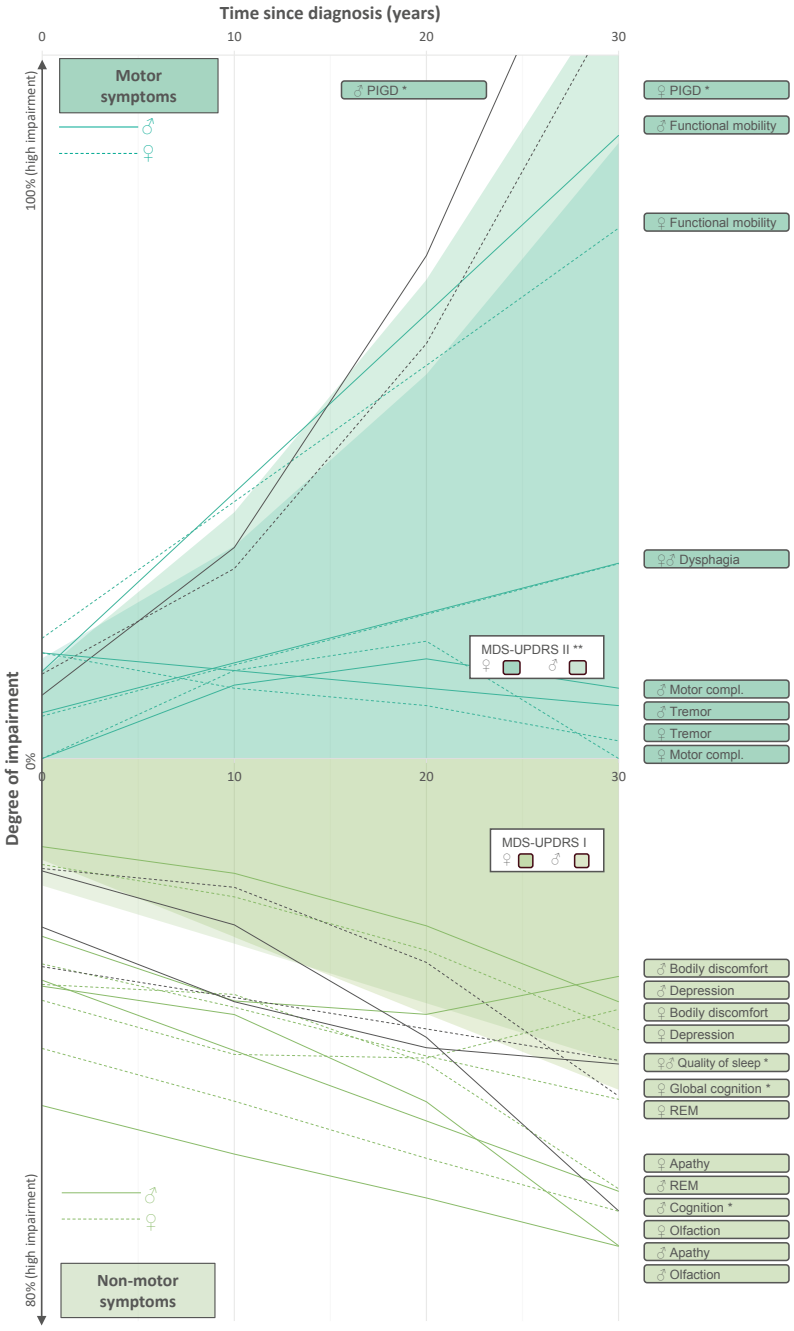

Figure 2 Progression of motor- and non-motor symptoms in men and women with typical PD. Degree of impairment = 0 – 100% (greater = worse). * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm), lines of significant results are highlighted in black, Abbreviations : PD : Parkinson's disease, PIGD : Postural Instabilities and Gait Disturbances, RBD : Rapid Eye Movement (REM) Behavior Disorder

Table 4 Fixed effects of non-motor symptoms in men and women and the interaction of sex with progression

	SAS[a]		MoCA[b]		BDI-I[a]		MDS-UPDRS I[a]	
Independent variables	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**
Intercept	13.501 (12.499 – 14.502)	<0.001	25.314 (24.661 – 25.967)	<0.001	9.401 (8.148 – 10.654)	<0.001	9.269 (8.198 – 10.340)	<0.001
Years since diagnosis	-0.105 (-0.275 – 0.065)	0.225	0.051 (-0.076 – 0.178)	0.435	0.164 (-0.048 – 0.377)	0.129	0.437 (0.300 – 0.573)	<0.001
Years since diagnosis^2	0.017 (0.009 – 0.025)	<0.001	-0.013 (-0.018 – -0.007)	<0.001	0.011 (0.001 – 0.021)	0.026	-	-
Time to diagnosis	-0.012 (-0.088 – 0.064)	0.748	-0.008 (-0.062 – 0.047)	0.787	0.025 (-0.062 – 0.113)	0.574	0.034 (-0.049 – 0.116)	0.420
Male sex	0.108 (-1.015 – 1.232)	0.850	-0.061 (-0.792 – 0.669)	0.869	-1.561 (-2.968 – -0.153)	0.030	-1.823 (-3.093 – -0.552)	0.005
Years since diagnosis: Male sex	0.110 (-0.037 – 0.257)	0.143	-0.159 (-0.272 – -0.046)	0.006*	-0.031 (-0.211 – 0.149)	0.733	0.130 (-0.038 – 0.297)	0.129
Random effects								
σ^2	9.39		1006.93		14.58		13.71	
τ_{00}	24.83 $_{ND}$		1711.10 $_{ND}$		40.99 $_{ND}$		31.43 ND	
τ_{11}	0.19 $_{ND.disease\_duration}$		2.40 $_{ND.disease\_duration}$		0.33 $_{ND.disease\_duration}$		0.29 $_{ND.disease\_duration}$	
ρ_{01}	-0.34 $_{ND}$		1.00 $_{ND}$		-0.54 $_{ND}$		-0.45 ND	
ICC	0.75		0.72		0.72		0.72	
N	739 $_{ND}$		633 $_{ND}$		738 $_{ND}$		751 ND	
Observations	2623		1664		2519		2832	
Marginal R^2 / Conditional R^2	0.091 / 0.777		0.029 / 0.727		0.084 / 0.748		0.146 / 0.761	

Note * = nominally significant, Abbreviations: [a]Greater = Worse, [b] Greater = Better, B = fixed effect (95% CI), MoCA: Montreal Cognitive Assessment, SAS: Starkstein Apathy Scale, BDI-I: Beck Depression Inventory, MDS: Movement Disorders Society, UPDRS: Unified Parkinson's Disease Rating Scale), PDQ-39: Parkinson's Disease Questionnaire-39, PDSS: Parkinson's Disease Sleep Scale, RBDSQ: RBD Screening Questionnaire

	Sniffin' sticks[b]		PDQ-39 subscale bodily discomfort[a]		RBDSQ[a]		PDSS[b]	
	B (CI 95%)	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**
	9.353 (8.831 – 9.875)	<0.001	34.586 (30.675 – 38.497)	<0.001	3.629 (3.104 – 4.154)	<0.001	105.934 (102.021 – 109.846)	<0.001
	-0.119 (-0.171 – -0.066)	<0.001	1.141 (0.521 – 1.761)	<0.001	0.085 (0.023 – 0.147)	0.007	-0.668 (-1.086 – -0.251)	0.002
	-	-	-0.037 (-0.063 – -0.010)	0.007	-	-	-	-
	0.008 (-0.032 – 0.047)	0.708	-0.075 (-0.357 – 0.208)	0.605	0.046 (0.005 – 0.088)	0.029	-0.103 (-0.397 – 0.191)	0.492
	-1.276 (-1.898 – -0.655)	<0.001	-9.125 (-13.518 – -4.732)	<0.001	0.303 (-0.320 – 0.925)	0.340	7.039 (2.391 – 11.687)	0.003
	0.013 (-0.053 – 0.078)	0.706	0.148 (-0.354 – 0.650)	0.562	0.045 (-0.031 – 0.121)	0.245	-0.716 (-1.229 – -0.203)	0.006*
	3.23		182.41		2.52		203.06	
	7.62_{ND}		366.48_{ND}		8.33_{ND}		417.36_{ND}	
	$0.01_{ND.disease\_duration}$		$0.90_{ND.disease\_duration}$		$0.05_{ND.disease\_duration}$		$0.91_{ND.disease\_duration}$	
	-0.57_{ND}		-0.35_{ND}		-0.43_{ND}		-0.45_{ND}	
	0.66		0.66		0.77		0.64	
	718_{ND}		746_{ND}		736_{ND}		741_{ND}	
	2319		2669		2590		2617	
	0.059 / 0.680		0.045 / 0.670		0.045 / 0.777		0.068 / 0.667	

Table 5 Fixed effects of motor symptoms in men and women and the interaction of sex with progression

	FMCS[b]		MDS-UPDRS II[a]		MDS-UPDRS III[a]		MDS-UPDRS IV[a]	
Independent variables	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**
Intercept	83.082 (79.747 – 86.417)	<0.001	7.269 (6.090 – 8.448)	<0.001	26.671 (24.355 – 28.987)	<0.001	0.054 (-0.321 – 0.429)	0.776
Years since diagnosis	-1.943 (-2.450 – -1.435)	<0.001	0.607 (0.370 – 0.844)	<0.001	1.072 (0.743 – 1.401)	<0.001	0.383 (0.287 – 0.479)	<0.001
Years since diagnosis^2			0.022 (0.012 – 0.032)	<0.001			-0.009 (-0.014 – -0.004)	<0.001
Time to diagnosis	-0.060 (-0.345 – 0.224)	0.676	0.043 (-0.056 – 0.143)	0.394	0.147 (-0.032 – 0.327)	0.107	-0.000 (-0.025 – 0.025)	0.998
Male sex	4.720 (0.777 – 8.663)	0.019	-0.957 (-2.277 – 0.362)	0.155	2.910 (0.174 – 5.645)	0.037	-0.260 (-0.665 – 0.146)	0.209
Years since diagnosis:Male sex	-0.597 (-1.217 – 0.023)	0.059	0.346 (0.120 – 0.572)	0.003**	0.197 (-0.206 – 0.600)	0.338	-0.018 (-0.101 – 0.065)	0.668
Random effects								
σ^2	81.89		14.35		84.54		4.93	
τ_{00}	341.79 $_{ND}$		30.49 $_{ND}$		111.92 $_{ND}$		0.00 $_{ND}$	
τ_{11}	6.42 $_{ND.disease\_duration}$		0.78 $_{ND.disease\_duration}$		1.36 $_{ND.disease\_duration}$		0.08 $_{ND.disease\_duration}$	
ρ_{01}	-0.38 $_{ND}$		-0.10 $_{ND}$		-0.24 $_{ND}$			
ICC	0.88		0.85		0.67			
N	742 $_{ND}$		755 $_{ND}$		753 $_{ND}$		753 $_{ND}$	
Observations	2645		2877		2536		2904	
Marginal R^2 / Conditional R^2	0.190 / 0.900		0.346 / 0.904		0.145 / 0.717		0.182 / NA	

Note * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm), Abbreviations: [a]Greater = Worse, [b] Greater = Better, B = fixed effect (95% CI), FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, UPDRS: Unified Parkinson's Disease Rating Scale, PIGD: Postural Instabilities and Gait Disturbances MDT: Munich Dysphagia Test

	MDS-UPDRS PIGD score[a]		MDS-UPDRS based tremor scale[a]		MDT-PD[a]	
	B (CI 95%)	**p-values**	**B (CI 95%)**	**p-values**	**B (CI 95%)**	**p-values**
	2.400 (1.888 – 2.911)	<0.001	0.537 (0.464 – 0.609)	<0.001	6.379 (4.551 – 8.206)	<0.001
	0.121 (0.006 – 0.236)	0.039	-0.014 (-0.023 – -0.005)	0.002	0.730 (0.481 – 0.978)	<0.001
	0.017 (0.012 – 0.022)	<0.001				
	0.008 (-0.034 – 0.051)	0.695	0.007 (0.001 – 0.012)	0.019	0.110 (-0.030 – 0.249)	0.124
	-0.718 (-1.287 – -0.149)	0.013	0.056 (-0.029 – 0.142)	0.196	-0.472 (-2.625 – 1.681)	0.667
	0.133 (0.025 – 0.241)	0.016*	0.004 (-0.007 – 0.015)	0.467	0.014 (-0.289 – 0.318)	0.927
	3.23		0.07		28.92	
	4.25_{ND}		0.14_{ND}		66.95_{ND}	
	$0.16_{ND.disease\_duration}$		$0.00_{ND.disease\_duration}$		$0.74_{ND.disease\_duration}$	
	0.05_{ND}		-0.38_{ND}		-0.23_{ND}	
	0.83		0.68		0.78	
	751_{ND}		753_{ND}		675_{ND}	
	2500		2503		2077	
	0.335 / 0.889		0.034 / 0.691		0.107 / 0.800	

Women overall demonstrated a slower progression than men. More specifically, men had a significantly faster progression in global cognition (MoCA) (-0.159, 95%CI: -0.272, -0.046, p = 0.006, Tab. 4), quality of sleep (PDSS) (-0.716, 95%CI: -1.229, -0.203, p = 0.006, Tab. 4) and postural instabilities and gait disturbance (MDS-based PIGD score) (0.133, 95%CI: 0.025, 0.241, p = 0.016, Tab. 5) on an unadjusted significance level and in patient-reported motor symptoms (MDS-UPDRS II) (0.346, 95%CI: 0.120, 0.572, p = 0.003, Tab. 5). The findings for patient-reported motor symptoms were significant after adjustment for FWER 5%. After controlling for age, the p-values for the interaction effect decreased from 0.006 to 0.004 while we did not identify any statistically significant differences for age, years since diagnosis or time to diagnosis at baseline between men and women with typical PD. Finally, the frequency of missing data at follow-up in women was not significantly higher than in men.

DISCUSSION

The present study described and illustrated the progression of motor- and non-motor symptoms in men and women with typical PD. Both men and women showed a progression (i.e., deterioration) in all symptoms except tremors. Comparing symptoms progression between men and women, women experienced a slower progression in cognition (MoCA), quality of sleep (PDSS), postural instabilities and gait disturbances (MDS-UPDRS based PIGD score) and patient-reported motor symptoms (MDS-UPDRS II). Finally, we observed similar trajectories for patient-reported outcomes compared to clinician-assessed outcomes in both men and women.

Non-motor symptoms

Previous reviews (Subramanian et al., 2022, Post et al., 2007, Marras et al., 2002) discussed the heterogeneous findings of sex-specific progression of PD. According to our findings, women tended to have a generally slower disease progression than men. However, in our study, women had worse bodily discomfort at baseline similarly to previous findings (Silverdale et al., 2018, Beiske et al., 2009, Martinez-Martin et al., 2012, Abraham et al., 2023). This may be due to different symptom expressions, such as the restless legs syndrome being more common and severe in women (Martinez-Martin et al., 2012), while this sex-specific effect modification was not identified in the longitudinal data. Similarly, in women, depression (BDI-I) was worse at baseline while no sex-specific effect modification was identified in the longitudinal data, similar to previous research (Picillo et al., 2022).

Our study confirmed that although they had similar scores at baseline, women were less likely to decline in cognitive performance (MoCA) over time (Iwaki et al., 2021). Moreover, we observed a similar progression of apathy (SAS), a feature of PD dementia (Emre et al., 2007). Finally, while women had a worse quality of sleep (PDSS) at baseline, we detected a faster progression in men compared to women.

Motor symptoms

Our results support previous longitudinal findings (Picillo et al., 2022, Iwaki et al., 2021) of women having higher disability scores at baseline, but men progressing faster. We did not detect any differences in the motor complications (MDS-UPDRS IV) while in women the mg/kg LEDD dose was significantly higher compared to men at baseline. Our results also confirm previous findings (Colombo et al., 2015) that the PIGD dominant phenotype is more frequent in women. However, we can not confirm previous findings (Kelly et al., 2015) describing impairments in global cognition were associated with more severe PIGD symptoms, as despite the more frequent PIGD dominant phenotype at baseline, women had slower cognitive decline (MoCA). As only half of the phenotypes remain stable over three years (Kohat et al., 2021) and postural instabilities and gait disturbances (PIGD) progressed slower in women, this finding needs to be further explored. Finally, while the sex-specific effect modification was not significant for the clinician-assessed motor symptoms (MDS-UPDRS III), we found a significant sex-specific effect modification for patient-reported motor symptoms (MDS-UPDRS II). This suggests, the clinical assessment of motor symptoms being less sensible to changes over time compared to the patient-reported measure.

Strengths and limitation

This study has some strengths and limitations. For instance, we enhanced the generalizability of our findings by analysing data of all participants of the Luxembourg Parkinson's study including people with PD or PDD from Luxembourg and the Greater Region, who were treated and lived in varying settings and environments. More specifically, the range of people with PD was broad, including men and women from 22 to 92 years with 1 to 30 years of education, living from 0 to 32 years with the disease and speaking different languages. 68.7% of the people with PD were in disease stages H&Y 1 – 2, the disease stages ranged from H&Y 1 to H&Y 5. Recruitment started in 2015 when the estimated prevalence of PD in Luxembourg was 565 – 1356 (Hipp et al., 2018, Pavelka et al., 2023). As 486 of the participants lived in Luxembourg, we might have captured 35.8 to 86.0% of the people with PD living in Luxembourg.

Moreover, we used advanced statistical methodology to estimate changes over time in our longitudinal dataset with mixed models taking into account correlations of the observations. Although our analysis is observational, our longitudinal study provided a comprehensive description of the individual progression of symptoms in Parkinson's disease while previous studies were mainly cross-sectional analyses with some exceptions (Urso et al., 2022, Picillo et al., 2022, Cholerton et al., 2018, Buczak-Stec et al., 2018). The COVID-19 pandemic and deaths since baseline assessment (101, 12.6%) may have led to missing data. For the MDT score, we noted higher rates of missing values, as it was added later during the study explaining the nature of the missing values. Nevertheless, the analyses on this outcome should be considered exploratory. Despite the potential sampling bias for the analyses

involving the onsite test MDS-UPDRS III, the frequency of missing data at follow-up was similar in both groups. Data collection standards have been developed to minimise missing data and information bias.

Our research described the progression since the diagnosis and is more applicable to the progression in the first twenty years. Future research should use data of risk and prodromal cohorts to describe the biological progression before the diagnosis of PD (Chahine et al., 2023). Moreover, the biological plausibility for the sex-specific progression in PD and the protective factors in women need to be further investigated. Sex-specific interventions to prevent cognitive decline (MoCA), progression of patient-reported motor symptoms (MDS-UPDRS II), quality of sleep (PDSS) and postural instabilities and gait disturbances (PIGD) in men need to be developed, while health-professionals should proactively monitor and offer interventions.

In conclusion, our study provided a comprehensive data-based description and illustration of the clinical progression of motor- and non-motor symptoms associated with Parkinson's disease for men and women. Moreover, the detailed interaction plots should aid interpretation by health professionals. Factors explaining the resilience in women with PD especially in global cognition, quality of sleep, patient-reported motor symptoms and postural instability and gait disturbances need to be explored further. To enhance well-being and personalised treatment in PD, we recommend considering a sex-specific approach to managing PD symptoms.

SUPPLEMENTAL MATERIAL

Table S1 Characteristics of the study participants at baseline (N = 802) incl. numbers of missing data for each variable of interest

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (Pct25-75)	Missing N (%)
Sociodemographic characteristics				
Age (y.)	67.1 (10.9)	22.0 – 92.9	68.2 (60.2 – 74.5)	1 (0.1%)
Female Sex	270 (33.7%)			0 (0.0%)
Years of Education	13.0 (4.1)	1.0 – 30.0	13.0 (10.0 - 16.0)	9 (1.1%)
Language most fluent				1 (0.1%)
French	227 (28.3%)			
German	129 (16.1%)			
Luxembourgish	345 (43.0%)			
Other	100 (12.5%)			
Marital status				5 (0.6%)
Single	44 (5.5%)			
Married / Partnered	606 (75.6%)			
Divorced / Bereaved	147 (18.3%)			
Health-related characteristics				
PD Diagnosis	707 (88.2%)			0 (0%)
Hoehn & Yahr (H&Y) Disease Stages				14 (1.7%)
H&Y 1	88 (11.0%)			
H&Y 1.5	69 (8.6%)			
H&Y 2	394 (49.1%)			
H&Y 2.5	105 (13.1%)			
H&Y 3	76 (9.5%)			
H&Y 4	40 (5.0%)			
H&Y 5	16 (2.0%)			
Disease Duration (y.)	5.0 (5.1)	0.0 – 32.3	3.2 (1.1 - 7.4)	54 (6.7%)
LEDD (mg.)	493.4 (400.4)	0.0 – 2062.0	400.0 (200.0 – 712.8)	24 (3.0%)
LEDD (mg./kg.)	7.3 (5.4)	0.0 – 36.9	5.8 (3.6 – 10.0)	34 (4.2%)
Time to Diagnosis (y.)	2.7 (5.1)	-1.0 – 46.0	1.0 (0.0 – 3.0)	30 (3.7%)
Weight (kg)	79.2 (16.4)	40.1 – 153.0	78.5 (67.7 – 89.4)	21 (2.6%)
Height (cm)	169.3 (9.7)	137.0 – 205.0	169.1 (162.2 – 176.2)	25 (3.1%)
Non-motor symptoms				
MoCA (0 – 30)b	24.6 (4.2)	5.0 – 30.0	25.0 (23.0 - 28.0)	22 (2.7%)
BDI-I (0 – 63)a	9.8 (7.3)	0.0 – 51.0	8.0 (5.0 - 14.0)	46 (5.7%)
SAS (0 - 42)a	14.0 (5.9)	1.0 – 36.0	13.0 (10.0 – 17.0)	54 (6.7%)
PDQ-39 (0 – 100)a	24.6 (17.3)	0.0 – 82.1	21.8 (10.9 – 34.6)	69 (8.6%)
MDT Score (3 - 103)[a]	8.7 (9.2)	0.0 – 56.0	6.0 (3.0 – 11.0)	375 (46.8%)
Sniffin' Sticks (0 - 16)[b]	8.1 (3.2)	1.0 – 16.0	8.0 (6.0 – 10.0)	60 (7.5%)
PDQ-39 Subscale Bodily Discomfort (0 – 100)[a]	33.2 (23.9)	0.0 – 100	33.3 (16.7 – 50.0)	44 (5.5%)
PDSS (0 - 150)[b]	105.4 (24.9)	17.0 – 150.0	108.4 (90.3 – 125.0)	59 (7.4%)
RBDSQ (0 - 13)[a]	4.5 (3.2)	0.0 – 13.0	4.0 (2.0 – 7.0)	64 (8.0%)
MDS-UPDRS I (0 – 52)[a]	10.4 (6.9)	0.0 – 39.0	9.0 (5.0 - 14.0)	33 (4.1%)

Table S1 Continued.

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (Pct25-75)	Missing N (%)
Motor symptoms				
MDS-UPDRS II (0 – 52)[a]	11.0 (8.4)	0.0 – 48.0	9.0 (5.0 - 15.0)	24 (3.0%)
MDS-UPDRS III (0 – 132)[a]	34.1 (16.7)	0.0 – 100.0	32.0 (22.0 - 44.0)	21 (2.6%)
MDS-UPDRS IV (0 – 24)[a]	1.6 (3.2)	0.0 – 16.0	0.0 (0.0 - 1.0)	17 (2.2%)
FMCS (0 – 100)[b]	74.6 (23.0)	0.0 – 100.0	81.2 (60.9 - 93.8)	46 (5.7%)
PIGD Score (0 – 20)[a]	3.5 (3.8)	0.0 – 20.0	2.0 (1.0 – 5.0)	25 (3.1%)
Tremor Scale (0 - 4)[a]	0.6 (0.4)	0.0 – 2.4	0.5 (0.3 – 0.8)	21 (2.6%)

Abbreviations [a] Greater = Worse, [b] Greater = Better

Table S2 Estimated marginal means (95%CI) 0, 10, 20, 30 and 40 years after diagnosis for patient-reported & clinician-assessed outcomes and performance tests

Patient-reported outcomes						
Y.	**Apathy** SAS (0 - 42)[a]		**Depression** BDI-I (0 – 63)[a]		**Dysphagia** MDT-PD (3 – 103)[a]	
	m	w	m	w	m	w
0	13.6 (12.9, 14.3)	13.5 (12.5, 14.4)	7.9 (7.0, 8.8)	9.5 (8.3, 10.7)	6.2 (5.0, 7.4)	6.7 (4.9, 8.5)
10	15.3 (14.7, 16.0)	14.1 (13.2, 15.0)	10.3 (9.6, 11.1)	12.4 (11.2, 13.2)	13.7 (12.4, 14.9)	14.0 (12.2, 15.8)
20	20.5 (18.8, 22.2)	18.2 (16.1, 20.3)	15.0 (12.9, 17.1)	17.2 (14.7, 19.7)	21.1 (18.3, 23.9)	21.3 (17.4, 25.2)
30	29.1 (24.8, 33.3)	25.7 (21.1, 30.3)	21.8 (16.5, 27.2)	24.3 (18.6, 30.0)	28.5 (24.1, 33.0)	28.6 (22.3, 34.9)
40	41.1 (32.7, 49.4)	36.6 (27.9, 45.2)	30.8 (20.3, 41.4)	33.6 (22.8, 44.5)	36.0 (29.8, 42.1)	35.9 (27.2, 44.6)
Y.	**Functional mobility** FMCS (0 – 100)[b]		**Non-motor symptoms** MDS-UPDRS I (0 – 52)[a]		**Patient-reported motor symptoms** MDS-UPDRS II (0 – 52)[a]	
	m	w	m	w	m	w
0	87.6 (85.4, 89.9)	82.9 (79.7, 86.1)	7.5 (6.8, 8.3)	9.4 (8.3, 10.4)	6.4 (5.6, 7.2)	7.4 (6.3, 8.5)
10	62.2 (59.5, 65.0)	63.5 (59.6, 67.4)	13.2 (12.5, 13.9)	13.7 (12.8, 14.7)	18.2 (17.1, 19.2)	15.7 (14.2, 17.2)
20	36.8 (30.9, 42.8)	44.1 (35.6, 52.5)	18.9 (17.4, 20.4)	18.1 (16.0, 20.2)	35.4 (31.6, 37.1)	28.4 (24.9, 31.9)
30	11.4 (2.0, 20.8)	24.6 (11.3, 38.0)	24.5 (22.1, 27.0)	22.5 (19.1, 25.9)	57.5 (48.6, 61.3)	45.5 (38.4, 52.6)
40	-14.0 (-26.9, -1.1)	5.2 (-13.1, 23.5)	30.2 (26.8, 33.6)	26.8 (22.1, 31.6)	84.6 (67.9, 92.1)	67.1 (54.4, 79.8)
Y.	**Bodily discomfort** PDQ-39 subscale bodily discomfort (0 - 100)[a]		**RBD** RBDSQ (0 – 13)[a]		**Quality of sleep** PDSS (0 – 150)[b]	
	m	w	m	w	m	w
0	25.3 (22.5, 28.0)	34.4 (30.6, 38.2)	4.1 (3.7, 4.4)	3.8 (3.3, 4.3)	114.0 (111.2, 116.9)	105.6 (101.8, 109.4)
10	34.5 (32.3, 36.7)	42.1 (39.1, 45.1)	5.4 (5.0, 5.7)	4.6 (4.2, 5.1)	98.1 (95.8, 100.3)	99.0 (96.0, 101.9)
20	36.4 (31.2, 41.6)	42.6 (36.1, 49.1)	6.7 (6.0, 7.4)	5.5 (4.5, 6.4)	88.3 (83.6, 93.1)	92.3 (86.2, 98.4)
30	31.0 (17.7, 44.4)	35.7 (21.2, 50.3)	8.0 (6.9, 9.1)	6.3 (4.8, 7.9)	84.8 (71.5, 98.1)	85.6 (75.6, 95.6)
40	18.3 (-8.6, 45.3)	21.5 (-6.3, 49.8)	9.3 (7.8, 10.8)	7.2 (5.0, 9.3)	87.5 (59.6, 115.5)	78.9 (64.9, 92.9)

Table S2 Continued.

Clinician-assessed outcomes and performance tests						
Y.	**Cognition** MoCA Score (0 – 30)[b]		**Clinician-Assessed motor symptoms** MDS-UPDRS III (0 – 132)[a]		**Motor complications** MDS-UPDRS IV (0 – 24)[a]	
	m	w	m	w	m	w
0	25.2 (24.8, 25.7)	25.3 (24.7, 25.9)	30.0 (28.5, 31.5)	27.1 (25.0, 28.9)	-0.2 (-0.5, 0.1)	0.1 (-0.3, 0.4)
10	22.9 (22.4, 23.4)	24.5 (23.8, 25.3)	42.7 (41.0, 44.4)	37.8 (35.5, 39.8)	2.5 (2.2, 2.9)	3.0 (2.5, 3.5)
20	18.1 (16.6, 19.5)	21.3 (19.6, 23.1)	55.4 (51.6, 59.1)	48.5 (43.7, 52.9)	3.4 (2.3, 4.5)	4.0 (2.7, 5.4)
30	10.7 (7.3, 14.2)	15.6 (11.8, 19.3)	68.1 (62.1, 74.0)	59.2 (51.7, 66.3)	2.4 (-0.4, 5.3)	3.2 (0.2, 6.3)
40	-	-	80.7 (72.5, 89.0)	70.0 (58.4, 81.6)	-	-
Y.	**Olfaction** Sniffin' Sticks (0 – 16)[b]		**Postural Instabilities and Gait Disturbances** MDS-UPDRS based PIGD score (0 - 20)[a]		**Tremor** MDS-UPDRS based tremor scale (0 – 4)[a]	
	m	w	m	w	m	w
0	8.1 (7.7, 8.5)	9.4 (8.9, 9.9)	1.8 (1.4, 2.1)	2.4 (1.9, 2.9)	0.6 (0.6, 0.7)	0.6 (0.5, 0.6)
10	7.0 (6.8, 7.3)	8.2 (7.8, 8.6)	6.0 (5.5, 6.5)	5.4 (4.6, 6.1)	0.5 (0.5, 0.6)	0.4 (0.4, 0.5)
20	6.0 (5.4, 6.5)	6.9 (6.3, 7.7)	14.3 (12.3, 15.1)	11.8 (10.0, 13.5)	0.4 (0.3, 0.5)	0.3 (0.1, 0.4)
30	4.9 (3.9, 5.8)	5.7 (4.6, 7.0)	26.5 (21.7, 28.1)	21.6 (18.1, 25.2)	0.3 (0.2, 0.5)	0.1 (-0.1, 0.3)
40	-	-	42.7 (33.4, 45.6)	34.9 (28.5, 41.3)	0.2 (-0.0, 0.4)	0.0 (-0.3, 0.3)

Note a Greater = Worse, b Greater = Better, Abbreviations: Y = years since diagnosis, Estimated marginal effects per outcome (95% CI), BDI-I: Beck Depression Inventory, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disturbances, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

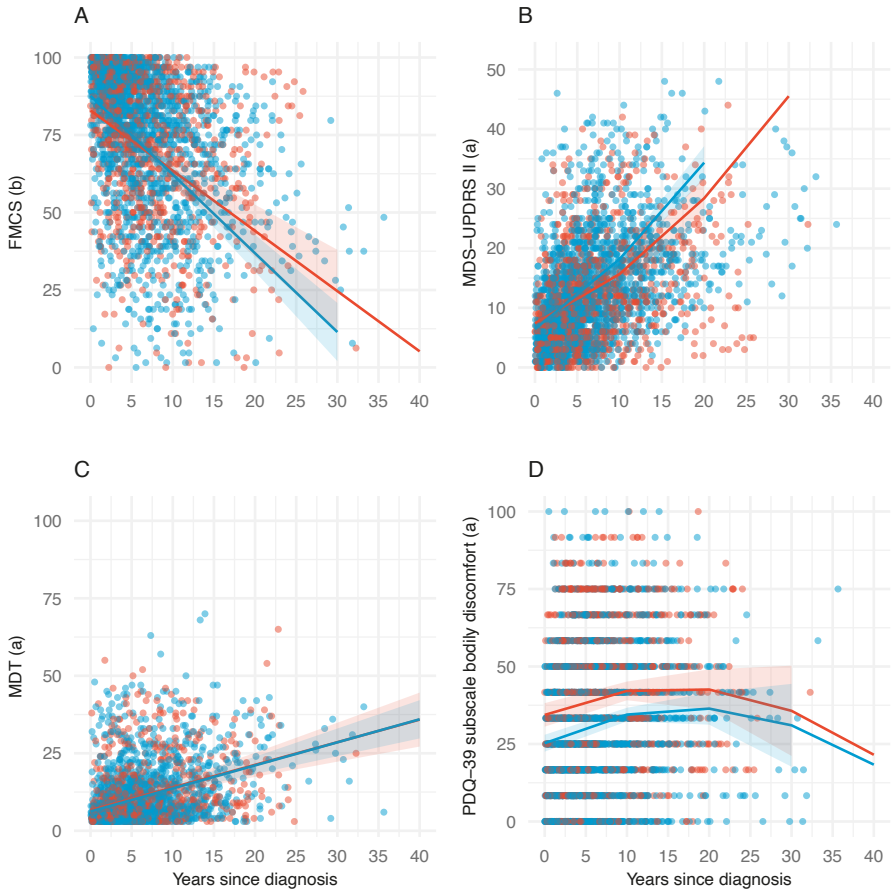

Figure S1 Progression of functional mobility (A), patient-reported motor symptoms (B), dysphagia (C) and pain (D), estimated marginal means (95% CI) 0 – 40 years after the diagnosis, a Greater = Worse, b Greater = Better, red = women, blue = men

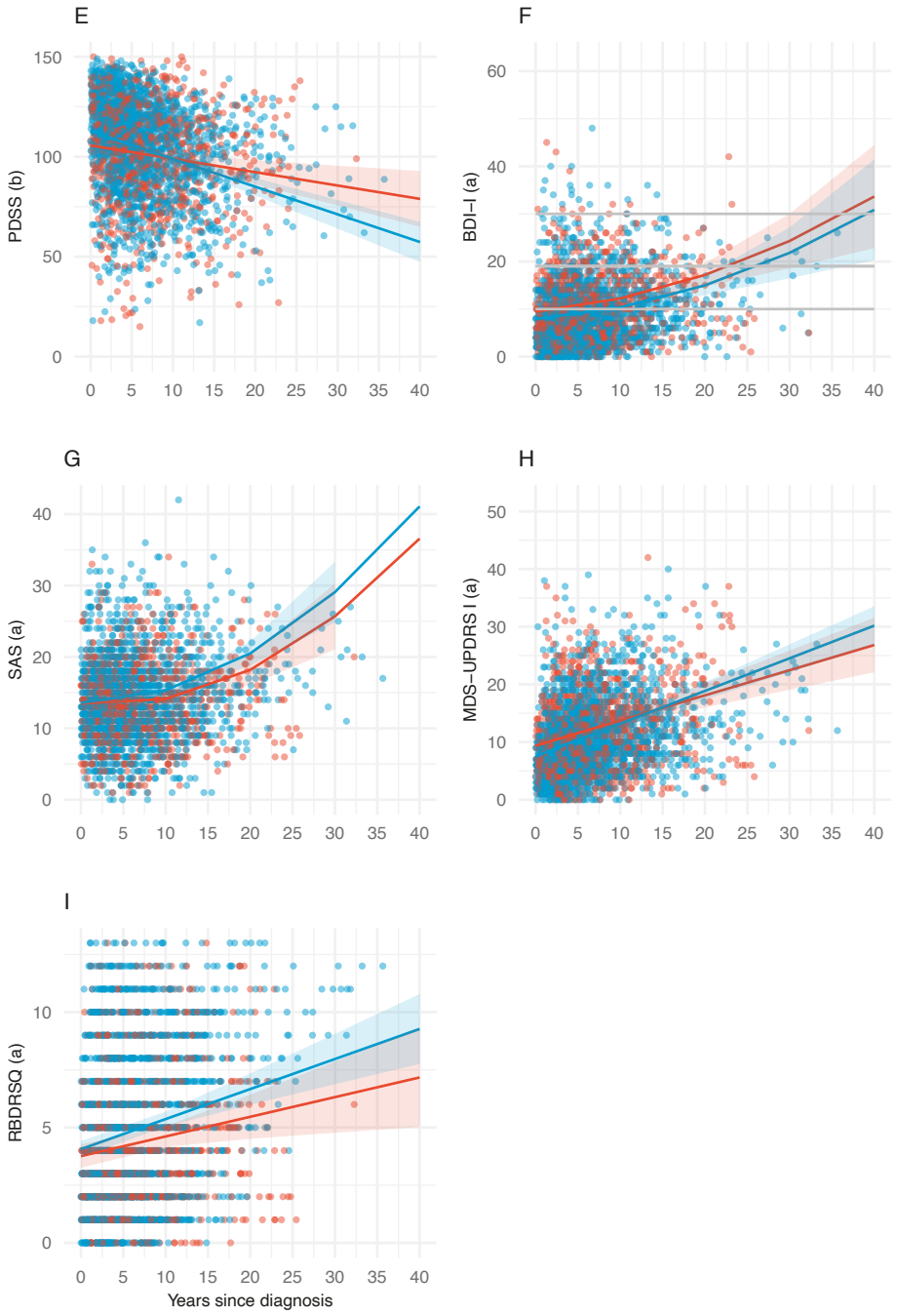

Figure S2 Progression of quality of sleep (E), depression (F), apathy (G), non-motor symptoms (H) and REM sleep behaviour disorder (I), estimated marginal means (95% CI) 0 – 40 years after the diagnosis, a Greater = Worse, b Greater = Better, Lines in panel F = Cutoff for mild (10 - 18), moderate (19 - 29) or severe (> 29) depression, red = women, blue = men

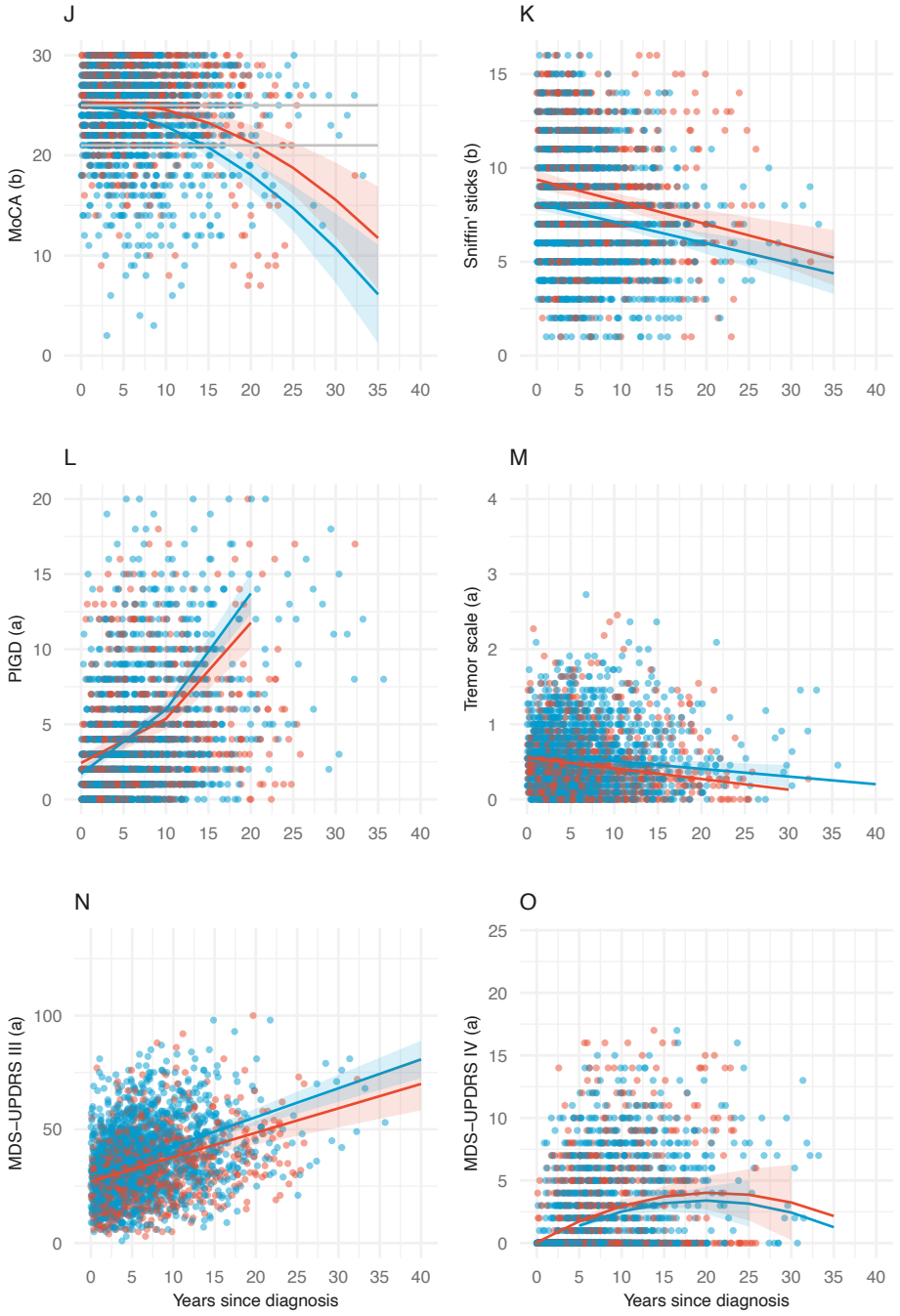

Figure S3 Progression of cognition (J), olfaction (K), postural instabilities and gait disturbances (L), tremor (M), clinician assessed motor symptoms (N) and motor complications (O), estimated marginal means (95% CI) 0 – 40 years after the diagnosis, a Greater = Worse, b Greater = Better, Lines in panel J = Cutoff for mild (21 - 25) and severe (< 21) cognitive impairment, red = women, blue = men

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CHAPTER 6

Progression of *GBA1* Gaucher-related and Parkinson's-risk variants: A longitudinal mixed model analysis

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ABSTRACT

BACKGROUND

Heterozygous variants in the gene glucocerebrosidase (*GBA1*) causing Gaucher's disease, a recessive lysosomal storage disorder, are involved in Parkinson's disease (PD) pathogenesis. An association of those Gaucher-related *GBA1* variants with the progression of non-motor symptoms in PD has been reported but the role of Parkinson's-risk (PD-risk) *GBA1* variants is less clear. Analysis of longitudinal changes in motor- and non-motor symptoms in carriers of the different *GBA1* variants compared to non-carriers could elucidate their pathogenic relevance.

OBJECTIVES

To compare progression of motor- and non-motor symptoms in people with PD carrying heterozygous Gaucher-related or PD-risk *GBA1* variants compared to non-carriers.

METHODS

We included longitudinal data of 733 individuals with typical PD. Next to non-carriers, we included 29 carriers of heterozygous Gaucher-related *GBA1* variants (22 and 7 carriers of severe and mild variants, respectively) and 47 carriers of heterozygous PD-risk *GBA1* variants. A two-level mixed model analysis examined interaction effects of carrying one of the three *GBA1* variants (PD-risk, mild or severe) compared to non-carriers with time since diagnosis to estimate gene-variant trajectories of motor- and non-motor symptoms.

RESULTS

Compared to non-carriers, at nominal 5% significance level, carrying PD-risk or Gaucher-related severe variants was associated with faster cognitive decline with standardized interaction effects of 0.291 (95%CI: 0.014, 0.567, p = 0.039) and 0.614 (95%CI: 0.193, 1.036, p = 0.040), respectively. Carrying PD-risk variants was associated with faster worsening of apathy (0.380, 95%CI: 0.115, 0.645, p = 0.005), quality of sleep (0.244, 95%CI: 0.017, 0.471, p = 0.035), tremor (0.258, 95%CI: 0.001, 0.515, p = 0.050), and non-motor symptoms (MDS-UPDRS I) (0.270, 95%CI: 0.014, 0.526, p = 0.039) compared to non-carriers, while we did not observe this tendency in people with Gaucher-related mild or severe variants. The findings were not significant after Bonferroni-adjustment for 15 outcomes and 3 variants. Finally, we observed an overall slower progression in non-motor symptoms in carriers of mild variants as compared to carriers of PD-risk or severe variants.

CONCLUSIONS

The study suggests associations of the PD-risk variants with a more rapid disease progression compared to non-carriers and thus, if findings are confirmed in an independent cohort, advocates for a reevaluation of their pathologic relevance.

BACKGROUND

The development of Parkinson's disease (PD) is mainly influenced by genetic and environmental factors (Simon et al., 2020). Variants in the glucocerebrosidase (*GBA1*) gene (*GBA1* [OMIM 606463]) can cause Gaucher's disease, a recessive lysosomal storage disorder, and lead to reduced activity of the lysosomal enzyme glucocerebrosidase (GCase), which, in turn, is linked to an increased alpha-synuclein aggregation involved in the pathogenesis of PD (Mazzulli et al., 2011, Sidransky and Lopez, 2012). While an association of these Gaucher-related *GBA1* variants with the progression of non-motor symptoms in PD has been reported (Gan-Or et al., 2015), the role of PD-risk *GBA1* variants is less clear (Goldstein et al., 2019, Menozzi and Schapira, 2021, Petrucci et al., 2020).

Based on the resulting pathogenicity for PD, the amino acid changes in the Gaucher-related *GBA1* variants can be classified as severe or mild, while the amino acid changes in the PD-risk *GBA1* variants can be considered as higher risk for PD (Höglinger et al., 2022). Regarding the Gaucher-related *GBA1* variants considered as severe, previous research suggested that people carrying these variants experienced an earlier onset and more severe motor, cognitive, olfactory, and psychiatric symptoms (Goldstein et al., 2019, Thaler et al., 2018, Liu et al., 2016). However, the progression of people with PD carrying the Gaucher-related *GBA1* variant p.N409S considered as mild remains unclear (Cilia et al., 2016, Menozzi and Schapira, 2021, Petrucci et al., 2020). The PD-risk variant p.E365K, is the most prevalent *GBA1* variant among people with PD in the Luxembourg Parkinson study (Pachchek et al., 2023). Moreover, these variants considered as PD-risk are associated with a higher risk for cognitive impairment (Straniero et al., 2020) and a lower risk for motor deterioration (Maple-Grodem et al., 2021) compared to non-carriers.

These findings emphasise the complexity of the relationship between *GBA1* and PD, and highlight the need for a better understanding of the mechanisms by which these variants contribute to PD (Goldstein et al., 2019). Thus, a description and analysis of longitudinal changes in motor- and non-motor symptoms in carriers of Gaucher-related *GBA1* variants and PD-risk *GBA1* variants compared to non-carries could elucidate their pathogenic relevance. Moreover, such comprehensive investigations of both motor and non-motor symptoms could help to estimate effect sizes for designing clinical trials for disease-modifying therapies. Hence, we aimed to compare the progression of motor- and non-motor symptoms in people with PD carrying heterozygous Gaucher-relatedand PD-risk *GBA1* variants compared to non-carriers using a large, single-center longitudinal cohort.

METHODS

Study design, setting, participants and study size

This retrospective analysis is part of the Luxembourg Parkinson's study, a nationwide, monocentric, observational, longitudinal-prospective and dynamic cohort (Hipp et al., 2018, Pavelka et al., 2023). The completed STROBE (Vandenbroucke et al., 2007) reporting guideline checklists are provided in Supplement 4. Our analysis includes participants diagnosed by a neurologist in the frame of the Luxembourg Parkinson's study with typical PD or PD with dementia (PDD) based on the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992). Participants resided either at home or in a nursing home within Luxembourg and the Greater Region (geographically proximate areas). Recruitment started in 2015 with subsequent annual follow-ups. The primary objective of the Luxembourg Parkinson's Study was to facilitate stratification and differential diagnosis of PD (Hipp et al., 2018, Pavelka et al., 2023).

Variables, data sources and measurement

The outcomes of interest were the progression (i.e., change per additional year of time since diagnosis) of fifteen motor and non-motor symptoms. Table 1 provides detailed information regarding the characteristics of these outcomes, their data sources and the assessment methods. All outcomes were numerical and evaluated during annual follow-ups, with variations of up to three months to minimize seasonal effects. As people with PD were enrolled at different time points (Twisk, 2013) due to the dynamic cohort study design, the progression could be distinguished from cohort or period effects. Only people with PD with data for time since diagnosis were included in the longitudinal analysis. We described differences in demographic and health-related characteristics at baseline between the three groups instead of controlling for confounders. We only included the time to diagnosis (years from the first motor symptoms to the diagnosis) to correct for delayed years since diagnosis.

Table 1 Instrument, assessment types and variable name of the included constructs

Construct intended to measure	Instrument	Assessment type	Details
Patient-reported outcomes			
Apathy	SAS (Starkstein et al., 1992)	PROM	Numerical score (0 – 42)
Depression	BDI-I (Beck et al., 1988)	PROM	Numerical score (0 – 63)
Dysphagia	MDT-PD (Buhmann et al., 2019, Simons et al., 2019)	PROM	Numerical score (3 – 103)
Functional mobility	FMCS (Hanff et al., 2023b)	PROM	Numerical score (0 - 100)
Non-motor symptoms	MDS-UPDRS I (Martinez-Martin et al., 2013)	Patient-Reported and Clinician Assessed Outcome Measure	Numerical score (0 – 52)
Motor symptoms	MDS-UPDRS II (Martinez-Martin et al., 2013)	PROM	Numerical score (0 - 52)

Table 1 Continued.

Construct intended to measure	Instrument	Assessment type	Details
Pain	PDQ-39 subscale bodily discomfort (Peto et al., 1995)	PROM	Numerical score (0 - 100)
Quality of sleep	PDSS (Chaudhuri et al., 2002)	PROM	Numerical score (0 – 150)
Rem-sleep behaviour disorders	RBDSQ (Stiasny-Kolster et al., 2007)	PROM	Numerical score (0 – 13)
Clinician-assessed outcomes or performance tests			
Global Cognition	MoCA Total Score (Nasreddine et al., 2005)	Performance test	Numerical score (0 – 30)
Motor symptoms	MDS-UPDRS III (Martinez-Martin et al., 2013)	Clinician-Assessed Outcome Measure	Numerical score (0 – 132)
Motor fluctuations	MDS-UPDRS IV (Martinez-Martin et al., 2013)	Clinician-Assessed Outcome Measure	Numerical score (0 – 24)
Olfaction	ODOFIN Sniffin' Sticks Identification Test 16	Performance test	Numerical score (0 – 16)
Postural instability and gait disorder	PIGD score (Stebbins et al., 2013, Jankovic et al., 1990)	Patient-Reported and Clinician Assessed Outcome Measure	Numerical score (0 – 20)
Tremor	Tremor scale (Forjaz et al., 2015, Jankovic et al., 1990)	Patient-Reported and Clinician Assessed Outcome Measure	Numerical score (0 – 4)
Exposure			
Time variant with baseline assessment and yearly follow-up	Time since diagnosis (y.): Date of assessment – Date of diagnosis	Interview	Numerical value
Covariates			
Time variant with baseline assessment and yearly follow-up	Time to diagnosis (y.): Date of diagnosis – Date of first motor symptoms	Interview	Numerical value
Moderators			
GBA1 variants	Name of the amino-acid changes	Genotyping	Variable with 13 categories
No of carrier of GBA1 variants in people with PD	Classification by Hoglinger et al. (2022)	Genotyping	Variable with 4 categories

Abbreviations PROM, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

DNA was extracted from peripheral blood samples. Samples underwent genotyping using the NeuroChip (Blauwendraat et al., 2017) and additional long-read PacBio sequencing targeting the *GBA1* locus (Pachchek et al., 2023). Variants in known PD-related genes were validated by Sanger sequencing for single nucleotide variants or Multiplex Ligation-dependent Probe Amplification (MLPA) for copy number variants (CNVs). Carriers of variants in other PD-related genes were excluded (Landoulsi et al., 2023, Pachchek et al., 2023). Table S1 in Supplement 1 shows the genotypes and amino acid changes for all individuals.

Out of 76 carriers of the most prevalent variant p.E365K, two were homozygous, and 74 heterozygous. Consequently, under the assumption of a dominant model we combined the heterozygous and the homozygous carriers. In total, we found twelve *GBA1* variants (PD-risk or Gaucher-related *GBA1* variants listed in Table 1). We rated the involvement of the variants in PD as risk, mild or severe according to the classification by Hogliner and colleagues (Höglinger et al., 2022). Thus, variants identified as pathogenic in Gaucher's disease but of undetermined severity were classified as mild (Odds ratio for developing PD ≤ 5) or severe (Odds ratio for developing PD = 10-15) (Straniero et al., 2020, Iwaki et al., 2019). Variants not considered pathogenic in Gaucher's disease but confirmed to increase the risk of PD (e.g., p.E365K and p.T408M) were classified as risk. Additionally, frameshift and nonsense *GBA1* variants were classified as severe. One variant, p.P161S, was not classified by Hogliner and colleagues (Höglinger et al., 2022). We annotated this variant as severe, because it was classified as pathogenic according to the American College of Medical Genetics and Genomics guidelines (Richards et al., 2015), as pathogenic for Gaucher's disease according to ClinVar (Landrum et al., 2014), and as a disease-causing mutation for Gaucher's disease according to the Human Gene Mutation Database (Human Gene Mutation Database (HGMD)). The other participants were considered as non-carriers of *GBA1* variant carriers. Table S2 describes the different variants and the classification by involvement in PD. Exonic or splice-site variants that are not mentioned in this article were subclassified as severe *GBA1* variants if they were annotated as pathogenic in the archive of reports of relationships among medically important variants and phenotypes (ClinVar, RRID:SCR_006169) (Landrum et al., 2014). In two cases, two nucleotide – protein changes were co-existing. Those indicated with an [a] or [b] in Table S2 were classified as a severe variant (Höglinger et al., 2022). Further details on genotyping, *GBA1* variant annotation and validation, as well as details on nomenclature and classification can be found in a study describing the original *GBA1* work (Landoulsi et al., 2023, Pachchek et al., 2023).

Statistical methods

Data analysis was carried out in R, version 4.3.2 (R Core Team, 2023). To analyse if being a carrier of *GBA1* variants considered as PD-risk, mild or severe is associated with a different effect of the time since diagnosis on motor- and non-motor symptoms, we created one interaction model per outcome and added a categorical variable of three groups of variants considered as PD-risk, mild or severe (reference group = non-carriers) as an interaction effect with the time since diagnosis on the outcome.

Consequently, we performed longitudinal two-level mixed model analyses (using the "lmer" function of the "lme4"-package (Bates et al., 2015)) using the maximum likelihood method with years since diagnosis as a fixed effect, a random intercept and a random slope for years since diagnosis on participant level. After adding the random intercept on subject-level we evaluated whether a random slope for time was necessary by performing a likelihood ratio

test (using the "anova"-function of the "lme4"-package[Bates et al., 2015], method = "lrt") to compare the model with and without a random slope for time (i.e., years since diagnosis). Finally, in addition to the linear fixed effect for time we tested a quadratic and a cubic function. We respected the hierarchy of effects by including main effects if including interaction effects. The estimates and their 95% confidence intervals (CI) for the interaction effect between time since diagnosis and the different *GBA1* variants describe the additional annual change (that occurred in the group of interest versus the reference group of non-carriers) in the fifteen outcomes. The modification of the effect of time since diagnosis on an outcome by the different *GBA1* variants was evaluated by the statistical significance of the interaction term (t-test) at a Bonferroni-adjusted significance level (alpha = 0.05/(15 outcomes*3 variants) = 0.001). Statistical significance and confidence intervals for the mixed models were obtained with the Kenward-Roger approximation for degrees of freedom. We emphasized the estimates and the uncertainty by explicitly discussing the lower and upper 95% confidence intervals. Thus, all p-values independent of the statistical significance will be reported (Amrhein et al., 2019). We calculated estimated marginal means (using "ggpredict"-function of the "ggeffects"-package (Lüdecke, 2018)), summarised the interaction coefficients and illustrated the interactions (using "plot_model"-function of package sjPlot (Lüdecke, 2022)).

Finally, the Kruskal-Wallis Rank Sum Test compared the frequency of the apolipoprotein E (APOE) ε4 between the *GBA1* variants considered as PD-risk, mild or severe and non-carriers (using the "stats" package (R Core Team, 2023)) at the nominal 5% level (p-value ≤ 0.05) as the role of APOE as genetic modifier of cognitive trajectories in *GBA1* carriers is largely unexplored (Koros et al., 2022). APOE genotypes were determined using NeuroChip array data (rs429358, rs7412) that distinguish the ε2, ε3, and ε4 alleles classifying the respective APOE carriers. The NeuroChip provides high accuracy of 98.1% for genotyping of APOE ε4 (Blauwendraat et al., 2017).

RESULTS

Table 2 summarizes key study characteristics to understand the potential applicability, and thus generalizability of the findings. As illustrated in the flowchart (Figure S1) in Supplement 2, until the date of data export (2024-01-31) 990 people with Parkinsonism participated in the Luxembourg Parkinson's Study. After the exclusion of people with atypical PD, without genetic testing or with other pathogenic PD-related variants, we included 733 people with typical PD with a baseline assessment between 2015-03-04 and 2024-01-29. Table S3 in Supplement 1 provides a description of the 733 study participants and missing data. 488 people with typical PD (66.6 %) were men. In the overall cohort at the first assessment, the median age was 68.2 years (IQR 14.5 y), and the median time since diagnosis was 3.2 y (IQR 6.3 y). The average number of visits per patient was 3.0 (IQR 3.0) and ranged from 1 to 8,

and 406 patients (55.4%) had 3 or more follow-up visits. The median MDS-UPDRS III score was 32.0 (IQR 22.0), and the median Hoehn & Yahr stage was 2.0 (IQR 0.5).

Table 3 describes the baseline characteristics of non-carriers and carriers of variants considered as PD-risk, mild or severe. We included 29 heterozygous carriers of Gaucher-related *GBA1* variants (22 and 7 carriers of severe and mild variants, respectively) and 47 carriers of heterozygous PD-risk *GBA1* variants while 657 people carried no *GBA1*-variant. In the carriers of the variants considered as severe we identified a significantly lower frequency of APOE ε4 (4.5%, p = 0.039) compared to the non-carriers (20.8%). Also, the carriers of severe variants had a longer time since diagnosis (7.2 y) compared to the non-carriers and carriers of risk variants (3.7 y), while the time since diagnosis was shortest in carriers of mild variants (0.9 y).

Table 2 Key characteristics

Sample size	733	
Data collection period	2015-03-04 – 2024-01-29	
Study design	Cohort	
Setting	People with typical PD living at home or in a nursing home in Luxembourg and the Greater Region	
Inclusion criteria	People with typical PD and PDD	
Outcomes Concept (Measure)	Apathy (SAS), depression (BDI-I), functional mobility (FMCS), LEDD (mg/kg), non-motor symptoms (MDS-UPDRS I), patient-reported motor symptoms (MDS-UPDRS II), clinician-assessed motor symptoms (MDS-UPDRS III), motor complications (MDS-UPDRS IV), dysphagia (MDT-PD), global cognition (MoCA), olfaction (Sniffin' Sticks), bodily discomfort (PDQ-39 subscale bodily discomfort), health-related quality of life (PDQ-39), quality of sleep (PDSS), postural instabilities and gait disturbances (MDS-based PIGD), REM sleep behaviour disorder (RBDSQ), tremor (MDS-based tremor scale)	
Gender	488 (66.6%) male 245 (33.4%) female	
Age	68.2 (IQR 14.5)	
Disease stage	2.0 (IQR 0.5)	
No. of Carrier of GBA1 variants stratified by involvement in PD	No GBA1 variant	657 (89.6%)
	PD-Risk p.E365K, p.T408M	47 (6.4%)
	Mild p.N409S	7 (1.0%)
	Severe p.F252I, p.G234W, p.G241R, p.G416S, p.L483P, p.P161S, p.R398X, p.R502H, c.115+1G>A	22 (3.0%)
Determinants	Time since diagnosis, time to diagnosis	

Note. Categorical variables: counts (%), numerical variables: Median (IQR)
Abbreviations: BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Table 3 Baseline characteristics of non-carriers and carriers of variants considered as PD-risk, mild or severe

Variables	Non-carriers (N = 657)	PD-risk variants (N = 47)	Mild variants (N = 7)	Severe variants (N = 22)
Sociodemographic characteristics				
Age (y)	68.2 (14.6)	68.8 (11.4)	75.2 (17.1)	63.9 (16.7)
Male sex	442 (64.2%)	28 (59.6%)	5 (71.4%)	13 (59.1%)
Years of education	13.0 (6.0)	12.0 (4.0)	15.0 (4.0)	14.0 (6.2)
Health-related characteristics				
Time since diagnosis (y)	3.2 (6.2)	3.7 (4.4)	0.9 (2.5)	7.2 (7.6)
Age at diagnosis (y)	63.0 (17.0)	63.0 (11.5)	73.0 (18.0)	57.0 (19.0)
Age at onset of motor symptoms (y)	61.0 (17.5)	59.0 (11.8)	70.0 (18.0)	56.5 (22.0)
Time to diagnosis (y)	1.0 (3.0)	2.0 (4.0)	1.0 (1.5)	1.0 (2.0)
APOE ε4 (ε2/ε4, ε3/ε4, ε4/ε4)	136 (20.7%)	6 (12.8%)	1 (14.3%)	1 (4.5%)
MDS-UPDRS I	9.0 (9.0)	8.0 (8.0)	9.0 (3.5)	16.0 (10.0)
MDS-UPDRS II	9.0 (11.0)	11.0 (9.5)	9.0 (9.0)	11.0 (7.0)
MDS-UPDRS III	32.0 (23.0)	28.5 (16.2)	30.0 (17.5)	32.0 (25.0)
MDS-UPDRS VI	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (4.8)

Note Categorical variables: counts (%), numerical variables: median (IQR), Time to diagnosis = Date of diagnosis – Date of first motor symptoms, y. = years, PDD: PD Dementia, APOE: Apolipoprotein E

While many outcomes showed a linear trajectory, this was not the case for apathy (SAS), global cognition (MoCA), bodily discomfort (PDQ-39 subscale bodily discomfort), patient-reported motor symptoms (MDS-UPDRS III), motor complications (MDS-UPDRS IV) and postural instability and gait disturbances (MDS-UPDRS based PIGD score) where adding the quadratic effect significantly improved the fit.

In Supplement 3 we describe the association of the different variants with progression of motor and non-motor symptoms. We illustrate the association of the different variants considered as PD-risk, mild or severe with progression in non-motor symptoms in the forest plot in Figure 1, while we illustrate the association with motor symptoms in Figure S2 in Supplement 2. Although, after Bonferroni-adjusted significance levels (alpha = 0.05/(15 outcomes*3 variants) = 0.001) the findings did not remain significant, on an unadjusted significance level (alpha = 0.05), the PD-risk variants (47 individuals carrying PD-risk variants) were associated with a faster progression compared to non-carriers, specifically change per year since diagnosis, in apathy (SAS), global cognition (MoCA), quality of sleep (PDSS), tremor (MDS-UPDRS based tremor scale) and non-motor symptoms (MDS-UPDRS I). The mild variants (seven individuals carrying mild variants) were associated with a slower progression compared to non-carriers in olfaction (Sniffin' sticks), while this was not the case for the PD-risk variants or severe variants. Finally, the severe variants (22 individuals carrying severe variants) were associated only with a faster cognitive decline (MoCA) compared to non-carriers.

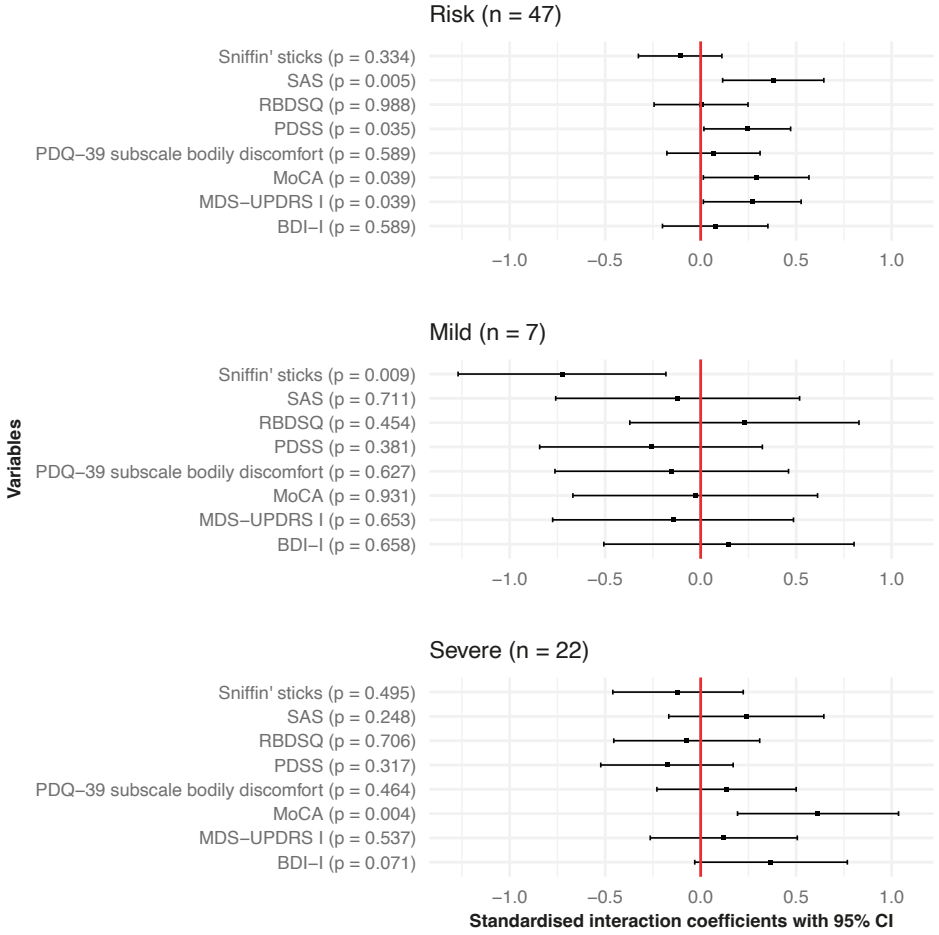


Figure 1 Association of variants considered as PD-risk, mild and severe variants with progression of non-motor symptoms (Interaction coefficients) **Note** Right side of the red line = associated with worse progression. Abbreviations: BDI-I: Beck Depression Inventory I, MDS: Movement Disorders Society, MoCA: Montreal Cognitive Assessment, PDQ-39: Parkinson's Disease Questionnaire-39, PDSS: Parkinson's Disease Sleep Scale, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

DISCUSSION

This study provides a comprehensive overview of the association of different types of *GBA1* variants with the progression of various symptoms in PD and explores the role of the PD-risk variant on disease progression. The findings were not significant after the conservative Bonferroni-adjustment, which could partially be explained by the high number of outcomes. As this is however a strength of our study and as we use longitudinal data, we discuss in the following paragraph the unadjusted significant results. Thus, those results need to be interpreted with caution until a validation of our findings is done in an independent cohort. First, carrying PD-risk or severe variants was associated with faster cognitive decline compared to non-carriers. Second, carrying PD-risk variants was associated with faster worsening of apathy, quality of sleep, tremor and non-motor symptoms (MDS-UPDRS I) compared to non-carriers, while we did not observe this tendency in people with Gaucher-related mild or severe variants. Finally, similarly to previous literature (Gan-Or et al., 2015), we observed a non-significant but general tendency for slower progression of non-motor symptoms (except RBD and depression) in carriers of mild variants as compared to non-carriers.

Association of different *GBA1* variant types with progression

Our findings suggest that PD-risk *GBA1* variants are associated with a more rapid worsening of non-motor symptoms and tremor, while we observed a general tendency for slower progression of carriers of mild, Gaucher-related variants (except RBD and depression). Specifically, we observed that, before Bonferroni adjustment, PD-risk and severe variants were associated with more pronounced cognitive decline. Additionally, carrying a *GBA1* variant considered as a PD-risk variant was associated with a faster worsening of apathy, while we did not observe this tendency in people with severe variants. Finally, although the confidence intervals were overlapping, the interaction effect of the *GBA1* variant and years since diagnosis on global cognition was stronger in people with variants considered as severe compared to people with PD-risk variants. Our results point in the same direction as previous research (Thaler et al., 2018) as we observed a non-significant tendency for faster progression of depression in people with severe variants while we did not observe this tendency in the more common PD-risk variant. The PD-risk variants were the only variants with evidence for an association with the progression of a motor symptom, i.e., tremor. Interestingly, the mild variants, while infrequent, were associated with slower progression (unadjusted significance) of olfaction, while this was not the case for the more frequent PD-risk and severe variants and thus advocates for a reevaluation of their pathologic relevance. At baseline and compared to non-carriers, we found a significantly lower frequency of APOE ε4 in carriers of a *GBA1* variant considered as severe. This was not the case in a previous study (Koros et al., 2022). However, as we observed a faster cognitive decline in carriers of severe *GBA1* variants compared to non-carriers, our results support the ongoing

discussion of *GBA1* as an independent driver of PD dementia linked to alpha-synuclein pathology (Kaivola et al., 2022).

Strengths and limitations

This study had several strengths and limitations. Notably, we enhanced the generalizability of our findings by analysing data of all participants of the Luxembourg Parkinson's Study including people with PD or PDD from Luxembourg and the Greater Region, who were treated and lived in varying settings and environments. More specifically, the demographic range included people with PD aged 32 to 93 years with years since diagnosis ranging from 0 to 32 years. A significant proportion (68.3%) of the people with PD were in disease stages H&Y 1 – 2, with disease stages ranging from H&Y 1 to H&Y 5.

In terms of methodology, we used advanced statistical techniques to estimate changes over time to provide a comprehensive description of symptom progression in carriers of a different *GBA1* variants compared to non-carriers. Our study encountered some limitations, including higher rates of missing values for the MDT score, likely due to its later inclusion in the study. Thus, the analyses on this outcome should be considered exploratory. Despite the potential sampling bias for the analyses involving the MDS-UPDRS III on-site test, the frequency of missing data at follow-up was similar in carriers and non-carriers. We assumed data missing at random (MAR) which can be handled by mixed models without requiring imputation (Twisk et al., 2013). To further minimise missing data and information bias we established data collection standards. Questionnaires were sent to the patients prior to their visit, allowing them to complete them at home at their convenience. In case a participant could not attend follow-up visits, neither at the centre nor by the mobile recruitment team, we offered a standardized telephone questionnaire with a reduced assessment.

As the classification of *GBA1* variants, in particular those of unknown significance, is still under discussion and as the numbers of the different variant types considered as PD-risk, mild or severe are still limited, our results provide hypotheses for future larger research projects, e.g. the monogenic GP-2 project (Lange et al., 2023).

Our research described the progression since the diagnosis. Future research should use data of risk and prodromal cohorts to describe the biological progression before the diagnosis of PD (Chahine et al., 2023). Thus, as we focussed on the progression of clinical symptoms, future research should also evaluate the biological progression by analysing a larger sample size of people with variants considered as PD-risk, mild or severe with a follow-up since the detection of an abnormal α-synuclein seed amplification assay (SAA), as the disease already biologically progressed before the manifestation of clinical symptoms (Chahine et al., 2023). As we used the MoCA score, a tool primarily developed and validated to screen for Mild Cognitive Impairment (Nasreddine et al., 2005), future research should

measure cognitive decline with a longitudinal detailed cognitive assessment including visuo-spatial functions to further differentiate progression of diverse cognitive sub-domains in people with and without *GBA1*. Furthermore, additional analyses of the interaction of APOE ε4 with faster cognitive decline in carriers of severe *GBA1* variants combined with longitudinal neuropsychological testing could shed more light on the role of the APOE ε4 allele and *GBA1* variants in cognitive decline and the different cognitive profiles in people with PD (Koros et al., 2022, Kaivola et al., 2022, Pu et al., 2022, Federoff et al., 2012, Mengel et al., 2016, Pavelka et al., 2022a, Pillai et al., 2021).

In conclusion, our study provides a comprehensive overview of the association of different *GBA1* variant types with the progression of motor- and non-motor symptoms based on longitudinal data. The detailed figures illustrating the progression should facilitate the interpretation of the symptoms' progression in people with the different *GBA1*-variants by health professionals. Our study helps to clarify the association of the PD-risk variants with disease progression and our results highlight the importance of including PD-risk variants in comprehensive research projects as we could not confirm previous results (Huh et al., 2020, Thaler et al., 2018, Omer et al., 2022) reporting non-motor symptoms progressing mainly in people with Gaucher-related *GBA1* variants. As the progression of mild and severe variants appears to be different, we recommend that they be studied separately (Thaler et al., 2018). Future research should test our nominally significant findings to further elucidate the pathogenic relevance of variants considered as PD-risk, mild or severe in men and women with Parkinson's disease.

SUPPLEMENTARY MATERIAL

Table S1 Variants in the GBA1 gene detected in PD patients stratified by allele

Variant	Homo-zygote wildtype/reference	Heterozygote (n = 74)	Homozygote (n = 2)
PD-risk			
p.T408M	713	18	0
p.E365K	700	28	[a]2
Total	682	46	2
Mild			
p.N409S	722	8	0
Severe			
p.G234W	729	1	0
p.G241R	728	2	0
p.G416S	729	1	0
p.L483P	718	12	0
p.P161S	728	2	0
p.R398X	729	1	0
p.R502H	729	1	0
p.F252I	729	1	0
c.115+1G>A	729	1	0
Total	708	22	0

Note [a]As we found only 2 people with PD with homozygous p.E365K variants, we assumed a dominant model and combined individuals with heterozygous and homozygous variants into a variable.

Table S2 Variants in the GBA1 gene detected in PD patients stratified by PD severity (Höglinger et al., 2022)

Markers	**PD-risk** (n = 47)	**Mild** (n = 7)	**Severe** (n = 22)
p.E365K	30	0	0
p.T408M	17[a]	0	0
p.N409S	0	7[b]	0
p.F252I	0	0	1
c.115+1G>A	0	0	1
p.G234W	0	0	1
p.G241R	0	0	2
p.G416S	0	0	1
p.L483P	0	0	12
p.P161S	0	0	2
p.R398X	0	0	1
p.R502H	0	0	1

Note [a] In one participant, the variant p.T408M (considered as PD-risk) were cooccured with p.F252I (severe). We allocated this participant to the group of people with a variant considered as severe as they are associated with a higher PD severity (Höglinger et al., 2022).
[b] In one participant variant p.N409S (considered as mild) were cooccuring p.L483P (severe). We allocated this participant to the group of people with a variant considered as severe as they are associated with a higher PD severity (Höglinger et al., 2022).

Table S3 Characteristics of the study participants at baseline (N = 733) incl. numbers of missing data for each variable of interest

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (Pct25-75)	Missing N (%)
Sociodemographic characteristics				
Age (y.)	67.2 (10.6)	31.6 – 92.9	68.2 (60.2 – 74.7)	0 (0%)
Male sex	488 (66.6%)			0 (0%)
Years of Education	13.0 (4.1)	1.0 – 30.0	13.0 (10.0 - 16.0)	4 (0.5%)
Language most fluent				0 (0%)
Luxembourgish	316 (43.3%)			
French	204 (28.0%)			
German	118 (16.2%)			
Other	91 (12.5%)			
Marital status				3 (0.4%)
Single	39 (5.3%)			
Married / Partnered	556 (75.9%)			
Divorced / Bereaved	135 (18.4%)			
Health-related characteristics				
Diagnosis				0 (0%)
Typical PD	649 (88.5%)			
PDD	84 (11.5%)			
Pathogenic *GBA1* carrier				0 (0%)
No	657 (89.6%)			
Yes	76 (10.4%)			
Pathogenic *GBA1* variants				0 (0%)
PD-Risk	47 (61.8%)			
Mild	7 (9.2%)			
Severe	22 (28.9%)			
Polygenic Risk Score	0.2 (1.0)	-2.3 – 3.3	0.2 (-0.4 – 0.9)	79 (10.8%)
APOE				79 (10.8%)
ε2/ε2	5 (0.7%)			
ε2/ε3	91 (12.4%)			
ε2/ε4	7 (9.6%)			
ε3/ε3	414 (56.5%)			
ε3/ε4	133 (18.2%)			
ε4/ε4	4 (0.6%)			
Hoehn and Yahr (H&Y) Disease Stages				16 (2.2%)
H&Y 1	76 (10.4%)			
H&Y 1.5	60 (8.2%)			
H&Y 2	362 (49.4%)			
H&Y 2.5	100 (13.6%)			
H&Y 3	69 (9.4%)			
H&Y 4	36 (4.9%)			
H&Y 5	14 (1.9%)			
Disease duration (y.)	4.9 (5.1)	0.0 – 32.3	3.2 (1.1 – 7.4)	48 (6.5%)
Age at diagnosis (y.)	62.6 (11.5)	30.0 – 91.0	63.0 (54.0 – 71.0)	8 (1.1%)

Table S3 Continued.

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (Pct25-75)	Missing N (%)
Age at onset of motor symptoms (y.)	59.7 (12.5)	17.0 – 88.0	61.0 (52.0 – 69.0)	19 (2.6%)
Time to diagnosis (y.)	2.7 (5.2)	-1.0 – 46.0	1.0 (0.0 – 3.0)	25 (3.4%)
LEDD (mg.)	491.3 (401.2)	0.0 – 2062.0	400.0 (200.0 – 700.0)	27 (3.7%)
PDQ-39 (0 – 100)[a]	24.5 (17.3)	0.0 – 82.1	21.2 (10.9 – 34.0)	59 (8.1%)
Non-motor symptoms				
MoCA (0 – 30)b	24.6 (4.3)	5.0 – 30.0	26.0 (23.0 – 28.0)	18 (2.5%)
SAS (0 – 42)a	14.0 (5.9)	1.0 – 16.0	13.0 (10.0 – 17.0)	43 (5.9%)
BDI-I (0 – 63)a	9.8 (7.3)	0.0 – 51.0	8.0 (4.8 – 14.0)	37 (5.0%)
Sniffin' sticks (0 - 16)b	8.1 (3.2)	1.0 – 16.0	8.0 (6.0 – 10.0)	49 (6.7%)
PDQ-39 subscale bodily discomfort (0 – 100)a	33.2 (23.9)	0.0 – 100	33.3 (16.7 – 50.0)	36 (4.9%)
PDSS (0 - 150)b	105.5 (24.8)	17.0 – 150.0	108.5 (90.5 – 125.0)	50 (6.8/%)
RBDSQ (0 - 13)a	4.6 (3.2)	0.0 – 13.0	4.0 (2.0 – 7.0)	52 (7.1%)
MDS-UPDRS I (0 – 52)a	10.4 (7.0)	0.0 – 39.0	9.0 (5.0 - 14.0)	25 (3.4%)
Motor symptoms				
MDS-UPDRS II (0 – 52)a	11.1 (8.4)	0.0 – 48.0	9.0 (5.0 - 15.0)	18 (2.5%)
MDS-UPDRS III (0 – 132)a	34.0 (16.8)	0.0 – 100.0	32.0 (22.0 - 44.0)	20 (2.7%)
MDS-UPDRS IV (0 – 24)a	1.5 (3.2)	0.0 – 16.0	0.0 (0.0 - 0.0)	13 (1.8%)
FMCS (0 – 100)b	74.8 (23.0)	1.6 – 100.0	81.2 (60.9 - 93.8)	40 (5.5%)
PIGD Score (0 – 20)a	3.5 (3.7)	0.0 – 20.0	2.0 (1.0 – 5.0)	19 (2.6%)
Tremor Scale (0 - 4)a	0.6 (0.5)	0.0 – 2.4	0.5 (0.3 – 0.8)	16 (2.2%)
MDT Score (3 - 103)a	8.9 (9.2)	0.0 – 56.0	6.0 (3.0 – 11.2)	345 (47.1%)

Note SD: Standard Deviation, IQR: Interquartilerange, Pct: percentile, y: year, Time to diagnosis = Date of diagnosis – Date of first motor symptoms, a higher = worse, b higher = better.
Abbreviations: BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Table S4 Fixed effects for the association of GBA1 variants with progression of non-motor symptoms

	SAS		MoCA		BDI-I		MDS-UPDRS I	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	-0.004 (-0.084 – 0.077)	0.924	0.106 (0.018 – 0.194)	0.018	0.065 (-0.008 – 0.138)	0.080	0.085 (0.014 – 0.156)	0.019
Disease duration (y.)	0.159 (0.090 – 0.227)	<0.001	0.286 (0.214 – 0.357)	<0.001	0.219 (0.151 – 0.288)	<0.001	0.366 (0.300 – 0.431)	<0.001
Time to diagnosis (y.)	-0.021 (-0.093 – 0.052)	0.577	0.005 (-0.066 – 0.077)	0.890	0.014 (-0.055 – 0.084)	0.689	0.013 (-0.056 – 0.082)	0.706
I(disease_duration^2)	0.084 (0.046 – 0.123)	<0.001	0.082 (0.043 – 0.121)	<0.001				
PD-Risk								
Disease duration: p.E365K (n = 30)	0.361 (0.020 – 0.702)	0.038	0.316 (-0.052 – 0.685)	0.092	0.229 (-0.130 – 0.588)	0.210	0.371 (0.046 – 0.696)	0.025
Disease duration: p.T408M (n = 17)	0.411 (0.001 – 0.822)	0.049	0.292 (-0.112 – 0.696)	0.157	-0.105 (-0.517 – 0.306)	0.615	0.111 (-0.292 – 0.515)	0.588
Mild								
Disease duration: p.N409S (n = 7)	-0.125 (-0.765 – 0.515)	0.701	-0.034 (-0.675 – 0.607)	0.917	0.129 (-0.520 – 0.779)	0.696	-0.147 (-0.777 – 0.484)	0.648
Severe								
Disease duration: p.F252I (n = 1)	-0.256 (-5.805 – 5.293)	0.928	-1.259 (-6.344 – 3.825)	0.627	5.598 (-0.062 – 11.259)	0.053	-1.147 (-4.610 – 2.316)	0.516
Disease duration: p.G234W (n = 1)	0.935 (-0.448 – 2.318)	0.185	1.555 (0.282 – 2.828)	0.017	0.602 (-0.717 – 1.922)	0.370	2.082 (0.790 – 3.375)	0.002
Disease duration: p.G241R (n = 2)	-0.662 (-1.669 – 0.346)	0.198	0.428 (-0.449 – 1.305)	0.337	-0.304 (-1.313 – 0.705)	0.554	-0.033 (-1.025 – 0.959)	0.948
Disease duration: p.G416S (n = 1)	0.908 (-1.046 – 2.861)	0.362	3.030 (1.187 – 4.872)	0.001	1.987 (-0.009 – 3.984)	0.051	2.378 (0.378 – 4.378)	0.020
Disease duration: p.L483P (n = 12)	0.599 (-0.040 – 1.237)	0.066	0.353 (-0.373 – 1.079)	0.340	0.772 (0.159 – 1.385)	0.014	-0.400 (-1.000 – 0.200)	0.191
Disease duration: p.P161S (n = 2)	2.431 (-2.152 – 7.014)	0.298	1.701 (-2.762 – 6.164)	0.455	0.956 (-3.556 – 5.468)	0.678	1.277 (-2.105 – 4.658)	0.459

Table S4 Continued.

	SAS		MoCA		BDI-I		MDS-UPDRS I	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Disease duration: p.R398X (n = 1)	-0.313 (-1.910 – 1.283)	0.700	-0.110 (-1.644 – 1.423)	0.888	-0.697 (-2.335 – 0.940)	0.403	2.144 (0.532 – 3.756)	0.009
Disease duration: p.R502H (n = 1)	0.263 (-2.263 – 2.789)	0.838	2.084 (-1.603 – 5.771)	0.268	1.068 (-1.510 – 3.646)	0.417	1.276 (-1.324 – 3.876)	0.336
Random effects								
σ^2	0.27		0.23		0.28		0.30	
τ_{00}	0.68_{ND}		0.86_{ND}		0.58_{ND}		0.58_{ND}	
τ_{11}	$0.15_{ND.disease\_duration}$		$0.18_{ND.disease\_duration}$		$0.17_{ND.disease\_duration}$		$0.14_{ND.disease\_duration}$	
ρ_{01}	0.26_{ND}		0.67_{ND}		0.11_{ND}		0.21_{ND}	
ICC	0.75		0.81		0.72		0.71	
N	683_{ND}		687_{ND}		683_{ND}		694_{ND}	
Observations	2562		2426		2456		2747	
Marginal R^2 / Conditional R^2	0.100 / 0.776		0.145 / 0.840		0.066 / 0.738		0.143 / 0.751	

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S4 Continued.

	PDQ-39 Subscale bodily discomfort		Sniffin' score		PDSS		RBDSQ	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	0.112 (0.036 – 0.188)	0.004	0.047 (-0.023 – 0.117)	0.189	0.057 (-0.012 – 0.126)	0.103	0.022 (-0.051 – 0.096)	0.549
Disease duration (y.)	0.165 (0.102 – 0.228)	<0.001	0.196 (0.140 – 0.253)	<0.001	0.227 (0.170 – 0.285)	<0.001	0.189 (0.125 – 0.253)	<0.001
Time to diagnosis (y.)	-0.016 (-0.084 – 0.053)	0.656	-0.027 (-0.097 – 0.042)	0.438	0.022 (-0.045 – 0.090)	0.515	0.077 (0.006 – 0.148)	0.034
I(disease_duration^2)	-0.058 (-0.093 – -0.023)	0.001						
PD-Risk								
Disease duration: p.E365K (n = 30)	0.033 (-0.269 – 0.335)	0.830	-0.266 (-0.536 – 0.004)	0.054	0.371 (0.085 – 0.656)	0.011	-0.062 (-0.378 – 0.254)	0.698
Disease duration: p.T408M (n = 17)	0.027 (-0.350 – 0.404)	0.889	0.175 (-0.179 – 0.529)	0.332	0.019 (-0.344 – 0.383)	0.917	0.089 (-0.294 – 0.472)	0.649
Mild								
Disease duration: p.N409S (n = 7)	-0.225 (-0.829 – 0.379)	0.465	-0.727 (-1.272 – -0.182)	0.009	-0.260 (-0.844 – 0.324)	0.383	0.228 (-0.375 – 0.831)	0.458
Severe								
Disease duration: p.F252I (n = 1)	-1.452 (-7.585 – 4.681)	0.643	-0.196 (-6.091 – 5.698)	0.948	-0.149 (-6.296 – 5.998)	0.962		
Disease duration: p.G234W (n = 1)	0.544 (-0.810 – 1.898)	0.431	-0.699 (-2.146 – 0.748)	0.343	1.090 (-0.240 – 2.420)	0.108	1.126 (-0.161 – 2.413)	0.086
Disease duration: p.G241R (n = 2)	0.780 (-0.167 – 1.726)	0.106	-0.907 (-1.832 – 0.018)	0.055	0.255 (-0.664 – 1.175)	0.586	0.071 (-0.871 – 1.013)	0.883
Disease duration: p.G416S (n = 1)	1.619 (-0.431 – 3.669)	0.121	-1.075 (-3.838 – 1.687)	0.445	0.144 (-1.896 – 2.185)	0.890	-0.929 (-2.746 – 0.887)	0.316
Disease duration: p.L483P (n = 12)	-0.178 (-0.746 – 0.390)	0.538	-0.159 (-0.785 – 0.467)	0.618	-0.736 (-1.355 – -0.118)	0.020	-0.366 (-0.966 – 0.235)	0.232
Disease duration: p.P161S (n = 2)	1.272 (-3.457 – 6.001)	0.598	-0.614 (-5.157 – 3.929)	0.791	2.339 (-2.319 – 6.998)	0.325	2.657 (-1.628 – 6.942)	0.224

Table S4 Continued.

	PDQ-39 Subscale bodily discomfort		Sniffin' score		PDSS		RBDSQ	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Disease duration: p.R398X (n = 1)	1.699 (0.082 – 3.316)	0.039	1.157 (-0.467 – 2.780)	0.163	-0.598 (-2.193 – 0.996)	0.462	-1.573 (-3.052 – -0.095)	0.037
Disease duration: p.R502H (n = 1)	-0.993 (-3.710 – 1.723)	0.473	-1.088 (-5.310 – 3.133)	0.613	-0.165 (-2.877 – 2.547)	0.905	-0.440 (-2.783 – 1.904)	0.713
Random effects								
σ^2	0.34		0.31		0.34		0.23	
τ_{00}	0.59_{ND}		0.57_{ND}		0.55_{ND}		0.63_{ND}	
τ_{11}	$0.06_{ND.disease\_duration}$		$0.03_{ND.disease\_duration}$		$0.05_{ND.disease\_duration}$		$0.14_{ND.disease\_duration}$	
ρ_{01}	-0.04_{ND}		-0.43_{ND}		-0.25_{ND}		0.13_{ND}	
ICC	0.66		0.66		0.64		0.77	
N	689_{ND}		666_{ND}		685_{ND}		681_{ND}	
Observations	2603		2243		2554		2530	
Marginal R^2 / Conditional R^2	0.041 / 0.670		0.055 / 0.678		0.069 / 0.666		0.055 / 0.778	

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S5 Fixed effects for the association of GBA1 variants with progression of motor symptoms

	FMCS		MDS-UPDRS II		MDS-UPDRS III		MDS-UPDRS IV	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	0.177 (0.095 – 0.259)	<0.001	0.164 (0.085 – 0.244)	<0.001	0.140 (0.062 – 0.219)	<0.001	0.093 (0.023 – 0.162)	0.009
Disease duration (y.)	0.555 (0.480 – 0.630)	<0.001	0.687 (0.617 – 0.757)	<0.001	0.395 (0.325 – 0.466)	<0.001	0.400 (0.332 – 0.469)	<0.001
I(disease_duration^2)					-0.014 (-0.055 – 0.028)	0.523	-0.087 (-0.129 – -0.045)	<0.001
Time to diagnosis (y.)	0.019 (-0.051 – 0.088)	0.599	0.017 (-0.048 – 0.082)	0.607	0.049 (-0.017 – 0.114)	0.144	0.003 (-0.041 – 0.048)	0.880
Disease duration: p.E365K (n = 30)	0.143 (-0.231 – 0.517)	0.453	0.075 (-0.277 – 0.427)	0.675	0.160 (-0.182 – 0.502)	0.359	-0.104 (-0.448 – 0.240)	0.553
Disease duration: p.T408M (n = 17)	0.036 (-0.405 – 0.477)	0.874	0.106 (-0.316 – 0.528)	0.621	-0.039 (-0.455 – 0.377)	0.854	-0.280 (-0.693 – 0.133)	0.183
Disease duration: p.N409S (n = 7)	-0.061 (-0.764 – 0.642)	0.865	-0.359 (-1.018 – 0.299)	0.285	-0.194 (-0.871 – 0.482)	0.573	-0.366 (-1.081 – 0.349)	0.315
Disease duration: p.F252I (n = 1)	1.004 (-3.325 – 5.333)	0.649	-0.483 (-3.347 – 2.382)	0.741			1.002 (-3.259 – 5.263)	0.645
Disease duration: p.G234W (n = 1)	-0.089 (-1.560 – 1.382)	0.905	0.232 (-1.119 – 1.583)	0.736	0.239 (-1.125 – 1.604)	0.730	-1.843 (-3.373 – -0.313)	0.018
Disease duration: p.G241R (n = 2)	-0.019 (-1.096 – 1.058)	0.972	-0.351 (-1.383 – 0.681)	0.505	0.461 (-0.445 – 1.367)	0.317	0.282 (-0.655 – 1.220)	0.554
Disease duration: p.G416S (n = 1)	1.365 (-0.512 – 3.241)	0.154	1.506 (-0.300 – 3.312)	0.102	0.348 (-1.788 – 2.485)	0.749	0.242 (-2.186 – 2.669)	0.845
Disease duration: p.L483P (n = 12)	0.094 (-0.545 – 0.733)	0.772	0.458 (-0.123 – 1.038)	0.122	0.532 (-0.186 – 1.250)	0.147	0.361 (-0.238 – 0.960)	0.238
Disease duration: p.P161S (n = 2)	2.432 (-1.451 – 6.315)	0.220	3.744 (0.612 – 6.876)	0.019	4.896 (0.057 – 9.735)	0.047	0.645 (-3.168 – 4.459)	0.740
Disease duration: p.R398X (n = 1)	1.887 (0.301 – 3.474)	0.020	1.735 (0.187 – 3.283)	0.028	0.633 (-1.089 – 2.355)	0.471	3.170 (1.225 – 5.116)	0.001
Disease duration: p.R502H (n = 1)	2.052 (-0.122 – 4.227)	0.064	-0.100 (-2.329 – 2.129)	0.930	0.923 (-1.868 – 3.715)	0.517	-0.573 (-5.687 – 4.540)	0.826

Table S5 Continued.

	FMCS	MDS-UPDRS II	MDS-UPDRS III	MDS-UPDRS IV
Random effects				
σ^2	0.16	0.18	0.35	0.45
τ_{00}	0.79_{ND}	0.77_{ND}	0.57_{ND}	0.37_{ND}
τ_{11}	$0.36_{ND.disease\_duration}$	$0.28_{ND.disease\_duration}$	$0.13_{ND.disease\_duration}$	$0.17_{ND.disease\_duration}$
ρ_{01}	0.56_{ND}	0.67_{ND}	0.49_{ND}	1.00_{ND}
ICC	0.88	0.85	0.66	
N	685_{ND}	696_{ND}	693_{ND}	698_{ND}
Observations	2578	2788	2459	2810
Marginal R^2 / Conditional R^2	0.196 / 0.901	0.280 / 0.893	0.133 / 0.709	0.206 / NA

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S5 Continued.

	PIGD		Tremore scale		MDT	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	0.123 (0.036 – 0.211)	0.006	0.012 (-0.063 – 0.087)	0.760	0.048 (-0.032 – 0.128)	0.239
Disease duration (y.)	0.672 (0.593 – 0.751)	<0.001	-0.160 (-0.228 – -0.092)	<0.001	0.356 (0.280 – 0.432)	<0.001
I(disease_duration^2)	0.158 (0.118 – 0.198)	<0.001				
Time to diagnosis (y.)	0.007 (-0.055 – 0.069)	0.820	0.088 (0.016 – 0.159)	0.017	0.055 (-0.017 – 0.127)	0.132
Disease duration: p.E365K (n = 30)	-0.155 (-0.551 – 0.241)	0.442	0.305 (-0.022 – 0.632)	0.067	0.039 (-0.354 – 0.433)	0.845
Disease duration: p.T408M (n = 17)	-0.051 (-0.512 – 0.410)	0.829	0.150 (-0.259 – 0.558)	0.472	0.057 (-0.375 – 0.488)	0.796
Disease duration: p.N409S (n = 7)	-0.381 (-1.111 – 0.348)	0.305	-0.221 (-0.858 – 0.416)	0.496	-0.261 (-0.975 – 0.453)	0.473
Disease duration: p.F252I (n = 1)			3.319 (-2.889 – 9.527)	0.295		
Disease duration: p.G234W (n = 1)	-0.944 (-2.436 – 0.548)	0.214	-0.400 (-1.703 – 0.904)	0.547	2.644 (0.466 – 4.822)	0.017
Disease duration: p.G241R (n = 2)	-0.623 (-1.748 – 0.501)	0.276	0.822 (-0.181 – 1.825)	0.108	0.114 (-0.880 – 1.108)	0.822
Disease duration: p.G416S (n = 1)	0.347 (-1.629 – 2.323)	0.730	-1.558 (-3.663 – 0.547)	0.147	0.483 (-1.402 – 2.368)	0.615
Disease duration: p.L483P (n = 12)	0.028 (-0.712 – 0.768)	0.941	-0.189 (-0.862 – 0.485)	0.582	0.274 (-0.439 – 0.987)	0.451
Disease duration: p.P161S (n = 2)	9.391 (4.999 – 13.783)	<0.001	-0.148 (-5.009 – 4.714)	0.952	2.743 (-1.681 – 7.167)	0.224
Disease duration: p.R398X (n = 1)	0.317 (-1.392 – 2.027)	0.715	-0.377 (-2.046 – 1.292)	0.658	1.696 (-0.280 – 3.673)	0.092
Disease duration: p.R502H (n = 1)	1.783 (-0.651 – 4.217)	0.151	0.093 (-2.676 – 2.862)	0.948	1.355 (-1.059 – 3.769)	0.271

Table S5 Continued.

	PIGD	Tremore scale	MDT
Random effects			
σ^2	0.22	0.35	0.24
τ_{00}	0.83_{ND}	0.64_{ND}	0.68_{ND}
τ_{11}	$0.34_{ND.disease\_duration}$	$0.10_{ND.disease\_duration}$	$0.17_{ND.disease\_duration}$
ρ_{01}	0.79_{ND}	0.12_{ND}	0.47_{ND}
ICC	0.84	0.68	0.77
N	693_{ND}	695_{ND}	630_{ND}
Observations	2430	2435	2055
Marginal R^2 / Conditional R^2	0.371 / 0.897	0.040 / 0.692	0.123 / 0.803

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S6 Fixed effects for the association of GBA1 variants considered as risk, mild or severe with progression of non-motor symptoms

	SAS		MoCA		BDI-I		MDS-UPDRS I	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	-0.004 (-0.084 – 0.076)	0.922	0.105 (0.017 – 0.193)	0.019	0.066 (-0.008 – 0.139)	0.080	0.086 (0.014 – 0.157)	0.019
Disease duration (y.)	0.160 (0.092 – 0.229)	<0.001	0.288 (0.217 – 0.359)	<0.001	0.222 (0.153 – 0.291)	<0.001	0.366 (0.301 – 0.431)	<0.001
Time to diagnosis (y.)	-0.021 (-0.094 – 0.051)	0.564	0.005 (-0.067 – 0.076)	0.894	0.015 (-0.055 – 0.084)	0.680	0.015 (-0.054 – 0.084)	0.662
I(disease_duration^2)	0.086 (0.048 – 0.124)	<0.001	0.086 (0.048 – 0.124)	<0.001				
Disease duration: PD-risk variants	0.380 (0.115 – 0.645)	0.005	0.291 (0.014 – 0.567)	0.039	0.076 (-0.200 – 0.352)	0.589	0.270 (0.014 – 0.526)	0.039
Disease duration: Mild variants	-0.120 (-0.759 – 0.518)	0.711	-0.028 (-0.669 – 0.612)	0.931	0.148 (-0.507 – 0.803)	0.658	-0.144 (-0.775 – 0.486)	0.653
Disease duration: Severe variants	0.239 (-0.167 – 0.645)	0.248	0.614 (0.193 – 1.036)	0.004	0.368 (-0.031 – 0.768)	0.071	0.121 (-0.264 – 0.506)	0.537
Random effects								
σ^2	0.27		0.23		0.29		0.30	
τ_{00}	0.69_{ND}		0.89_{ND}		0.60_{ND}		0.59_{ND}	
τ_{11}	$0.16_{ND.disease\_duration}$		$0.19_{ND.disease\_duration}$		$0.18_{ND.disease\_duration}$		$0.15_{ND.disease\_duration}$	
ρ_{01}	0.27_{ND}		0.67_{ND}		0.16_{ND}		0.22_{ND}	
ICC	0.75		0.82		0.73		0.71	
N	683_{ND}		687_{ND}		683_{ND}		694_{ND}	
Observations	2562		2426		2456		2747	
Marginal R^2 / Conditional R^2	0.094 / 0.777		0.142 / 0.842		0.062 / 0.744		0.135 / 0.750	

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S6 Continued.

	PDQ-39 Subscale bodily discomfort		Sniffin' sticks		PDSS		RBDSQ	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	0.111 (0.035 – 0.187)	0.004	0.047 (-0.023 – 0.117)	0.187	0.058 (-0.011 – 0.126)	0.100	0.022 (-0.051 – 0.096)	0.549
Disease duration (y.)	0.165 (0.101 – 0.228)	<0.001	0.197 (0.141 – 0.254)	<0.001	0.227 (0.170 – 0.285)	<0.001	0.189 (0.125 – 0.253)	<0.001
Time to diagnosis (y.)	-0.015 (-0.084 – 0.055)	0.678	-0.027 (-0.097 – 0.043)	0.452	0.024 (-0.044 – 0.091)	0.492	0.076 (0.005 – 0.146)	0.036
I(disease_duration^2)	-0.056 (-0.091 – -0.021)	0.002						
Disease duration: PD-risk variants	0.051 (-0.190 – 0.291)	0.680	-0.107 (-0.326 – 0.111)	0.334	0.244 (0.017 – 0.471)	0.035	0.002 (-0.244 – 0.248)	0.988
Disease duration: Mild variants	-0.218 (-0.825 – 0.389)	0.480	-0.726 (-1.270 – -0.182)	0.009	-0.260 (-0.843 – 0.323)	0.381	0.229 (-0.371 – 0.829)	0.454
Disease duration: Severe variants	0.157 (-0.202 – 0.517)	0.391	-0.119 (-0.460 – 0.223)	0.495	-0.176 (-0.523 – 0.170)	0.317	-0.073 (-0.455 – 0.309)	0.706
Random effects								
σ^2	0.34		0.31		0.34		0.24	
τ_{00}	0.60_{ND}		0.58_{ND}		0.56_{ND}		0.64_{ND}	
τ_{11}	$0.07_{ND.disease\_duration}$		$0.03_{ND.disease\_duration}$		$0.06_{ND.disease\_duration}$		$0.14_{ND.disease\_duration}$	
ρ_{01}	0.00_{ND}		-0.41_{ND}		-0.25_{ND}		0.13_{ND}	
ICC	0.66		0.66		0.64		0.77	
N	689_{ND}		666_{ND}		685_{ND}		681_{ND}	
Observations	2603		2243		2554		2530	
Marginal R^2 / Conditional R^2	0.023 / 0.672		0.044 / 0.679		0.060 / 0.664		0.043 / 0.777	

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S7 Fixed effects for the association of GBA1 variants considered as risk, mild or severe with progression of motor symptoms

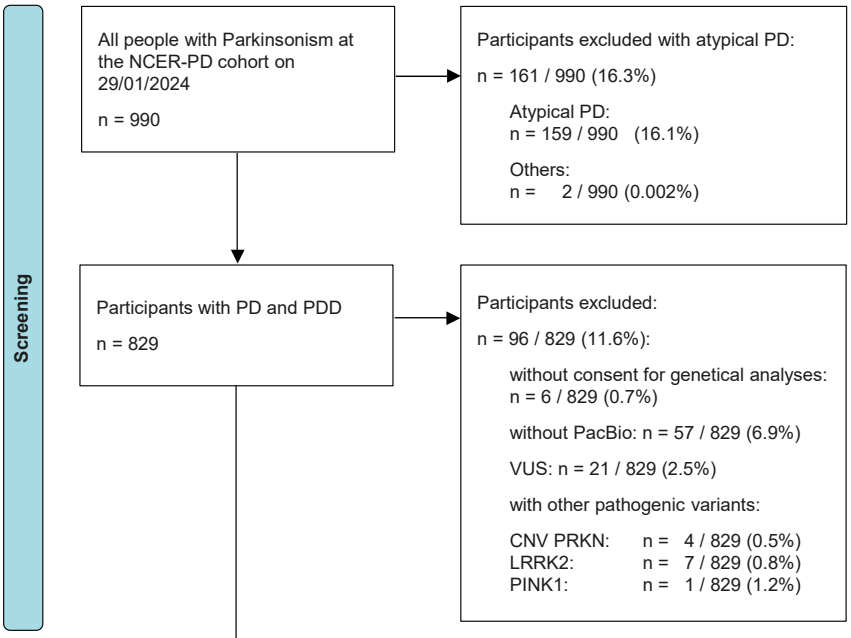
	FMCS		MDS-UPDRS II		MDS-UPDRS III		MDS-UPDRS IV	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	0.177 (0.095 – 0.259)	<0.001	0.165 (0.085 – 0.244)	<0.001	0.140 (0.061 – 0.219)	0.001	0.093 (0.024 – 0.162)	0.009
Disease duration (y.)	0.555 (0.481 – 0.630)	<0.001	0.687 (0.618 – 0.757)	<0.001	0.396 (0.326 – 0.467)	<0.001	0.400 (0.332 – 0.469)	<0.001
I(disease_duration^2)					-0.012 (-0.054 – 0.029)	0.550	-0.087 (-0.129 – -0.046)	<0.001
Time to diagnosis (y.)	0.020 (-0.049 – 0.089)	0.573	0.018 (-0.047 – 0.082)	0.594	0.049 (-0.016 – 0.115)	0.138	0.004 (-0.040 – 0.049)	0.847
Disease duration: PD-risk variants	0.109 (-0.178 – 0.397)	0.455	0.090 (-0.183 – 0.362)	0.518	0.081 (-0.186 – 0.348)	0.552	-0.174 (-0.442 – 0.093)	0.201
Disease duration: Mild variants	-0.059 (-0.757 – 0.639)	0.868	-0.359 (-1.013 – 0.296)	0.282	-0.191 (-0.866 – 0.484)	0.579	-0.366 (-1.080 – 0.347)	0.314
Disease duration: Severe variants	0.216 (-0.208 – 0.640)	0.317	0.284 (-0.108 – 0.676)	0.156	0.218 (-0.193 – 0.629)	0.298	0.246 (-0.131 – 0.624)	0.200
Random effects								
σ^2	0.16		0.18		0.35		0.46	
τ_{00}	0.81_{ND}		0.78_{ND}		0.59_{ND}		0.37_{ND}	
τ_{11}	$0.36_{ND.disease\_duration}$		$0.28_{ND.disease\_duration}$		$0.14_{ND.disease\_duration}$		$0.17_{ND.disease\_duration}$	
ρ_{01}	0.56_{ND}		0.67_{ND}		0.51_{ND}		1.00_{ND}	
ICC	0.88		0.85		0.67			
N	685_{ND}		696_{ND}		693_{ND}		698_{ND}	
Observations	2578		2788		2459		2810	
Marginal R^2 / Conditional R^2	0.198 / 0.902		0.284 / 0.893		0.133 / 0.714		0.191 / NA	

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA

Table S7 Continued.

	PIGD		Tremor scale		MDT	
Predictors	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*	*stand. B (CI 95%)*	*P-Value*
Intercept	0.124 (0.036 – 0.211)	0.006	0.012 (-0.063 – 0.086)	0.759	0.048 (-0.031 – 0.128)	0.235
Disease duration (y.)	0.671 (0.593 – 0.749)	<0.001	-0.160 (-0.228 – -0.093)	<0.001	0.356 (0.281 – 0.432)	<0.001
I(disease_duration^2)	0.157 (0.117 – 0.196)	<0.001				
Time to diagnosis (y.)	0.007 (-0.055 – 0.069)	0.821	0.089 (0.017 – 0.160)	0.015	0.055 (-0.016 – 0.127)	0.130
Disease duration: PD-risk variants	-0.106 (-0.407 – 0.196)	0.491	0.258 (0.001 – 0.515)	0.050	0.047 (-0.245 – 0.340)	0.750
Disease duration: Mild variants	-0.382 (-1.104 – 0.340)	0.299	-0.221 (-0.855 – 0.413)	0.493	-0.261 (-0.970 – 0.448)	0.470
Disease duration: Severe variants	-0.122 (-0.576 – 0.332)	0.598	-0.077 (-0.474 – 0.320)	0.702	0.363 (-0.068 – 0.794)	0.098
Random effects						
σ^2	0.22		0.35		0.24	
τ_{00}	0.83_{ND}		0.64_{ND}		0.68_{ND}	
τ_{11}	$0.34_{ND.disease\_duration}$		$0.11_{ND.disease\_duration}$		$0.18_{ND.disease\_duration}$	
ρ_{01}	0.79_{ND}		0.12_{ND}		0.47_{ND}	
ICC	0.83		0.68		0.78	
N	693_{ND}		695_{ND}		630_{ND}	
Observations	2430		2435		2055	
Marginal R^2 / Conditional R^2	0.372 / 0.896		0.033 / 0.692		0.121 / 0.803	

Note The main effects included in the model can be found on the OSF-project page: 10.17605/OSF.IO/NCWTA



	Non-carriers	Risk	Mild	Severe
Baseline	657	47	7	22
Follow-up 1	540	42	7	19
Follow-up 2	459	37	5	13
Follow-up 3	361	28	5	12
Follow-up 4	295	18	4	11
Follow-up 5	192	12	3	6
Follow-up 6	122	10	3	3
Follow-up 7	77	7	1	2

Figure S1 Flow diagram of patient recruitment

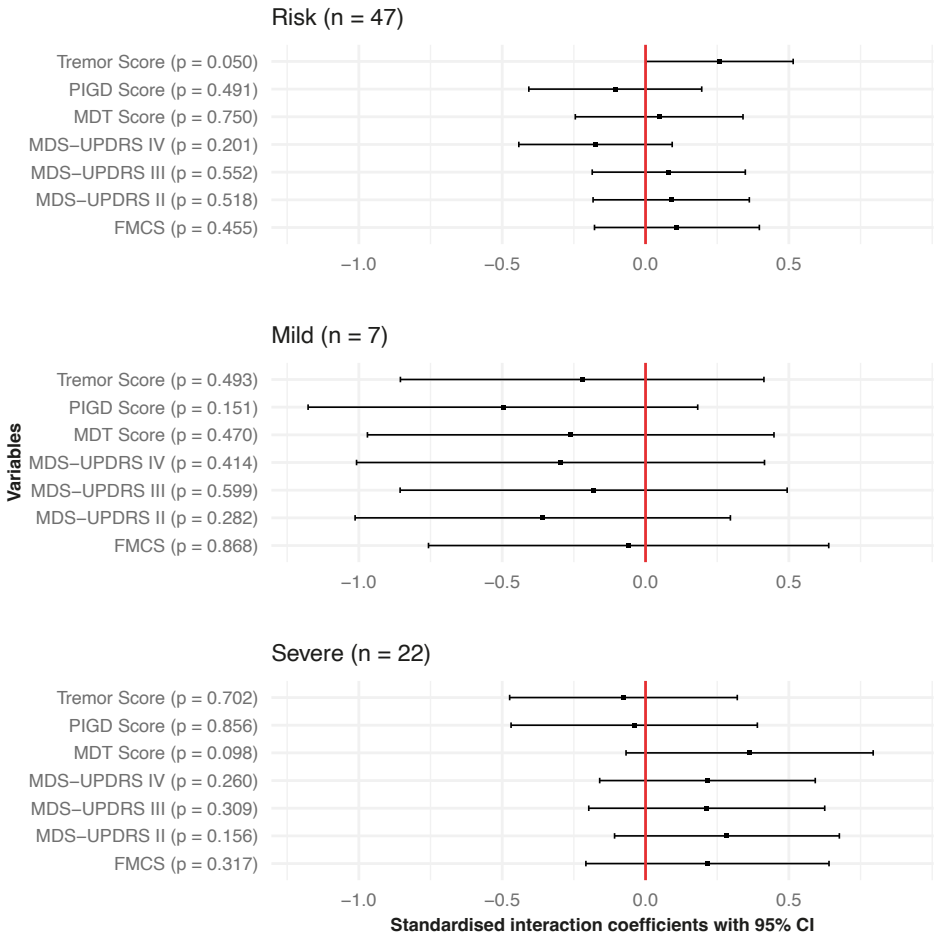


Figure S2 Association of mild, risk and severe variants with progression of motor symptoms, right side of the red line = associated with worse progression compared to non-carriers. Abbreviations: FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, UPDRS: Unified Parkinson's Disease Rating Scale

Description of the association of the different *GBA1* variants with progression of motor and non-motor symptoms

To analyse if different amino-acid changes are associated with a different effect of the time since diagnosis on motor- and non-motor symptoms we created one interaction model per outcome and added a categorical variable of twelve variants changes (see Table S2, reference group = non-carriers) as an interaction effect with the time since diagnosis and the outcome.

We reported the standardised interaction coefficients of the different variants in Tables S4 – S5 in the Supplement. Thus, no significant associations were detected after Bonferroni-adjusted significance level (alpha = 0.05/(15 outcomes12 variants) = 0.0003). On an unadjusted significance level (alpha = 0.05), while few in numbers, compared to non-carriers, the thirty carriers of at least one allele of p.E365K, a variant considered as risk-variant, were associated with a faster progression in apathy (SAS) (0.361, 95%CI: 0.020, 0.702, p = 0.038), non-motor symptoms (MDS-UPDRS I) (0.371, 95%CI: 0.046, 0.696, p = 0.025), and in quality of sleep (PDSS) (0.371, 95%CI: 0.085, 0.656, p = 0.011), while, compared to non-carriers, the seventeen carriers of p.T408M, a variant considered as PD-risk variant, were associated with a faster progression in apathy (SAS) only (0.411, 95%CI: 0.001, 0.822, p = 0.049). Finally, compared to non-carriers, the twelve carriers of at least one allele in variant p.L483P, a variant considered as severe variant, were associated with a faster progression in depression (BDI-I) (0.772, 95%CI: 0.159, 1.385, p = 0.014) and a slower worsening of quality of sleep (PDSS) (-0.736, 95%CI: -1.355, -0.118, p = 0.020). The other amino acid changes were too low in numbers (n ≤ 2) and thus difficult to interpret.

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All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CHAPTER 7

Understanding unexpectedly stable functional mobility in people with Parkinson's disease: A mixed methods study.

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ABSTRACT

BACKGROUND

As Parkinson's disease (PD) progresses, mobility declines. Reserves (biological, physiological, cognitive, emotional, economical or relational) may help us to understand the phenomenon of unexpectedly stable trajectories of patient-reported functional mobility.

OBJECTIVES

To investigate reserves moderating the trajectories of patient-reported functional mobility and to understand their daily experience by people with PD. To describe the characteristics of individuals with unexpectedly stable trajectories of functional mobility.

METHODS

In this explanatory sequential mixed methods study, we combined longitudinal mixed models and qualitative interviews with individuals with unexpectedly stable trajectories of functional mobility. Specifically, we first analysed the reserves moderating the associations between years since diagnosis and patient-reported functional mobility followed by a subsequent collection and analysis of qualitative interviews helping to understand the meaning of these quantitative findings.

RESULTS

While not significant after correction for multiple testing, functional mobility declined slower in men with 10 to 16 years of education but not in women. By comparing the group with an unexpectedly stable to the group with a decreasing trajectory, the group with an unexpectedly stable trajectory showed, after adjustment for years since diagnosis and multiple testing less patient-reported motor- and non-motor symptoms. The deductive analyses of the semi-structured interviews identified the transport service, i.e., a driving license or the disponibility of someone with a car living in the same household as central facilitating factor of functional mobility. Finally, according to the inductive content analysis psychosocial factors, e.g., self-efficacy, characterised individuals with unexpectedly stable trajectories of functional mobility despite disability (years since diagnosis) and a challenging context (living without a partner or children in rural areas).

CONCLUSIONS

Trajectories of functional mobility in PD seem to be multifactorial in nature, with little evidence for general determinants. Our study highlights the importance of a driving license for functional mobility and supports the provision of local amenities within walking distance to enable active and healthy ageing in place. Psychosocial factors characterised individuals with unexpectedly stable trajectories of functional mobility despite a challenging context. Further research could investigate our generated hypotheses to inform interventions promoting functional mobility.

BACKGROUND

As Parkinson's disease (PD) progresses, mobility declines, accompanied by impaired postural control, decreased ability to sit down or stand up from a chair, increased metabolic cost of walking, and an overall slowing-down of motor function (Mollà-Casanova et al., 2022). Mobility in PD is determined by different factors. A previous systematic review (Hanff et al., 2024b) highlighting the potential of environmental factors, despite determinants related to body structures and functions being most frequently investigated in the literature.

Interestingly, we (Hanff et al., 2022a) recently observed in cross-sectional data unexpectedly high functional mobility in people with typical PD (a patient-reported functional mobility composite score (FMCS) above the median of all participants, despite a Postural Instabilities and Gait Disturbances (PIGD) dominant phenotype). Thus, a salutogenic (Antonovsky, 1979) approach, instead of the traditional pathophysiological approach, could help to better understand unexpectedly stable trajectories of functional mobility and the protective factors involved. Individuals with unexpectedly high functional mobility can be identified by having a look at their longitudinal trajectory. Among others, Corbin and Strauss (2010) describe phases of normalisation and stabilisation in the trajectory of a chronic disease. Normalisation indicates physical and psychological recovery following an acute phase. Overall, such trajectories show an upward trend, and coping strategies aim to achieve physical well-being, regain functionality and also cope with the illness and resulting disability. A phase is stable when there are no changes for better or worse in the course of the illness. The disease may slowly change over the years, with fewer or no noticeable signs. Coping aims to maintain this stability.

Reserves (biological, physiological, cognitive, emotional, economical or relational) may help people with PD to overcome PD-related vulnerability (Cullati et al., 2018). Consequently, they may help us to better understand why some people with PD show the previously described phases of normalisation or stability while others show a decline in patient-reported functional mobility by describing and explaining inter-individual differences in developmental trajectories (Cullati et al., 2018).

We aimed to investigate the reserves moderating the trajectories of patient-reported functional mobility and understand the daily experience of people with PD. Also, we aimed to describe the characteristics of individuals with unexpectedly stable/normalising trajectories of functional mobility.

METHODS

In this explanatory sequential mixed methods study, we combined longitudinal mixed models and qualitative interviews with individuals with unexpectedly stable/normalising trajectories of functional mobility. Specifically, we first (Tab. 1) analysed the reserves moderating the associations between years since diagnosis and patient-reported functional mobility followed by a subsequent collection and analysis of qualitative interviews helping to understand the meaning of these quantitative findings (Creswell and Plano Clark, 2018). Also, the quantitative findings were used to identify interview partners for the follow-up qualitative phase as detailed further below.

Table 1 Visual display for the mixed methods study design procedure

Steps	Procedures	Products
Quantitative data collection	Luxembourg Parkinson's study, a nationwide, monocentric, observational, longitudinal-prospective study (Hipp et al., 2018)	Tab. S1: Characteristics of included constructs
Quantitative data analysis	Descriptive statistics: Sex/Gender	Tab. 2: Sociodemographic and health-related characteristics across sex/gender
	Descriptive statistics: Educational attainment, partner, children, place of residence	Tab. S4 – S8: Sociodemographic and health-related characteristics across reserves
	Longitudinal linear mixed effects model stratified by sex/gender and social generations	Tab. S9: Moderation by reserves in men and women
	Extraction of random effects and grouping into tertiles	Fig. 1: Individual trajectories of functional mobility in men and women from the tertiles 1 and 3
	Group-comparison: 225 individuals with decreasing (tertile 1 of random effects) and 225 individuals with stable/normalising (tertile 3 of random effects) trajectories of functional mobility	Tab. 3: Comparator groups at baseline – Individuals with a declining and stable/normalising trajectory of functional mobility
Purposeful Sampling : Interview Protocol Development	Maximum variation sampling (Polit and Beck Tatano, 2017)	Fig. S3 and S4: Trajectories of individuals with stable/normalising trajectories with and without the reserves
		Fig. S1: Flow chart of participant recruitment into the qualitative part
	Development of interview questions	Tab. S2: Interview guide with the rationale for the questions
Qualitative data collection	Semi-structured interview of +/- 60 minutes	Interview transcripts
Qualitative data analysis	Coding & deductive-inductive qualitative content analysis according to Elo and Kyngas (2008)	Fig. S2: Coding tree and unconstrained data matrix of unexpectedly stable/normalising FM by handling the progression of mobility impairment
		Tab. S10: Theme summary table of the deductive analysis
		Tab. S11: Theme summary table of the inductive analysis
		Quotations

Table 1 Continued.

Steps	Procedures	Products
Integration of quantitative & qualitative results	Interpretation & explanation of the quantitative & qualitative results	Tab. 4: Statistics-by-theme joint display
	Aim: Understand why the individuals with a stable/normalising trajectory of functional mobility differ from the norm and how they manifest the reserves potentially protecting from a decline in functional mobility.	Discussion

Phase 1: Quantitative study

We analysed data from the Luxembourg Parkinson's study, a nationwide, monocentric, observational, longitudinal-prospective study (Hipp et al., 2018, Pavelka et al., 2023). The completed STROBE reporting guideline checklist (Vandenbroucke et al., 2007) is included in the Supplement.

Variables, data sources and measurement

The outcome of interest was the change of patient-reported functional mobility per additional year since diagnosis, while the reserves (educational attainment, place of residence, partner and children) were included as moderators. Patient-reported functional mobility was assessed by the patient-reported functional mobility composite score (FMCS) (Hanff et al., 2023b) during baseline assessment and annual follow-ups (mean number of follow-ups: 3.1, SD: 1.9) varying by a maximum of three months to minimise seasonal influences. We relied on proxies to assess the reserves (Tab. S1), .e.g, years of education as proxy for a cognitive and socioeconomic reserve (Stern, 2009, Liberatos et al., 1988, Galobardes et al., 2006, Cullati et al., 2018), having children or a partner as proxies of relational reserve (Kalmijn and van Groenou, 2016, Dykstra and Hagestad, 2016) and the place of residence as a proxy for a socioeconomic reserve (Liberatos et al., 1988, Galobardes et al., 2006, Cullati et al., 2018). Further descriptions of baseline and follow-up assessments can be found in the primary study (Hipp et al., 2018, Pavelka et al., 2023).

Children may have sex-specific consequences for the functional mobility of people with PD. Specifically, in men without a partner, childlessness was a source of vulnerability (Dykstra and Hagestad, 2016). Consequently, we expected different effect sizes and signs for the reserves across sex/gender (Hanff et al., 2023a) and stratified our analyses by sex/gender (Hernan et al., 2011, Rothmann et al., 2008).

Statistical methods

Data analysis was done in R, version 4.3.1 (R Core Team, 2023). We investigated in men and women with PD, if the reserves (educational attainment, place of residence, partner, children) moderated the change of patient-reported functional mobility per additional year since diagnosis (dynamic time predictor). We created one longitudinal two-level mixed

model per static reserve (educational attainment, partner, children, place of residence) stratified by sex/gender (using the "lmer"-function of the "lme4"-package (Bates et al., 2015)). The research questions have been visualized with directed acyclic graphs (using the web-based DAGitty (Textor et al., 2016)) and statistical analyses adjusted accordingly. Specifically, we included fixed effects for years since diagnosis, country of residence and educational attainment, a random intercept on participant level and a random slope for years since diagnosis. After modelling the linear development over time, we first extended the fixed effects with a quadratic time component, i.e. the square of time. To evaluate whether or not this second-order polynomial should be added to the linear component, we compared the model with and without quadratic time component. Finally, if the model with a quadratic time component added to the linear component fitted significantly ($\alpha = 0.05$) better to the data, this model was then compared to the model with an additional cubic time component. Models were compared by a likelihood ratio test (using "anova"-function of the "lme4"-package (Bates et al., 2015), method = "lrt").

In addition to the tables describing the fixed and random effects (using "tab_model"-function of "sjPlot"-package (Lüdecke, 2022)), we illustrated the moderation in interaction plots (using "plot"-function of the "ggplot2"-package (Wickham, 2016)). We estimated the models using the maximum likelihood method while the statistical significance ($\alpha \leq 0.05$) and confidence intervals for the moderators were obtained with the Kenward-Roger approximation for degrees of freedom. In addition to the unadjusted significant p-values marked with *, we indicated significant p-values after adjustment for multiple comparison (FWER with Bonferroni-Holm (Cao and Zhang, 2014)) with **.

Finally, in preparation for the qualitative study, we extracted the random effects (random slopes for years since diagnosis) with the "ranef"-function of the lme4-package in R (Bates et al., 2015) and ordered individuals from high to low random effects. We created two groups, i.e., individuals with stable/normalising trajectories of functional mobility in the 3rd tertile of (high) random effects and individuals with decreasing trajectories of functional mobility in the 1st tertile of (low) random effects. The two-sided Wilcoxon rank-sum test and the Kruskal-Wallis test for discrete variables and the chi-squared test for categorical variables compared baseline characteristics across tertiles, sex/gender and reserves (educational attainment, partner and children, place of residence) (using the "stats" package (R Core Team, 2023)). We illustrated the distribution of the residuals in a histogram and inspected the residuals VS fitted values plot for homogeneity of residual variance.

Phase 2: Qualitative study

The following research questions guided the qualitative phase of our mixed-methods study: What barriers and facilitators do participants with a stable/normalising trajectory of functional mobility perceive related to cognitive, relational and socioeconomic reserves?

What characterises individuals with a stable/normalising trajectory of functional mobility?

The completed COREQ reporting guideline checklist (Tong et al., 2007) is included in the Supplement. The qualitative study was guided by the qualitative content analysis process (Elo and Kyngas, 2008). The mobility framework (Webber et al., 2010), the health promotion theory - salutogenesis (Antonovsky, 1979), the chronic illness trajectory model (Corbin, 1991) and the process of becoming bedridden through gradual local confinement (Zegelin, 2008) and of regaining physical mobility (Adlbrecht and Mayer, 2018), together with the quantitative findings informed the design of the unconstrained categorisation matrix (Fig. S2), the interview schedule and the analysis of the transcripts. Specifically, we assumed that the decline of functional mobility can be influenced by the pathology of immobility, the progression of an illness, the individuality of the person and the attitude of the carer.

The research team and reflexivity

The first author (A-MH) and interviewer is a female PhD researcher with a background in nursing and research within the field of PD, with training in both quantitative research methods and qualitative data collection and analysis. The interviewer sought continuous feedback from two groups of peer researchers (Network Clinical Nursing Sciences Luxembourg and the multidisciplinary researchers from the National Centre for Excellence in Research on Parkinson's disease (NCER-PD) in Luxembourg). This exchange encouraged reflexivity and prevented the interviewer from losing her critical distance and perspective, i.e., "going native" (Braun and Clarke, 2022).

Participant selection and setting

Eligible participants were recruited from 2023-12-01 to 2024-05-29 as part from the ongoing Luxembourg Parkinson study (Hipp et al., 2018), approved by the National Ethics Board (CNER Ref: 201407/13). We used purposive and criterion sampling methods to focus on deviant cases, selecting the tertile with the best trajectory of patient-reported functional mobility. This approach helped to understand why those individuals outside the norm with a stable/normalising trajectory differed from the expected declining trajectory. Additionally, we used maximum variation sampling (Polit and Beck Tatano, 2017) by selecting interview participants based on the identified differences between people with unexpectedly stable/normalising and decreasing trajectories of functional mobility. Thus, we selected individuals with a stable/normalising trajectory with varying reserves (e.g., different levels of educational attainment, with and without children) and the characteristics of the group with a declining trajectory (Tab. 3). As women showed an overall slower progression of motor- and non-motor symptoms (Hanff et al., 2023a), we included only women with characteristics promising the most insights. This strategy aimed to identify individuals with an opportunity to learn and challenge the emerging themes. Consequently, according to the information power concept (Malterud et al., 2016), we anticipated a high information power per interview.

Data collection and analysis

The interview questions focused on participants' experiences of cognitive (educational attainment), relational (partner, children) and socioeconomic reserves (place of residence). We illustrated individual trajectories of patient-reported functional mobility compared to the mean trajectory of functional mobility (marginal means) and other dimensions of wellbeing according to Murray et al. (2024) of all interview participants who were selected (Fig. S3 and S4) and reviewed the figures during the interview. We asked the participants about how they explained their unexpectedly stable/normalising trajectory and which reserves they experienced in daily life ,which might influence or help to understand their unexpectedly stable/normalising trajectory. We piloted and continually developed the interview guide (Tab. S2), ordering the questions from general to specific to ensure new insights could be investigated in future interviews.

All semi-structured interviews were conducted once at a location chosen by the participant without the partner unless otherwise requested by the participant. The interviews were recorded with the Windows "Voice recorder" and directly saved on a secured laptop. They lasted approximately 60 minutes, were transcribed verbatim, and the transcripts were returned to participants for comment and/or correction. The interviewer also removed all personal identifying information from the transcript. The MaxQDA software (VERBI Software, 2024) was used for interview transcription and coding. According to the main phases of qualitative content analysis (preparation, organising, reporting) (Elo and Kyngas, 2008), we first familiarised ourselves with the dataset by reading/listening to the transcripts and making notes about any insights. Then, in deductive content analysis, after an unconstrained categorisation matrix had been developed (Fig. S2), all data were reviewed and coded for correspondence with the predefined categories and creating additional categories within its bounds, following the principles of inductive content analysis (Elo and Kyngas, 2008).

Finally, we coded remaining factors that did not fit the categorisation frame. Themes that emerged from this inductive content analysis were then examined across cases to identify commonalities and variations of the themes (Ayres et al., 2003, Vaughan Dickson et al., 2011). The interviewer documented her ideas about how some themes were interrelated in analytic memos. Participant quotations were used to illustrate the findings. Lastly, in April 2024, the participants were invited to a presentation of the preliminary findings and were asked to consider the findings and their level of agreement with them in relation to their experience.

Phase 3: Data integration

Integration occurred at the participant selection, e.g., we graphically displayed the trajectories of functional mobility of individuals with PD in the different tertiles of random effects to identify individuals with divergent trajectories (Creswell and Plano Clark, 2018). Moreover, we recruited women experiencing the lack or presence of different reserves to

"unlock" an analysis by providing insight into processes the phenomenon of unexpectedly stable/normalising functional mobility (Bazeley, 2018). Finally, we connected quantitative and qualitative results in a joint "statistics-by-themes" display juxtaposing quantitative (moderation) and qualitative findings (themes) to allow comparisons for concordance and discordance. Thus, we examined patterns in the stable/normalising group across people with and without reserves aiming to understand how the individuals with a stable/normalising trajectory of functional mobility differ from the norm and how they manifest the reserves potentially protecting from a decline in functional mobility (Guetterman et al., 2015).

RESULTS

Phase 1: Quantitative study

We included 829 people with typical PD with a baseline assessment in the NCER-PD cohort between 2015-03-04 and 2024-01-29 (date of data export). The average number of follow-ups was 3.2, while 107 (13.2%) participants died between baseline and data export. The summary measures of functional mobility over time (Tab. S3) showed decreasing median functional mobility (FMCS) with a left-skewed distribution and increasing number of missing values per visit. Comparison of sociodemographic and health-related characteristics of men and women at baseline (Tab. 2) indicated a significantly higher frequency of married/partnered men than women ($p < 0.001$) with lower symptoms of depression (BDI-I) ($p < 0.001$) after correction for multiple testing. Although they completed more years of education, men had lower scores for global cognition (MoCA) ($p = 0.010$) compared to women. We did not detect a lower age in women ($p = 0.361$). Tab. S4 – S8 describe compare sociodemographic and health-related characteristics across reserves.

Table 2 Sociodemographic and health-related characteristics across sex/gender

		Men (n = 549)		Women (n = 280)	p-value
Age	68.3	(14.6)	68.0	(14.3)	0.361
Married/Partnered	456	(83.5%)	169	(60.8%)	< 0.001**
Children (n)	2.0	(2.0)	2	(1.0)	0.017*
Years of education	13.0	(5.0)	12.0	(5.0)	< 0.001**
Central place of residence	306	(57.4%)	174	(64.0%)	0.086
Luxembourgish as first spoken language	243	(44.3%)	119	(42.7%)	0.862
Country of residence Luxembourg	352	(64.2%)	162	(57.9%)	0.087
Years since diagnosis	3.0	(5.7)	3.3	(6.6)	0.146
Age at diagnosis	64.0	(16.8)	63.0	(17.0)	0.216
Hoehn & Yahr stage	2.0	(0.5)	2.0	(0.5)	0.533
MoCA (0 – 30)[b]	25.0	(5.0)	26.0	(5.0)	0.010*
PDD diagnosis	71	(12.9%)	26	(9.3%)	0.153
BDI-I (0 – 63)[a]	8.0	(9.0)	9.5	(9.0)	< 0.001**
MDS-UPDRS I (0 – 52)[a]	9.0	(8.0)	10.0	(9.0)	0.009*
MDS-UPDRS II (0 – 52)[a]	9.0	(10.0)	9.0	(9.5)	0.627
MDS-UPDRS III (0 – 132)[a]	32.0	(21.0)	31.0	(23.0)	0.147
MDS-UPDRS IV (0 – 24)[a]	0.0	(0.0)	0.0	(2.0)	0.255
PIGD Score (0 – 20)[a]	2.0	(3.0)	2.0	(4.0)	0.093
FMCS (0 – 100)[b]	82.8	(31.2)	76.6	(34.4)	0.048*

Note * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm). Categorical variables: counts (%), numerical variables: median (IQR)

Reserves protecting from a decline of functional mobility

A linear mixed model with a random slope intercept and a random slope for time (years since diagnosis) fitted best to the data. As previously described (Hanff et al., 2023a) and as expected from a chronic progressive disorder, men and women with typical PD showed progression yearly decline in patient-reported functional mobility (FMCS) by -2.67 points (CI95%: -3.04, -2.30, $p < 0.001$) and -1.89 (CI95%: -2.29, -1.48, $p < 0.001$).

After correction for multiple testing we did not detect any significant moderation by the reserves in men or women (Tab. S9). However, we found a nominal significant slower decline of functional mobility in men with 10 to 16 years of education (0.333, 95%CI: 0.081, 0.584, $p = 0.010$, Tab. S9) compared to those with less than ten years of education. The variance inflation factor (VIF) (using CAR package (Fox and Weisberg, 2019)) indicated no signs of multicollinearity (VIF < 10) (Bowerman and O'Connell, 1990). Transformation of the outcome variable by taking the logarithm of the FMCS did not enhance normal distribution of the residuals.

Comparison of people with a declining and stable/normalising trajectory

Fig. 1 illustrates the individual trajectories of functional mobility in women and men of participants grouped by the amount that each subject's functional mobility differed (tertiles) from the average functional mobility (marginal means). We highlighted the individual trajectory of interview participant 2 to visualise the link between the quantitative and the qualitative study. After adjustment for multiple testing, compared to individuals in tertile 1 and independent of years since diagnosis, people in tertile 3, i.e. with a stable/normalising trajectory of functional mobility, showed lower age and age at diagnosis, respectively, less frequent diagnosis of PD dementia and better global cognition (MoCA), fewer symptoms of depression (BDI-I), patient-reported motor- and non-motor symptoms, less postural instability and gait disturbances (PIGD) and better functional mobility at baseline (Tab. 3).

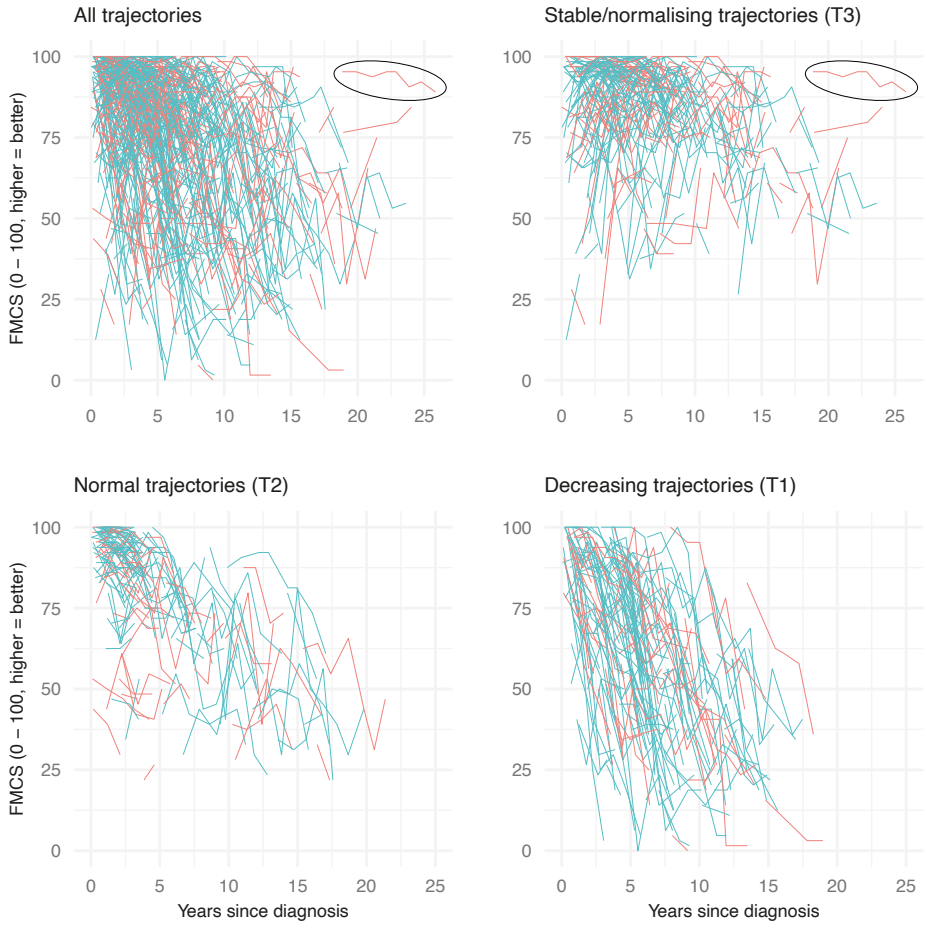


Figure 1 Individual trajectories of functional mobility in women (red) and men (blue) in different teriles (T), black oval: Individual trajectory of interview participant 2

Table 3 Comparator groups at baseline – Individuals with a declining and stable/normalising trajectory of functional mobility

	Tertile 1 Decreasing (n = 225)	**Tertile 3 Stable/normalising** (n = 225)	**p-value**
Change in FMCS / year	-1.4 (1.8)	1.4 (1.1)	-
Sociodemographic characteristics			
Country of residence			0.852
Luxembourg	145 (64.4%)	139 (61.8%)	
Belgium	12 (5.3%)	17 (7.6%)	
France	39 (17.3%)	38 (16.9%)	
Germany	28 (12.4%)	29 (12.9%)	
Other	1 (0.4%)	2 (0.9%)	
Age (y)	71.7 (10.7)	67.8 (12.5)	< 0.001**
Female sex	63 (28.0%)	75 (33.3%)	0.261
Marital status			0.553
Single	5 (2.2%)	9 (4.0%)	
Divorced / Widowed	39 (17.3%)	37 (16.4%)	
Married / Partnered	179 (79.6%%)	179 (79.6%)	
Children (n)	2.0 (2.0)	2.0 (1.0)	0.188
Having children	198 (88.0%)	191 (84.9%)	
Years of education	13.0 (6.0)	13.0 (6.0)	0.855
< 10 y	43 (19.1%)	42 (18.7%)	
10 – 16 y	110 (48.9%)	117 (52.0%)	
> 16 y	64 (28.4%)	66 (29.3%)	
Living in central areas	132 (58.7%)	145 (64.4%)	0.672
Health-related characteristics			
Final diagnosis PDD	53 (23.8%)	13 (5.9%)	< 0.001**
Years since diagnosis	4.1 (6.4)	3.2 (6.0)	0.589
Age at diagnosis	67.0 (11.0)	62.0 (13.0)	< 0.001**
Time to diagnosis (y.)	1.0 (3.0)	1.0 (3.0)	0.882
LEDD (mg./kg.)	6.2 (7.6)	5.6 (6.1)	0.033*
MoCA (0-30) [b]	24.0 (5.0)	26.0 (5.0)	< 0.001**
BDI-I (0-63) [a]	10.0 (8.8)	7.0 (7.0)	< 0.001**
SAS (0-42) [a]	14.0 (7.0)	13.0 (6.0)	0.006*
Social support (0-100) [b]	91.7 (25.0)	100.0 (16.7)	0.009*
Stigma (0-100) [a]	12.5 (37.5)	12.5 (25.0)	0.040*
Pain (0-100) [a]	33.3 (33.3)	25.0 (29.3)	0.067
PDSS (0-150) [b]	106.0 (37.1)	110.0 (29.3)	0.013*
RBDSQ (0-13) [b]	4.0 (5.5)	3.0 (4.0)	0.073
Sniffin' sticks (0-16) b	7.0 (5.0)	8.0 (5.0)	0.068
MDS-UPDRS I (0-52) [a]	10.0 (9.8)	8.0 (7.0)	< 0.001**
MDS-UPDRS II (0-52) [a]	13.0 (14.0)	8.0 (8.0)	< 0.001**
MDS-UPDRS III (0-132) [a]	37.0 (26.0)	32.5 (19.8)	0.003*
MDS-UPDRS IV (0-24) [a]	0.0 (2.0)	0.0 (0.0)	0.394
PIGD (0-20) [a]	3.0 (7.0)	2.0 (2.0)	< 0.001**

Table 3 Continued.

	Tertile 1 Decreasing (n = 225)	Tertile 3 Stable/normalising (n = 225)	p-value
FMCS (0-100) [b]	71.9 (45.3)	85.9 (26.6)	< 0.001**
Tremor (0-4) [a]	0.5 (0.7)	0.5 (0.6)	0.699

Note * = nominally significant, ** significant after adjustment for FWER (Bonferroni-Holm). Categorical variables: counts (%), numerical variables: median (IQR), a : Greater = worse, b : Greater = better, numerical variables : two-sided Wilcoxon rank-sum test and Kruskal-Wallis test, categorical variables : chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disturbances, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Phase 2: Qualitative study

114 out of 225 individuals with PD with a stable/normalising trajectory were eligible for the qualitative study according to the in- and exclusion criteria (Fig. S1). While the trajectories of functional mobility of PwP 1, 3 and 5 showed a normalising trend, the trajectories of the remaining participants seemed stable despite the other co-occurring motor- and non-motor symptoms, in particular higher age and age at diagnosis, symptoms of depression (BDI-I), patient-reported motor- and non-motor symptoms, and postural instability and gait disturbances (PIGD). We indicated events, e.g., a breakup with a partner, on the individual trajectories of motor- and non-motor symptoms (Fig. S3 and S4), that might help to understand the normalising or stable trajectories. In addition to heterogenous symptoms' progression, we observed psychological and social trajectories (PDQ-39 subscale social support, Beck depression inventory) running in parallel and reflecting periods of greater social support or depression. Those trajectories were not always related to PD-symptoms progression but to other physical or social health changes alongside the ongoing progression of PD as described by Murray et al. (2024).

Experience of reserves associated with slower decline of functional mobility

Participants experienced no effect of educational attainment or the diploma on how they handled their trajectory of functional mobility. Moreover, they experienced educational attainment as a "means to an end", i.e., a requirement for getting a qualification, and highlighted the importance of life experience, lifelong learning and curiosity as they help them to find creative solutions to challenges of functional mobility (Tab. S10).

In the deductive analysis, the subthemes identified in individuals with and without a partner were similar (Tab. S10). Specifically, the transport service by someone else was mentioned as the most facilitating factor. Most participants no longer had their driving license. Thus, in individuals with a partner, the partner provided the transportation service (PwP 3, PwP 4). In individuals without a partner, the 24-hour professional caregiver (PwP 5), children (PwP 2) or neighbours (PwP 5) provided the service. The availability of the person providing the

transportation service, living in the same house and sharing activities of daily living (partner, via a 24-hour caregiver) guaranteed autonomous decision-making in functional mobility. This was not the case for the individual without a partner and a 24-hour caregiver (PwP 2), who negatively experienced her dependency from the others (family members) availability. The individual's trajectory of functional mobility (Fig. S3 and S4) declined after a break-up with a partner (PwP 1). However, subsequently emotional wellbeing increased and the PwP 1 reported a reactivation of the social network. Thus, a partner can be an enabling or restricting factor for functional mobility depending on their willingness and capacity to satisfy unmet needs of the person with PD. Specifically, in one case, the restricted functional mobility of the partner due to the flu promoted the functional mobility of the person with PD, as it forced them to take over the responsibility for daily activities that require functional mobility, e.g., grocery shopping (PwP 4). However, some social activities were not continued alone (PwP4). Joint activities with the partner or the 24-hour caregiver included grocery shopping, going to the restaurant or coffee shop, going for a walk, meeting family and friends, concerts or holidays. The partner helped to integrate the restrictions into the daily routine by organising activities accordingly (e.g., not too late in the evening) (PwP 1), or by reminding or waking their partner up for the medication to avoid motor complications (e.g., dyskinesia, off-phases,...) (PwP 3).

If walking by foot, using public transport or driving the car were not possible or the destination was not easy to reach, children provided a "transport service". Also, they accompanied their parent with PD for joint recurring activities, e.g., walking by foot to the weekly food market (PwP 4). Sometimes people with PD feel that children invade their privacy by asking intrusive questions (PwP 2). This impression co-occurred with feelings of worry destabilising the individual with PD and not helping to create a safe level of mobility (PwP 5). Particularly grandchildren incentivised their grandparents for activities outside their daily routine, e.g., watching their concerts or visiting them at their workplace (PwP 4). Weekly mealtime visits of grandchildren stimulated people with PD to go to the grocery shopping and prepare a meal (PwP 2, PwP 4). Moreover, by sharing pictures and a small diary, children and grandchildren helped the individual with PD with a mobility radius inside their country of residence, to participate in their travels and to feel involved (Tab. S10).

In the deductive analysis, the subthemes identified in individuals living in rural compared to those living in central areas were similar (Tab. S10). Independent of a central or rural place of residence, a car was required to meet an unmet need (grocery shopping). If no transport service was provided by someone else, individuals tried to continue to drive by themselves. Specifically, they weighted the risk of having a car accident versus the gained autonomy. Independent of their place of residence, people with PD experienced gardening or walking tours in nature as facilitating factors. On the other side, inaccessibility of important destinations (grocery shops, bus stop) by foot or public transport due to a walking distance

of more than 500 meters or uphill on the way home were factors experienced as restricting functional mobility. Due to the limited flexibility of the buses organised by the municipality this was no valuable option. Finally, only one individual (PwP 1) living in the city center described the flexibility to decide autonomously when to go where without the need of a car (Tab. S10).

Characteristics of individuals with unexpectedly stable/normalising functional mobility

In the inductive content analysis, we identified additional factors that might explain and characterise individuals with unexpectedly stable/normalising functional mobility (Tab. S11). Specifically, the interview participants did not shy away from confrontation. They showed openness towards new experiences (also towards new technology), helpfulness and asking for help, and life affirmation. They had high self-efficacy beliefs, had a sociable attitude and a physically active lifestyle while adapting their expectations and accepting the limits. Finally, unexpectedly stable functional mobility in people with Parkinson's Disease in some cases co-occurred with inflammatory comorbidities, i.e., chronic arthritis, colitis ulcerosa, and Morbus Chrohn that involved medical treatment. Specifically, one interview participant (PwP 2) with an unexpectedly stable/normalising trajectory of functional mobility reported several joint surgeries due to arthritis. Although the participant experienced challenging times during the normalisation phase during rehabilitation, she "always recovered quickly". Thus, she did not experience a sudden and substantial change in her mobility profile.

Phase 3: Data integration

Statistics by theme joint display

The integrated results matrix, e.g., the statistics by theme joint display in Tab. 4 juxtaposes interaction effects and qualitative (sub)themes while we discuss meta-inferences of the side-by-side comparisons in the discussion (Guetterman et al., 2015).

Table 4 Statistics by theme joint display

Moderation by the socioeconomic and cognitive reserve: Educational attainment		
Quantitative results		**Qualitative results**
Trajectories of functional mobility and moderation by reserve		**Subthemes**
While we detected a significiant slower decline of functional mobility in men with 10 – 16 years of education to men with less than 10 years of education, we didn't find any effect in women.		No impact experienced (means to an end)
Change in functional mobility per additional year since diagnosis in women	**Change in functional mobility per additional year since diagnosis in men**	Life experience and lifelong learning experienced as more important
< 10y: Reference	< 10 y: Reference	
10-16 y: 0.027 (95%CI: -0.227, 0.280, p = 0.837)	10-16 y: 0.333 (95%CI: 0.081, 0.584, p = 0.010)	
> 16 y: 0.078 (95%CI: -0.229, 0.384, p = 0.618)	> 16 y: 0.220 (95%CI: -0.049, 0.489, p = 0.109)	
Trajectories of functional mobility in men and women with less than 10, 10 to 16 and more than 16 years of education		

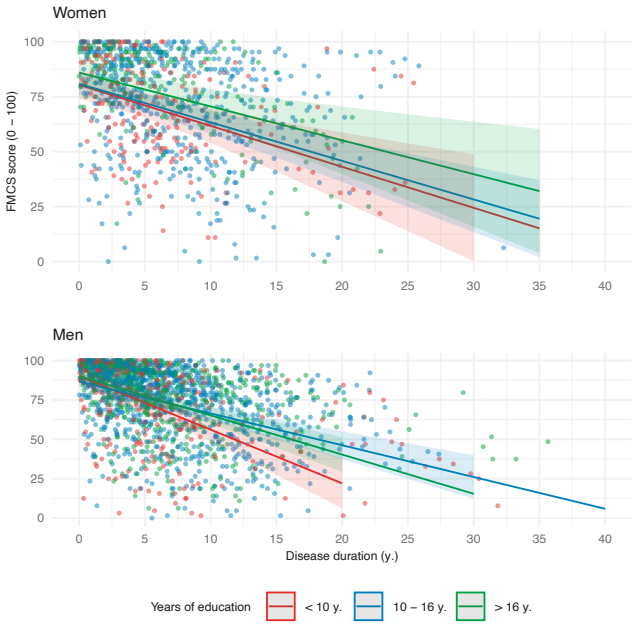


Table 4 Continued.

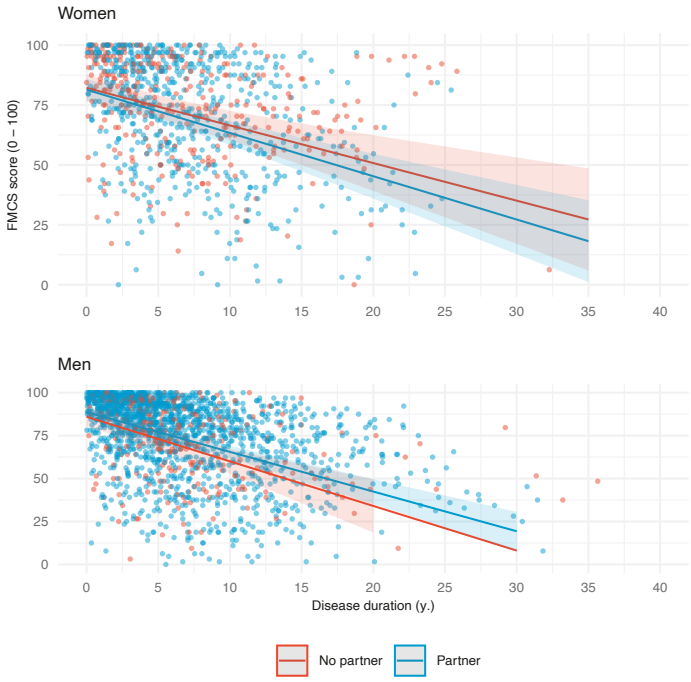
Moderation by the relational reserve: Partner			
Quantitative results		**Qualitative results**	
Trajectories of functional mobility and moderation by reserve		**Subthemes**	
We did not detect any moderations by the presence of a partner neither in men nor in women.		Barriers	Impaired health of the partner
Change in functional mobility per additional year since diagnosis in women	**Change in functional mobility per additional year since diagnosis in men**	Barriers	Worry
Single/widowed/divorced : Reference	Single/widowed/divorced : Reference	Barriers	No participation in joint activities
Partnered/Married: -0.057 (95CI: -0.258, 0.144, p = 0.577)	Partnered/Married: 0.069 (95%CI: -0.171, 0.309, p = 0.575)	Barriers	Loose friends out of sight
Trajectories of functional mobility in men and women with and without a partner		Facilitators	Impaired health of the partner
		Facilitators	"Transport service"
		Facilitators	Joint activities
		Facilitators	Structuring the day

Table 4 Continued.

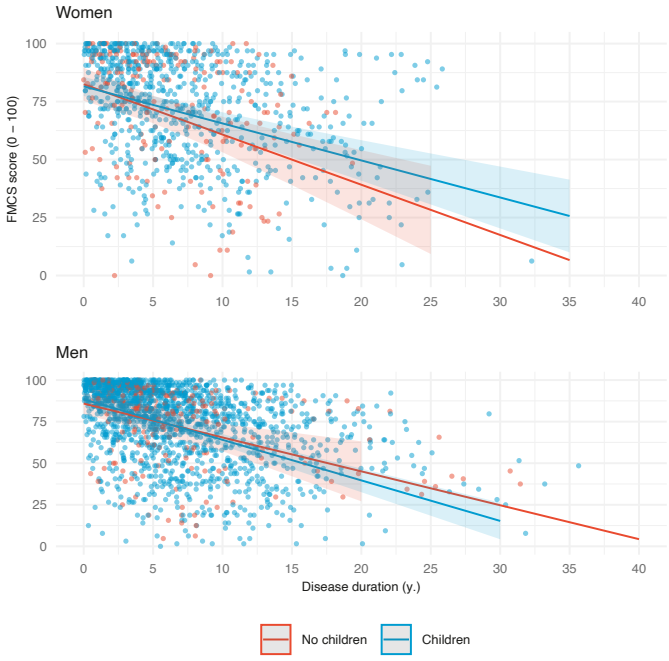
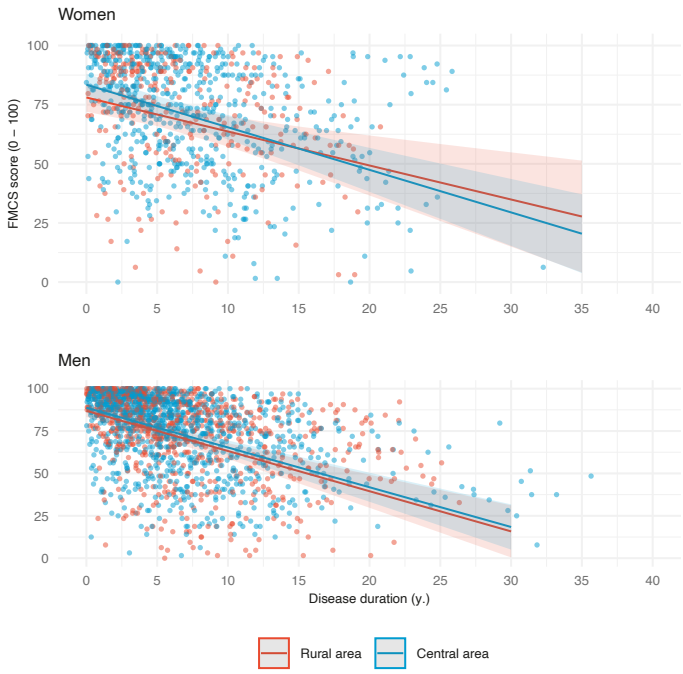
Moderation by the relational reserve: Having children			
Quantitative results		**Qualitative results**	
Trajectories of functional mobility and moderation by reserve		**Subthemes**	
We did not detect any moderations by having children neither in men nor in women.		Barriers	Violation of privacy
Change in functional mobility per additional year since diagnosis in women	**Change in functional mobility per additional year since diagnosis in men**	Barriers	Worry
No children : Reference	No children : Reference	Barriers	Take over activities without the need
Children: 0.136 (95%CI: -0.101, 0.373, p = 0.258)	Children: -0.095 (95%CI: -0.367, 0.176, p = 0.490)	Facilitators	Transport service
Trajectories of functional mobility in men and women with and without children		Facilitators	Leisure activities with children and grandchildren
		Facilitators	Take it easy
		Facilitators	Take over activities if needed

Table 4 Continued.

Moderation by the socioeconomic reserve: Place of residence			
Quantitative results		**Qualitative results**	
Trajectories of functional mobility and moderation by reserve		**Subthemes**	
We did not detect any moderations by the place of residence neither in men, nor in women.		Barriers	Walk back home
Change in functional mobility per additional year since diagnosis in women	**Change in functional mobility per additional year since diagnosis in men**		Ups & downs
Rural area: Reference	Rural area : Reference		Long distances
Central area : -0.087 (95%CI: -.0301, 0.128, p = 0.426)	Central area: 0.006 (95%CI: -0.171, 0.184, p = 0.945)		Safety issues (due to much traffic, road constructions, bad light conditions)
			No public toilets
Trajectories of functional mobility in men and women with a rural or central place of residence			No flexibility & long travel duration of public transports
			Bus stop 500 m
			Parking too big
		Facilitators	Unmet (grocery) needs
			Nature
			Short distances
			Walking aids
			Car for grocery shopping
			Taxi
			Autonomous choice when to go where
			Grocery shops close by
			Help with entering / exiting the bus
			Bus stop close by (5 min. walk)

DISCUSSION

This study provided an overview of unexpectedly stable trajectories in functional mobility in Parkinson's Disease and to what extent different reserves protected from a decline of functional mobility, which were explored quantitatively as well as qualitatively regarding the lived experience of individuals with PD. The statistical findings for the moderation of the reserves were not significant after the adjustment for multiple testing, which could partially be explained by the stratified analyses, a major strength of our longitudinal study. In addition to the results of the group-comparison, that were significant after multiple testing, we discuss the unadjusted significant results for the purpose of hypothesis generation; these results should be interpreted with caution until they are validated in an independent cohort.

First, while not significant after correction for multiple testing, functional mobility declined slower in men with 10 to 16 years of education compared to men with less than 10 years of education but not in women or men with more than 16 years of education. Secondly, by comparing the group with an unexpectedly stable/normalising trajectory to the group with a decreasing trajectory, independent of years since diagnosis, the group with an unexpectedly stable/normalising trajectory showed, after adjustment for multiple testing, lower age and age at diagnosis, respectively, less frequent diagnosis of PD dementia and better global cognition, less symptoms of depression, patient-reported motor- and non-motor symptoms, less postural instability and gait disturbances and better functional mobility at baseline. Thirdly, the deductive analyses of the semi-structured interviews identified similar themes for people with and without a reserve. However, the transport service, i.e., driving license or the disponibility of someone with a car living in the same household was experienced as central facilitating factor of functional mobility and was related to all reserves (partner, children, place of residence) except for educational attainment. Thus they could autonomously switch between places to accomplish and participate in activities of daily living, an important factor as described by Zegelin (2008). Finally, in the inductive content analysis, we identified additional psychosocial factors that might explain and characterise women with unexpectedly stable/normalising functional mobility.

Moderation by the reserves and their daily experience

Educational attainment

According to previous studies about clinical significance (Peto et al., 2001, Fitzpatrick et al., 2004, Hanff et al., 2023), the slower decline of functional mobility per additional year since diagnosis in men with 10 to 16 years of education in this study(+1.393, 95%CI: 0.340, 2.446, p = 0.010) can be considered as meaningful every three years since diagnosis. However, the effect was neither significant for women, nor for men with more than 16 years of education or after adjustment for multiple testing. Thus, this result needs to be considered as tentative

and in need of validation. Similarly, at baseline a lower educational attainment was related to more clinical-assessed motor symptoms, worse patient-reported functional mobility and postural instabilities and gait disturbances. These findings are in line with the concept of "motor reserve" where people with PD with higher educational attainment previously showed significantly fewer motor deficits than those with lower educational attainment despite greater reductions in dopamine levels (Sunwoo et al., 2016, Blume et al., 2017). Moreover, our findings indicate that in men the knowledge and skills attained through education (10 to 16 years) may make them more receptive to health education messages, or more able to communicate with and access appropriate health services (Galobardes et al., 2006). Similarly, according to Lee et al. (2024) they might show increased self-care monitoring. In our qualitative analysis, women with unexpectedly stable/normalising trajectories of functional mobility experienced similar psychosocial characteristics independent of the educational attainment. Thus, the contribution of the educational attainment to increased self-care needs to be further investigated.

We detected no moderation by educational attainment in women. Similarly, women interview participants experienced no impact of educational attainment on how they handled their trajectory of functional mobility. Moreover, they experienced educational attainment as a "means to an end", suggesting that the participants did not assign intrinsic value to schooling but rather viewed schooling as extrinsic requirement for getting a qualification while the inductive analysis revealed the importance of life experience and lifelong learning. As interview participants were aged 60 years and more and educational attainment in men and women changed over the decades (Galobardes et al., 2006), these experiences might not represent those of younger women and men with PD. Also, the effect of educational attainment might be abstract, act subconsciously and thus be difficult to reflect on interviews.

Finally, we have evidence that a higher educational attainment is associated with a central place of residence pointing to the socioeconomic aspect of educational attainment reflecting material and other resources of the family of origin with an impact on functional mobility (Beebe-Dimmer et al., 2004). Moreover, according to Webber et al. (2010), economic resources dictate activity options away from home and accessible modes of transportation. Specifically, people with lower incomes are at greater risk for mobility disability (Shumway-Cook et al., 2005).

Relational reserves

Testing the extent to which having children or a partner moderated trajectories of functional mobility, the quantitative analyses were inconclusive, suggesting no general contribution of being a parent or the partner on functional mobility. The qualitative study provided some context to those statistical results. The interviewed women with unexpectedly stable/

normalising trajectories of functional mobility experienced the partner providing the transport service combined with the joint activities as a central facilitating factor. They guaranteed an autonomous switch between places to accomplish and participate in activities of daily living. As participants without a partner experienced a similar enabling effect by a 24h caregiver living in the same household, the key facilitating factor may be less the effect of the partner himself, but the availability of a person with a driving license living in the same household and sharing the daily activities. Also, the caregivers contributions differs between men and women according to a sex-specific meta-analysis (Pinquart and Sorensen, 2006). Thus, further interviews with men with and without a partner (with and without a driving license) will help to further investigate the sex-specific role of the partner in addressing car dependency as in our interviews all partnered women with PD reported their partner being the usual car driver. Although the practical help of the partner is highly valued and noticeable in daily life, it might not always lead to statistically significant changes. Moreover, the effect of the partner might be diverse and thus challenge an adequate capture by the applied quantitative methods. Similar to worryied children, a worrying partner or caregiver was experienced as a barrier to functional mobility, while an impaired health status of the partner was experienced as barrier and facilitator depending on how the individual handled the situation (e.g., stay at home vs. go alone). Individuals with and without a partner had similar charcteristics at baseline except those with a partner had more children and where more often men, supporting analyses stratified by sex/gender taking into account life transitions (divorce, widowhood) as they have an impact on one's reserve of significant others (Kalmijn and van Groenou, 2016, Webber et al., 2010). Specifically, we observed a decline in functional mobility and social support in one participant (PwP 1) following a break-up with her husband as the partner no longer provided the transport service (Webber et al., 2010). Interestingly, we observed a subsequent improvement in emotional wellbeing and the PwP 1 reported a reactivation of the social network. Thus, future studies should not exclude potential improvements after life transitions.

In qualitative findings having children showed to have nuanced effects, as interview participants experienced not only facilitating but also hindering effects by the children. Barriers of functional mobility by their children and grandchildren were mainly reported to be violation of privacy, worrying and the children taking over of activities, thus supporting dependency of the person with PD. Specifically, worrying by the children additionally restricted participants' confidence in their functional mobility. At the same time, similar to the partners, the offpsring enhanced functional mobility by providing the transport service to important destinations. However, this dependency on their children was perceived as a burden due to limited flexibility, while dependency on the partner living in the same household was considered less problematic. Weekly mealtime visits by the grand-children were experienced as facilitator of functional mobility as it presumed grocery shopping, the most commonly reported objective for functional mobility. Joint leisure activities with

children and grandchildren tended to be more frequent in those living close by similar to the findings by Levasseur et al. (2015) in rural area, indicating children living in the neighbourhood enhanced older people's social participation. Thus, further analyses of the effect modification of children taking into account the distance of their place of residence could bring further insights. Finally, our results confirm previous findings (Shergold et al., 2012) of family, friends and neighbours providing social and practical support to older people in rural areas and helping when public transport is unavailable although the interviewed women experienced the effect of the children on patient-reported functional mobility not as that facilitating as the effect of the partner.

Place of residence

Our inconclusive statistical findings might be better understood by the qualitative findings. Thus, interviewed women with a stable/normalising trajectory experienced no effect of a central place of residence as due to the spatial distribution of local resources they were depending on a car for grocery shopping and other activities, despite living in a central area with usually more favourable social and physical surrounding areas (Balfour and Kaplan, 2002, Bowling et al., 2006). Thus, car dependence probably reduced the effect of the central place of residence on functional mobility since mobility largely depended on the ability to drive rather than the characteristics of the living environment. Our findings are in line with another mixed-methods study reporting car dependence as a barrier to actively ageing in place (John and Gunter, 2016). However, further residential neighbourhood conditions might enable older adults (with PD) to "age in place" (Duncan et al., 2018). While our interview participants experienced the accessibility of the grocery shops and public transports as facilitating factor, Levasseur et al. (2015) indicated that in rural areas accessibility to critical resources (within walking distance, i.e., reachable within a 10 or 20-minutes walk from home, Levasseur et al. (2015)), having a driver's license and more years lived in the current dwelling were factors enhancing older people's social participation.

Interestingly, one interview participant (PwP 1, younger living in the city centre) with low educational attainment experienced the effect of the central place of residence allowing flexibility to accomplish and participate in activities of daily living without a car. Thus, further analyses with a refined classification of the place of residence should be conducted. Finally, some interviewed women showed an unexpectedly stable/normalising trajectory of functional mobility despite limited physical mobility due to car dependency and having neither a partner nor children. Further characteristics of those individuals were explored in the inductive analysis.

Characteristics of individuals with unexpectedly stable/normalising trajectories

The quantitative study provided little evidence for general determinants of functional mobility over time. While the maximum variation sampling of participants with varying

reserves led to a heterogeneous group of interview participants, all women participants with unexpectedly stable/normalising trajectories of functional mobility had some common (psychosocial) characteristics: they reported resilience in the face of social confrontations and openness towards new experiences (also towards new technology), they provided and asked for support and they demonstrated a life-affirming, sociable attitude, with high self-efficacy beliefs while adapting their expectations and accepting their limits. Also they refered to self-care activities promoting a physically active lifestyle.

The psychosocial characteristics identified in the inductive analysis describe the individuality of the person influencing the process of becoming bedridden as described by Zegelin (2008). Specifically, the adaptation of their expectations and acceptance of the limits can be seen as a way to reduced the Calman's gap (the difference between expectations and the actual experience, Calman (1984)). According to Prell et al. (2020), the expectations of people with PD differed from the actual experience most for physical functions requiring functional mobility. While depression (probably linked to our identified psychosocial characteristics) increased a female sex/gender and/or a partner decreased the Calman's gap. In the current study, the group with stable/normalising patient-reported functional mobility was characterised by less symptoms of depression, experiencing an adaptation of their expectations. Consequently, we expect a smaller Calman's gap in this group and thus a better experience of patient-reported functional mobility compared to the decreasing group. Further research could help to understand the sex-specific role of those factors, the partner, psychosocial characteristics on the Calmans's gap in people with fluctuating motor and non-motor symptoms. Finally, the identified psychosocial characteristics are in line with the self-efficacy theory, which explains that self-efficacy motivates behaviour and performance (Bandura, 1986). Thus, participants with an unexpectedly stable/normalising trajectory experienced psychosocial factors similar to self-efficacy motivating self-care to maintain health by pursuing healthy behaviours and managing disease (Riegel et al., 2012). This self-care is similar to the biographical, illness-related and everyday life work of the individual (Corbin and Strauss, 2010, Corbin, 1991). The unexpectedly stable/normalising trajectories of functional mobility could be seen as an indicator of effective maintenance of health through self-care.

In our inductive analysis, we also identified a way of self-care (physically active lifestyle) as a further characteristic in individuals with unexpectedly stable/normalising trajectory of functional mobility. This finding aligns with the elaborations by Bouca-Machado et al. (2018) and the findings of a recent systematic review (Ernst et al., 2023) providing evidence of beneficial effects on the severity of motor symptoms and quality of life for most types of physical exercise for people with PD. Thus, a physically active lifestyle might be one of the healthy behaviours in self-care helping women with PD to maintain a stable/normalising trajectory of functional mobility.

Finally, in three of the five interview participants reported the co-existence of another chronic inflammatory comorbidity with similar antibody treatments. A comprehensive, multi-faced and interdisciplinary case description involving neurologists and rheumatologists could lead to new insights.

Strengths and limitations

Integrating quantitative and qualitative data in a mixed-methods design provided an in-depth understanding of meanings, contexts and processes of unexpectedly functional mobility in people with PD. Moreover, the selection of interview participants based on extracted random effects and available sociodemographic and health-related characteristics helped to identify, and thus purposively select participants for the interviews, helping us understand the core experiences of people with unexpectedly stable/normalising functional mobility.
Although an analysis taking into account the temporality of the changes could be a more robust approach, we assumed the included reserves were time constant (e.g., educational attainment) as they probably preceded the diagnosis of PD and deterioration and did not change during the observation period. While the characteristics at baseline of women and men as well as of individuals with and without reserves differed, according to the assumptions in the directed acyclic graphs, no further adjustments were required. Qualitative interviews combined with yearly longitudinal data helped to fill out the details of the events and to understand the motives and mechanisms involved in their occurrence (Bazeley, 2018). Moreover, future research needs to consider multiple causes for unexpectedly stable/normalising trajectories of functional mobility and interactions among the different reserves and determinants of functional mobility (Webber et al., 2010).

Although data collection standards were applied to minimise missing data and information bias, the COVID-19 pandemic and deaths since baseline assessment (107, 12.9%) may be responsible for some proportion of missing data. We included only women in the qualitative study restricting the generalisability of the qualitative study to women with PD. However, our narrow aim and high specificity due to the semi-structured interviews and deductive content analysis (based on quantitative findings and theories (Webber et al., 2010, Adlbrecht and Mayer, 2018, Zegelin, 2008, Antonovsky, 1979, Corbin, 1991)) helped to get to the point of data saturation. Our interviews retrospectively reflected a longitudinal trajectory over several years. Future research should try to conduct longitudinal recurrent interviews and more in-depth investigations of the social structural processes by advanced qualitative methods, followed by systematic testing with statistical techniques (exploratory sequential mixed methods design).

Our work is not exhaustive since not all potentially relevant variables were available in the dataset of the Luxembourg Parkinson's Study (Hipp et al., 2018) and the sample was not large enough to arrive at narrow confidence intervals. Specifically, the small marginal R^2

and the large conditional R^2 suggest a limited moderation by the included fixed effects and thus a trajectory independent of the reserves. In addition, despite the bigger sample size, the confidence intervals of the reserves for men were wider than for women indicating a lot of variation and suggesting that other factors may help to understand unexpectedly stable/normalising functional mobility. By investigating the facilitators identified in our study and by taking into account the change of meaning of the reserves over time, future research can help to reveal the unexplained variance.

Implications

Functional mobility is an important prerequisite for living autonomously and carrying out activities of daily living. Our study highlights the opportunities to empower individuals with PD to maintain or develop self-efficacy. Furthermore, the increasing gap between the current and the desired state as disease progresses and functional mobility decreases, may lower the individuals' quality of life and requires special attention by the health care professionals. Thus, instead of focussing on the physiological progression of the disease alone, the active role of people in shaping the trajectory of a disease needs to taken into account (Corbin and Strauss, 2010). Specifically, individuals with PD should be involved as equal partners by jointly discussing their individual trajectories of motor- and nonmotor symptoms (Riggare et al., 2021) compared to the average progression (Hanff et al., 2023a). This might help them to develop realistic expectations and a treatment plan empowering them to manage the symptoms and control the disease trajectory. At the same time and as previously described by Mason et al. (2016), interview participants often thought changes were part of ageing. Thus, familiarising individuals with the possibilities and raising realisitic expectations of health is also essential to avoid individuals setting low expectations leading to a tolerance of restricted autonomy (Carr et al., 2001). Also, individuals with PD might benefit from further alternatives to the car as means of transportation independent of their place of residence, as well as housing arrangements with better support structures.

Finally, in individuals with a co-existing chronic inflammatory comorbidity, we observed two trajectories running in parallel, with the more rapidly progressing trajectories or distressing symptoms (pain, incontinence) taking up the largest effort. Thus, in addition to PD-related symptoms' trajectories, parallel psychological, social and other illness trajectories not directly related to PD require adapted interventions by health professionals.

CONCLUSION

Unexpectedly stable trajectories of functional mobility in PD have clinical and care relevance for affected individuals, our quantitative analyses did not provide evidence for general determinants of functional mobility over time. From the qualitative data, the study supports

the provision of local amenities within walking distance to enable active and healthy ageing in place. As this proactive design of living areas is not yet put in place, our qualitative findings highlight the importance of a driving license, a 24-hour caregiver or a partner living in the same household and sharing activities of daily living with the individual with PD for functional mobility. Moreover, in the qualitative analyses, psychosocial factors similar to self-efficacy and a physically active lifestyle helped to understand the phenomenon of functionality (functional mobility) despite disability (years since diagnosis) and a challenging context (living without a partner or children in rural areas). Finally, further research could further explore our generated hypotheses to inform interventions promoting functional mobility and healthy aging across diverse populations.

SUPPLEMENTARY MATERIAL

Table S1 Characteristics of included constructs

	Source of identification	Role in statistical analysis	Moment of assessment	Construct intended to measure
Relational reserves				
1	Clinical reasoning and theoretical framework for mobility (Webber et al., 2010)	Effect modifier	Time constant since baseline assessment	Having children
2	Theoretical framework for mobility (Webber et al., 2010)	Effect modifier	Time constant since baseline assessment	Being married or partnered
Socioeconomic reserve				
3	Clinical reasoning and theoretical framework for mobility (Webber et al., 2010)	Effect modifier	Time constant since baseline assessment	Place of residence Surrogate outcome for socioeconomic reserve
Socioeconomic & cognitive reserve				
4	Clinical reasoning and theoretical framework for mobility (Webber et al., 2010)	Covariate Effect modifier	Time constant since baseline assessment	Educational status Surrogate outcome for socioeconomic and cognitive reserve
Others				
5	Clinical reasoning and theoretical framework for mobility (Webber et al., 2010)	Exposure	Time variant with baseline assessment and yearly follow-up	Years since diagnosis
6	Literature review (Lindh-Rengifo et al., 2021, Ryder-Burbidge et al., 2022) and theoretical framework for mobility (Webber et al., 2010)	Covariate	Time constant since baseline assessment	Age at baseline assessment
7	Literature review (Ryder-Burbidge et al., 2022, Lindh-Rengifo et al., 2021) and theoretical framework for mobility (Webber et al., 2010)	Stratification	Time constant since baseline assessment	Sex/Gender
8	Theoretical framework for mobility (Webber et al., 2010)	Covariate	Country of residence	Country of residence

Note MDS: Movement Disorders Society, UPDRS: Unified Parkinson's Disease Rating Scale, PDQ39 : Parkinson's disease questionnaire

4 0 = No, > 0 = Yes

5 Single, widowed or divorced [reference], partnered or married

6 Rural area = Rural farm or rural non farm; Central area = Large city, suburb of a large city, midsized city, large town or small town Rural area [reference], central_area

	Instrument	Type	Assessment type	Variable name in R code
	Question at baseline assessment: How many children do you have ?	Dichotomized numerical variable[4]	Interview	dm_children_cat
	Question at baseline assessment: What is your actual maritial status ?	Categories[5]	Interview	partner_cat
	PD-RFQ-U: At the time you lived there, was this residence located in a large city, suburb of a large city, midsized city, large town, small town, rural – farm, rural – non farm ?	Dichotomized categories[6]	Patient-Reported Outcome Measure	rural_area_cat
	Years of education	Numerical Categorised numerical variable	Interview	dm_educ_y_cat
	Date of assessment – Date of diagnosis	Numerical	Interview	disease_duration
	Question : What is your date of birth ?	Numerical variable	Interview	dm_years
	Question : What is your sex ?	Dichotomous	Interview	dm_gender_cat
	Question: What is your actual address?	Dichotomized categories	Interview	Country_of_residence_cat

Table S2 Interview guide with the rationale for the questions

Relevant quantitative findings	Interview question	Rationale for the question
225 individuals in the 3rd tertile experienced an unexpectedly stable/ normalising trajectory	You were diagnosed with Parkinson's disease X years ago. Parkinson's disease can restrict your mobility and independence…	
	1. How do you experience your mobility and independence today?	Decision for or against further mobility is affected by experiences during mobilisation (Zegelin, 2008)
	2. Regarding your mobility and independence, what is your goal?	Elicit the individuality of the person (Zegelin, 2008) and their goal to tackle reduced independence resulting from declining mobility (Depending on their goals, they might not exploit their capabilities to their maximum as they tend not to overachieve their goals (Adlbrecht and Mayer, 2018))
	3. In what perimeter were you mobile in the past year? (Room to Abroad)	Elicit experiences of a safe level of mobility (Adlbrecht and Mayer, 2018)
	4. Can you describe an average week?	Assess the current level of functional mobility (Zegelin, 2008)
	5. How autonomous can you decide when and how to be mobile?	Elicit experience of autonomous decision-making in switching between places (Zegelin, 2008)
	6. Has your mobility and independence changed in recent years? How did you experience this?	Elicit conscious reflection about the nature of the stable/normalising trajectory of functional mobility
	7. Over the years, have there been any challenging moments/ situations? Can you describe them to me?	Elicit experience of an immobility event (Zegelin, 2008)
	8. Over the years, which symptoms have caused you the most difficulties with your mobility and independence? (See individual trajectories)	Elicit experience of an immobility event (Zegelin, 2008)
	9. How did you cope with these situations? What helped you? Can you give some examples?	Elicit the work undertaken by people with PD (biographical, illness-related, everyday life work) in the management of Parkinson's disease (Corbin, 1991)
		Elicit experience of the better trajectory
		Elicit experiences of a safe level of mobility (Adlbrecht and Mayer, 2018)
		Elicit experience of sex-specific differences (Webber et al., 2010)
		Elicit the individuality of the person (Zegelin, 2008) and their goal to tackle reduced independence resulting from declining mobility (Adlbrecht and Mayer, 2018)

Table S2 Continued.

Relevant quantitative findings	Interview question		Rationale for the question
225 individuals in the 3rd tertile experienced an unexpectedly stable/ normalising trajectory	10.	Please have a look at your individual trajectory compared to the average trajectory.	Elicit the work undertaken by people with PD (biographical, illness-related, everyday life work) in the management of Parkinson's disease (Corbin, 1991)
		If you look at your trajectory of functional mobility now, does this trajectory correspond to your experience?	Elicit experience of the better trajectory
		What comes to your mind when you look at your trajectory compared to the average trajectory?	Elicit experiences of a safe level of mobility (Adlbrecht and Mayer, 2018)
		How do you explain your trajectory?	Elicit experience of sex-specific differences (Webber et al., 2010)
		How did you experience particular negative moments in your trajectory?	Elicit the individuality of the person (Zegelin, 2008) and the objective to tackle reduced independence due to mobility decline (Adlbrecht and Mayer, 2018)
		How did you experience particular positive moments in your trajectory?	Elicit practical recommendations to maintain functional mobility
		You have shown a better progression than most of the other participants. What can the others learn from you? Do you have any tips? If so, which ones?	
Further questions			
No significant moderation by the partner	11.	How do you experience the role of your partner in handling challenging mobility situations?	Elicit the attitude (goals), knowledge and burden of the carers (Zegelin, 2008)
No significant moderation by the children	12.	How do you experience the role of your children in handling challenging mobility situations?	Elicit the role of engagement in social activities (Adlbrecht and Mayer, 2018)
	13.	Do you feel that the challenging situations were a burden for your family and friends? Can you elaborate on this?	Elicit experience of sex-specific differences (Webber et al., 2010)
	14.	Do you feel that those around you knew how to help themselves and you? Can you give examples?	Elicit experience of autonomous decision-making in switching between physical locations (Zegelin, 2008)
10 to 16 years of education is associated with a slower decline in functional mobility in men	15.	How do you experience the role of your diploma degree/ educational attainment in handling challenging mobility situations?	Elicit financial and environmental factors (Webber et al., 2010)
No significant moderation by the place of residence	16.	How do you experience the role your place of residence and arrangements might play in handling challenging mobility situations?	
	17.	How do you experience the role of a driving license in your place of residence?	

Table S3 Summary measures of patient-reported functional mobility over time

Visit (n)	Mean (SD) / n (%)	Min. - Max.	Median (IQR)	Missing N (%)	Skewness
Baseline (829)	74.9 (22.8)	0.0 – 100.0	81.2 (31.2)	48 (5.8%)	-1.06
1st follow-up (649)	77.0 (20.9)	0.0 – 100.0	82.8 (28.1)	69 (10.6%)	-1.00
2nd follow-up (545)	75.1 (22.4)	0.0 – 100.0	82.8 (31.2)	74 (13.6%)	-1.05
3rd follow-up (428)	73.4 (22.3)	1.6 – 100.0	78.9 (32.8)	66 (15.4%)	-0.93
4th follow-up (347)	71.4 (23.5)	1.6 – 100.0	76.6 (31.2)	52 (15.0%)	-0.94
5th follow-up (229)	69.8 (24.0)	4.7 – 100.0	76.6 (40.6)	44 (19.2%)	-0.69
6th follow-up (144)	68.6 (23.8)	4.7 – 100.0	75.0 (34.4)	21 (14.6%)	-0.83
7th follow-up (93)	69.4 (23.9)	6.3 – 100.0	75.0 (35.9)	8 (0.%)	-0.79

Table S4 Sociodemographic and health-related characteristics across individuals with different years of education

	< 10 y. (n = 162)		10–16 y. (n = 428)		> 16 y. (n = 230)		p-value
Age	72.9	(10.6)	67.5	(14.0)	66.0	(14.3)	<0.001**
Male sex/gender	94	(58.0%)	274	(64.0%)	175	(76.1%)	<0.001**
Married/Partnered	118	(73.3%)	323	(75.6%)	178	(77.7%)	0.151
Children (n)	2.0	(1.0)	2.0	(1.0)	2.0	(2.0)	0.108
Central place of residence	85	(52.8%)	246	(58.7%)	146	(66.7%)	0.020*
Luxembourgish as first spoken language	91	(56.2%)	189	(44.2%)	78	(33.9%)	<0.001**
Country of residence Luxembourg	124	(76.5%)	240	(56.1%)	144	(62.9%)	<0.001**
Years since diagnosis	3.2	(5.1)	3.5	(6.7)	2.6	(4.8)	0.045*
Age at diagnosis	70.0	(14.0)	62.0	(15.0)	60.0	(16.0)	<0.001**
MoCA (0 – 30)[b]	23.0	(5.0)	26.0	(5.0)	26.0	(4.0)	<0.001**
PDD diagnosis	38	(23.5%)	42	(9.8%))	16	(7.0%)	<0.001**
BDI-I (0 – 63)[a]	8.0	(10.0)	8.0	(9.0)	8.0	(8.0)	0.343
MDS-UPDRS I (0 – 52)[a]	10.0	(8.2)	9.0	(8.0)	9.0	(8.0)	0.204
MDS-UPDRS II (0 – 52)[a]	10.0	(11.5)	10.0	(10.0)	8.0	(8.2)	0.099
MDS-UPDRS III (0 – 132)[a]	37.0	(23.0)	32.0	(23.0)	29.0	(19.0)	< 0.001**
MDS-UPDRS IV (0 – 24)[a]	0.0	(0.0)	0.0	(2.0)	0.0	(1.0)	0.006*
PIGD Score (0 – 20)[a]	3.0	(5.0)	2.0	(4.0)	2.0	(3.0)	< 0.001**
FMCS (0 – 100)[b]	81.2	(34.4)	78.1	(31.2)	85.9	(23.4)	0.008**

Note * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm). Categorical variables: counts (%), numerical variables: median (IQR), a: Greater = worse, b: Greater = better, discrete variables: Kruskal-Wallis test , categorical variables: chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MoCA: Montreal Cognitive Assessment, PIGD: Postural Instabilities and Gait Disturbances, UPDRS: Unified Parkinson's Disease Rating Scale

Table S5 Sociodemographic and health-related characteristics across individuals with and without a partner/married

	Single/ Divorced/Widowed (n = 199)		∑	Partnered/ Married (n = 625)	p-value
Age	67.9	(15.5)	68.2	(13.9)	0.954
Male sex/gender	90	(45.2%)	456	(73.0%)	<0.001**
Children (n)	1.0	(2.0)	2.0	(2.0)	<0.001**
Years of education	12.0	(6.0)	13.0	(6.0)	0.224
Central place of residence	129	(66.8%)	348	(57.3%)	0.028*
Luxembourgish as first spoken language	94	(47.2%)	264	(42.0%)	0.250
Country of residence Luxembourg	128	(64.3%)	381	(61.1%)	0.458
Years since diagnosis	3.3	(6.3)	3.0	(6.1)	0.358
Age at diagnosis	63.0	(18.0)	63.0	(16.0)	0.788
MoCA (0 – 30)[b]	26.0	(5.2)	25.0	(5.0)	0.968
PDD diagnosis	22	(11.1)	75	(12.0)	0.815
BDI-I (0 – 63)[a]	9.0	(8.0)	8.0	(9.0)	0.045
MDS-UPDRS I (0 – 52)[a]	10.0	(8.5)	9.0	(8.0)	0.132
MDS-UPDRS II (0 – 52)[a]	9.0	(8.8)	9.0	(10.0)	0.422
MDS-UPDRS III (0 – 132)[a]	31.0	(25.8)	32.0	(21.0)	0.541
MDS-UPDRS IV (0 – 24)[a]	0.0	(1.0)	0.0	(1.0)	0.937
PIGD Score (0 – 20)[a]	2.0	(4.0)	2.0	(4.0)	0.741
FMCS (0 – 100)[b]	78.9	(29.7)	81.2	(31.2)	0.345

Note * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm). Categorical variables: counts (%), numerical variables: median (IQR), a: Greater = worse, b: Greater = better, numerical variables: two-sided Wilcoxon rank-sum test, categorical variables: chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MoCA: Montreal Cognitive Assessment, PIGD: Postural Instabilities and Gait Disturbances, UPDRS: Unified Parkinson's Disease Rating Scale

Table S6 Sociodemographic and health-related characteristics across individuals with and without children

	No children (n = 124)		Children (n = 701)		p-value
Age	65.6	(15.5)	68.6	(14.3)	0.954
Male sex/gender	70	(56.5%)	477	(68.1%)	0.016*
Married/Partnered	65	(52.8%)	558	(79.9%)	<0.001**
Years of education	13.0	(5.0)	13.0	(6.0)	0.346
Central place of residence	71	(58.7%)	407	(59.9%)	0.887
Luxembourgish as first spoken language	59	(47.6%)	302	(43.1%)	0.030*
Country of residence Luxembourg	74	(59.7%)	438	(62.6%)	0.609
Years since diagnosis	2.7	(5.7)	3.2	(6.2)	0.357
Age at diagnosis	59.5	(18.0)	64.0	(16.0)	0.009*
MoCA (0 – 30)[b]	26.0	(5.0)	25.0	(6.0)	0.583
PDD diagnosis	12	(9.7%)	85	(12.1%)	0.529
BDI-I (0 – 63)[a]	8.0	(9.0)	8.0	(10.0)	0.714
MDS-UPDRS I (0 – 52)[a]	9.0	(9.0)	9.0	(9.0)	0.985
MDS-UPDRS II (0 – 52)[a]	8.5	(11.0)	9.0	(10.0)	0.622
MDS-UPDRS III (0 – 132)[a]	29.5	(20.2)	32.0	(22.0)	0.161
MDS-UPDRS IV (0 – 24)[a]	0.0	(0.0)	0.0	(1.0)	0.837
PIGD Score (0 – 20)[a]	2.0	(3.0)	2.0	(4.0)	0.798
FMCS (0 – 100)[b]	82.8	(34.4)	81.2	(31.2)	0.448

Note * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm). Categorical variables: counts (%), numerical variables: median (IQR), a: Greater = worse, b: Greater = better, numerical variables: two-sided Wilcoxon rank-sum test, categorical variables: chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MoCA: Montreal Cognitive Assessment, PIGD: Postural Instabilities and Gait Disturbances, UPDRS: Unified Parkinson's Disease Rating Scale

Table S7 Sociodemographic and health-related characteristics across central and rural place of residences

	Rural (n = 325)		Central (n = 480)		p-value
Age	67.7	(17.4)	68.8	(12.5)	0.016*
Male sex/gender	227	(69.8%)	306	(63.8%)	0.016*
Married/Partnered	259	(80.2%)	348	(73.0%)	0.063
Children (n)	2.0	(2.0)	2.0	(1.0)	0.070
Years of education	12.0	(5.0)	13.0	(6.0)	<0001**
Luxembourgish as first spoken language	166	(51.1%)	184	(38.4%)	0.002**
Country of residence Luxembourg	209	(64.3%)	287	(59.8%)	0.223
Years since diagnosis	3.4	(6.3)	3.1	(6.0)	0.457
Age at diagnosis	62.0	(18.0)	64.0	(15.0)	0.009*
MoCA (0 – 30)[b]	26.0	(6.0)	25.0	(5.0)	0.536
PDD diagnosis	42	(12.9%)	55	(11.5%)	0.606
BDI-I (0 – 63)[a]	8.0	(10.0)	8.0	(9.0)	0.969
MDS-UPDRS I (0 – 52)[a]	9.0	(8.0)	9.0	(9.0)	0.712
MDS-UPDRS II (0 – 52)[a]	10.0	(10.8)	9.0	(9.0)	0.187
MDS-UPDRS III (0 – 132)[a]	34.0	(24.8)	31.0	(22.0)	0.004*
MDS-UPDRS IV (0 – 24)[a]	0.0	(1.0)	0.0	(1.0)	0.691
PIGD Score (0 – 20)[a]	2.0	(4.0)	2.0	(4.0)	0.647
FMCS (0 – 100)[b]	79.7	(31.2)	81.2	(32.8)	0.337

Note * = nominally significant, ** significant after adjustment for FWER 5% (Bonferroni-Holm). Categorical variables: counts (%), numerical variables: median (IQR), a: Greater = worse, b: Greater = better, numerical variables: two-sided Wilcoxon rank-sum test, categorical variables: chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MoCA: Montreal Cognitive Assessment, PIGD: Postural Instabilities and Gait Disturbances, UPDRS: Unified Parkinson's Disease Rating Scale

Table S8 Characteristics of the study participants at baseline (N = 829) incl. numbers of missing data for each variable of interest

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (Pct25-75)	Missing N (%)
Sociodemographic characteristics				
Age (y.)	67.0 (10.8)	22.0 – 92.9	68.2 (60.0 – 74.4)	2 (0.2%)
Sex				0 (0.0%)
Female	280 (33.8%)			
Male	549 (66.2%)			
Years of Education	13.1 (4.1)	1.0 – 30.0	13.0 (10.0 - 16.0)	9 (1.1%)
Country of residence				1 (0.1%)
Luxembourg	514 (62.1%)			
Outside Luxembourg	314 (37.9%)			
Marital status				5 (0.6%)
Single	45 (5.5%)			
Married / Partnered	625 (75.9%)			
Divorced / Bereaved	154 (18.7%)			
Health-related characteristics				
Final diagnosis				0 (0%)
Typical PD	732 (88.3%)			
PDD	97 (11.7%)			
Hoehn and Yahr (H&Y) Disease Stages				17 (2.1%)
H&Y 1	90 (10.9%)			
H&Y 1.5	70 (8.4%)			
H&Y 2	412 (49.7%)			
H&Y 2.5	107 (12.9%)			
H&Y 3	77 (9.2%)			
H&Y 4	40 (4.8%)			
H&Y 5	16 (1.9%)			
Years since diagnosis	4.9 (5.0)	0.0 – 32.3	3.1 (1.1 - 7.3)	59 (7.1%)
Age at diagnosis (y.)	62.5 (11.7)	18.0 – 91.0	63.0 (54.0 – 71.0)	12 (1.5%)
Time to diagnosis (y.)	2.7 (5.1)	-1.0 – 46.0	1.0 (0.0 – 3.0)	35 (4.2%)
Non-motor symptoms				
MoCA (0 – 30)[b]	24.6 (4.2)	5.0 – 30.0	25.0 (23.0 - 28.0)	19 (2.3%)
BDI-I (0 – 63)[a]	9.9 (7.4)	0.0 – 51.0	8.0 (5.0 - 14.0)	47 (5.7%)
MDS-UPDRS I (0 – 52)[a]	10.4 (6.9)	0.0 – 39.0	9.0 (5.0 - 14.0)	34 (4.1%)
Motor symptoms				
MDS-UPDRS II (0 – 52)[a]	10.9 (8.3)	0.0 – 48.0	9.0 (5.0 - 15.0)	25 (3.0%)
MDS-UPDRS III (0 – 132)[a]	33.8 (16.7)	0.0 – 100.0	32.0 (22.0 - 44.0)	21 (2.5%)
MDS-UPDRS IV (0 – 24)[a]	1.5 (3.2)	0.0 – 16.0	0.0 (0.0 - 1.0)	17 (2.1%)
PIGD Score (0 – 20)[a]	3.5 (3.8)	0.0 – 20.0	2.0 (1.0 – 5.0)	26 (3.1%)
FMCS (0 – 100)[b]	74.9 (22.8)	0.0 – 100.0	81.2 (62.5 - 93.8)	48 (5.8%)

Note a: Greater = worse, b: Greater = better, numerical variables: two-sided Wilcoxon rank-sum test, categorical variables: chi-squared test, Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disturbances, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Table S9 Moderation by reserves in men and women

	Educational attainment					
	Men			Women		
Predictors	**stand. B (CI 95%)**	**P-Value**	**df**	**stand. B (CI 95%)**	**P-Value**	**df**
(Intercept)	-0.358 (-0.598 – -0.118)	0.003	490.244	-0.256 (-0.537 – 0.025)	0.074	268.397
Years since diagnosis	-0.814 (-1.037 – -0.592)	<0.001	433.134	-0.447 *** (-0.670 – -0.224)	<0.001	202.051
Fixed effect: Age (years)	-0.156 (-0.230 – -0.082)	<0.001	493.939	-0.080 (-0.197 – 0.037)	0.180	266.208
Fixed effect: Country of residence [Outside Luxembourg]	-0.148 (-0.312 – 0.015)	0.075	487.258	0.006 (-0.238 – 0.250)	0.960	255.978
Fixed effect: Years of education						
Fixed effect: Years of education [10 - 16 y of education]	0.263 (-0.001 – 0.527)	0.051	475.271	0.057 (-0.256 – 0.371)	0.719	256.878
Fixed effect: Years of education [>16 y of education]	0.275 (-0.006 – 0.556)	0.055	474.623	0.350 (-0.039 – 0.740)	0.078	255.803
Effect modification: years since diagnosis × [10 - 16 y of education]	0.333 (0.081 – 0.584)	0.010	410.081	0.027 (-0.227 – 0.280)	0.837	189.097
Effect modification: years since diagnosis × [> 16 years of education]	0.220 (-0.049 – 0.489)	0.109	418.452	0.078 (-0.229 – 0.384)	0.618	171.661
Fixed effect: Have a partner [Yes]						
Effect modification: years since diagnosis × Have a partner [Yes]						
Random effects						
σ2	0.17			0.15		
τ00	0.78 ND			0.74 ND		
τ11	0.42 ND.disease_duration			0.17 ND.disease_duration		
ρ01	0.58 ND			0.34 ND		
ICC	0.87			0.86		
N	515 ND			257 ND		
Observations	1882			913		
Marginal R2 / Conditional R2	0.228 / 0.901			0.165 / 0.884		

	Partner					
	Men			Women		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
	-0.289 (-0.518 – -0.061)	0.013	469.504	-0.077 (-0.309 – 0.155)	0.514	265.680
	-0.621 (-0.843 – -0.399)	<0.001	430.367	-0.376 (-0.541 – -0.210)	<0.001	197.590
	-0.164 (-0.240 – -0.089)	<0.001	491.638	-0.094 (-0.212 – 0.024)	0.118	268.621
	-0.162 (-0.326 – 0.001)	0.052	483.429	-0.007 (-0.249 – 0.235)	0.956	259.034
	0.054 (-0.019 – 0.127)	0.149	483.936	0.053 (-0.059 – 0.165)	0.350	251.627
	0.204 (-0.038 – 0.446)	0.098	454.738	-0.110 (-0.363 – 0.143)	0.393	247.010
	0.069 (-0.171 – 0.309)	0.575	414.285	-0.057 (-0.258 – 0.144)	0.577	176.474
	0.17			0.15		
	0.77 ND			0.75 ND		
	0.43 ND.disease_duration			0.16 ND.disease_duration		
	0.58 ND			0.34 ND		
	0.87			0.86		
	512 ND			257 ND		
	1871			913		
	0.214 / 0.900			0.154 / 0.882		

Table S9 Continued.

	Children					
	Men			Women		
Predictors	**stand. B (CI 95%)**	**P-Value**	**df**	**stand. B (CI 95%)**	**P-Value**	**df**
(Intercept)	-0.125 (-0.391 – 0.142)	0.359	480.412	-0.258 (-0.545 – 0.029)	0.078	244.545
Years since diagnosis	-0.487 (-0.744 – -0.230)	<0.001	445.379	-0.519 (-0.734 – -0.303)	<0.001	199.007
Fixed effect: Age (y)	-0.154 (-0.229 – -0.080)	<0.001	495.484	-0.093 (-0.211 – 0.024)	0.120	265.324
Fixed effect: Country of residence [Outside Luxembourg]	-0.144 (-0.308 – 0.020)	0.085	486.718	-0.019 (-0.264 – 0.226)	0.880	259.401
Fixed effect: Years of education	0.051 (-0.023 – 0.125)	0.174	485.279	0.056 (-0.056 – 0.169)	0.324	251.603
Fixed effect: Children [Yes]	-0.008 (-0.284 – 0.267)	0.952	456.539	0.145 (-0.163 – 0.454)	0.355	238.561
Effect modification: Children [Yes]	-0.095 (-0.367 – 0.176)	0.490	423.595	0.136 (-0.101 – 0.373)	0.258	177.660
Fixed effect: Place of residence [Central]						
Effect modification: Place of residence [Central]						
Random effects						
σ2	0.17			0.15		
τ00	0.78 ND			0.75 ND		
τ11	0.43 ND.disease_duration			0.16 ND.disease_duration		
ρ01	0.59 ND			0.34 ND		
ICC	0.87			0.86		
N	513 ND			256 ND		
Observations	1872			909		
Marginal R2 / Conditional R2	0.211 / 0.900			0.148 / 0.881		

	Place of residence					
	Men			Women		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
	-0.181 (-0.335 – -0.027)	0.021	502.034	-0.218 (-0.457 – 0.021)	0.074	262.395
	-0.566 (-0.705 – -0.428)	<0.001	406.239	-0.344 (-0.531 – -0.158)	<0.001	215.380
	-0.165 (-0.240 – -0.090)	<0.001	488.004	-0.106 (-0.228 – 0.016)	0.089	264.769
	-0.151 (-0.315 – 0.013)	0.071	481.697	-0.026 (-0.274 – 0.222)	0.837	253.189
	0.044 (-0.031 – 0.119)	0.248	481.364	0.036 (-0.081 – 0.152)	0.549	249.294
	0.089 (-0.096 – 0.273)	0.347	465.113	0.120 (-0.152 – 0.391)	0.386	248.426
	0.006 (-0.171 – 0.184)	0.945	381.604	-0.087 (-0.301 – 0.128)	0.426	181.114
	0.17			0.15		
	0.78 ND			0.75 ND		
	0.43 ND.disease_duration			0.18 ND.disease_duration		
	0.58 ND			0.32 ND		
	0.87			0.86		
	508 ND			251 ND		
	1875			907		
	0.211 / 0.900			0.150 / 0.884		

Table S10 Theme summary table for the deductive analysis

Reserves	Subthemes	Description	Quotations from interview participants
Marital status	Barriers: Impaired health of the partner, worry, no participation in joint activities, loose friends out of sight Facilitators: Impaired health of the partner, "Transport Service", joint activities, structuring the day	The subthemes identified in individuals with and without a partner were similar. The transport service was mentioned the most, as most participants didn't have their driving license anymore and the partner took over the transportation service (PwP 3, PwP 4). In individuals without a partner, the 24h professional caregiver (PwP 5), children (PwP 2) or neighbours (PwP 5) took over the transportation service. In individuals without a partner reporting flexibility, the person in charge of the transportation service, i.e., 24h caregiver, lived in the same house (PwP 5). This guaranteed autonomous decision-making in functional mobility. However, individuals without a partner negatively experienced their dependency from the others availability. This was less the case for individuals living with a partner or the 24h caregiver who lived in the same house and were accessible all the time. As observable in the individual trajectories, after a break up with a partner functional mobility decreased. We assume this is the case as he didn't assume anymore the role of transport service. However, after a break up emotional wellbeing increased and the PwP 1 reported a reactivation of the social network. Also, a partner can be a support or a burden depending on his health state, functional mobility and age. Specifically, the restricted functional mobility of the partner due to a flu can promote the functional mobility of the person with PD by taking over the responsibility for carrying out the daily activities that require being functionally mobile, e.g., grocery shopping. However, during the illness of the partner some activities were not continued alone (PwP4). Joint acitivites with the partner or the 24h caregiver were grocery shopping, go to the restaurant or coffeeshop, take a walk, meet family and friends, concert or holidays. The partner can help to integrate the chronic disease into the daily routine by organising acitvities accordingly (e.g., not to late in the evening) (PwP 1), or by reminding the individual with PD for the medication intake or even by waking him/her up, when he/she falls asleep prior to the last medication intake to avoid motor complications (e.g., dyskinesia, off-phases,...) (PwP 3).	PwP 2: "That you don't always have to ask someone who is not available: "Grandma, not today. Today, I have to study here, tomorrow I have to study there." "Tomorrow we'll go buying plants if she has nothing else planned. That's what annoys me. The flowers have been here at home for a week now. Those are the things that annoy me." PwP 5: "Or what also bothers me is that I always have to ask someone, always have to rely on someone else." PwP 3: "My partner takes me everywhere, picks me up and waits patiently." PwP 4: " My husband drives me. (...) No, I have no problem getting anywhere." PwP 5: "We (PwP5 and 24h caregiver) go shopping in the afternoon. We don't have a fixed programme. When the fridge is empty, we go." PwP 1: "And at some point, when I was a bit cautious about the relationship, I thought to myself: "I think I need to reach out to my old friends again and revive this contact" and I have to say that was quite good." PwP 4: "When my husband was ill, I went to the (supermarket) with my caddy. He had to stay home. He was very ill. and didn't drive his car then. I didn't say anything. Then I took my caddy and walked to the grocery shop." PwP 4: "He had caught Corona and we were at home for 7-8 weeks. I stayed at home then too."

Table S10 Continued.

Reserves	Subthemes	Description	Quotations from interview participants
Children	Facilitators: "Transport service", Leisure activities with children and grandchildren, take it easy, take over activities if needed Barriers: "Violation of privacy", worry, take over activities without the need	If walking by foot, the use of public transport or the car is not possible or the destination is not easy to reach, children assume a "transport service" to doctor appointments, grocery shopping etc. to enable a functional mobility in daily life. Also, they accompanied their parent with PD for joint recurring activities e.g. walking by foot to the weekly food marked. In people without children, friends or 24h caregiver took over this rule. Sometimes people with PD feel that children intruse their privacy by children asking intrusive questions. This cooccured with feelings of worry destabelising the individual with PD and not helping to create a safe level for mobility Particularly grandchildren incentivised their grandparents for activities outside their daily routine, e.g., watching their basketball games or visiting them at their workplace. Weekly visits of grandchildren, e.g., for lunch, stimulated people with PD to walk/drive to the grocery shopping and prepare a meal. Moreover, by sharing pictures and a small report in a diary, the children and the grandchildren helped people with PD with a mobility radius inside their country of residence, to participate in their travels and to feel involved.	PwP 2: "What are you doing there again?", "Are you going to the hairdresser again? You only went to the hairdresser recently.", "What do you need from the (shop) again?". PwP 5: "that I say to myself: "They don't trust you anymore." This trust does (not) exist. And then they are afraid, and if they are afraid, then I mustn't do anything, otherwise I would increase their fear even more. And that (...) then pulls the rug from under your feet when they say: "Oh, you can't do that anymore", "You can't do that anymore!", "Oh God, you can't go there! You can't do that!" PwP 4: "Although we don't go anywhere anymore, not on holiday. But then they go on holiday and then they send us cards and reports (on an app) with photos (and reports). I said: "Do that! Then Grandma can see where you are. Then I'll imagine I'm there too."

Table S10 Continued.

Reserves	Subthemes	Description	Quotations from interview participants
Place of residence	Barriers: Walk back home, ups & downs, long distances, safety issues (due to much traffic, road constructions, bad light conditions), no public toilets, no flexibility & long travel duration of public transports, bus stop 500 m, Parking too big Facilitators: Unmet (grocery) needs, nature, short distances, walking aids, car for grocery shopping, taxi, autonomous choice when to go where, grocery shops close by, help with enter / exit of the bus, bus stop close by (5 Min. walk)	The subcategories identified in individuals living in a rural compared to those living in a central area were similar. If the partner had no driving license or was unavailable, individuals tried to continue to drive by themselves. Specifically, they weighted the risk of having a car accident versus the gained autonomy in the choice when to go where. They tried to guarantee safety by driving short distances in moments with less traffic and avoiding dark daylight hours or unfamiliar roads. Independent of their place of residence, people with PD reported gardening or walking tours in the nature as a factor motivating them to be active. In all, except one participant (PwP1), a car was required to meet an unmet need (grocery shopping) as the grocery shop was not accessible by foot, public transport did not drive to destinations that matter to the individuals or the bus stop was not accessible (distance of 500 meter, uphill for the way home). The buses organised by the municipality were not perceived as an option due to the limited flexibility. Finally, the only flexibility to decide autonomously when to go where without the need of a car was described by only one younger individual (PwP 1) living in the city center. So a place of residence in the city center might enhance functional mobility.	PwP 2: “I don’t like to drive my car anymore. Because I am not used anymore to the new roads. When we drive from here to the (rehabilitation centre), then it’s a bit of a story, isn’t it? At the (new) roundabout (with the 4 lanes and traffic lights), that one always lines up correctly.” “If you don’t go there (by car) every day, you’ll say: “Hm, should you come back here (by car)?” PwP 5: “For me, when I’m driving short distances, the danger isn’t too serious… you know, when I’m in the city, or on the highway, the cars come rushing to all sides, and I get annoyed.” “(I take the car) here in the neighbourhood to drive to the grocery shop, to (village - 3.6 km) or to the (city abroad - 26 km)… Although, no, I don’t drive to (town abroad) any more. There’s too much traffic for me”. PwP 2: “You can walk down, but if you then walk all the way through the park… We don’t have a bus that goes up here. The bus stop is at the municipality (500 metres away).” PwP 2: “The Flexibus would then take me there. That’s all possible, but you’re still tied to the time. But if I was finished (with shopping) and I hadn’t found anything yet, then I couldn’t go to (another shop).” PwP 1: “For me, it’s also important to live in the city or so close that you can do everything by foot and don’t actually need a car.” The importance of the car is illustrated by this participant living in a central area: PwP 2: “Yes, but without a car you’re still not a human being!”

Table S10 Continued.

Reserves	Subthemes	Description	Quotations from interview participants
Education	Mean to an end Lifelong learning	Participants experience no effect of years of education or the diploma on how they handle their trajectory of functional mobility. Moreover, they experienced education as "Means to an end" and highlighted the importance of life experience, life long learning and curiosity.	PwP 4: "Yes, through experience too. Life experience. We've been married for 63 years now. That's a long time. And what do we know? Nothing. All self-taught: cooking, household." PwP 5: "I (studied) 3 years after my final exams. But I don't know whether this is... For me, it was just something I had to do."
Sex/gender and age		Participants mainly discussed the psychological changes, e.g. wisdom, with ageing. Healthy ageing, i.e., biological age instead of the chronological age were linked to functional mobility. Thus, with increasing restrictions in vision, arthrosis,... the walking and driving ability was more impaired. Additionally, those restrictions or other chronic disease were experienced as having a higher impact than the disease duration of their Parkinson's disease. As interviewed women only, we can not compare the experience of enhancing and restricting factors in both groups. However, the driving license, partner and children might play a different role for men compared to women.	PwP 1: "Age at diagnosis plays a big role. Because if someone is older and has never done any sports, you won't be able to get them to exercise for Parkinson's so that it gets better. And if someone is younger, you might be able to get them to realise that exercise really helps. But the older you get, the more difficult it is. Someone who has never done any sport. To then torture them further with their illness and say: "Go for a run in town, do this, do that, it's good for you", I think that's more difficult. But someone who has always done a lot of sport, I don't think age plays a role." PwP 2: "You've been through so much. It's a life experience, isn't it?". PwP 3: "I mean, some people have a kind of "wisdom of old age". I'm also approaching 80. You think that you can be happy with smaller things. That you have to be satisfied with less, I think." "I am also an ordinary older person, and not only Parkinson's patient." PwP 4: "Because I think I would only be 25 years old. Just to say you don't feel that old. You're old, but you don't feel that way." "Maybe I don't blame Parkinson's, but old age. Everyone says: "I'm slowing down." So I don't notice it as much." PwP 5: "I always say: "You are always as old as you feel. If I start to make myself feel old, then I am old." "

Table S11 Theme summary table for inductive analysis

Themes	Subthemes	Quotations from interview participants
Psychosocial factors	**Don't shy away from confrontation**	PwP 1: *"That was outrageous! I complained afterwards and she disappeared from the radar for a while, but that's not acceptable!"*
		PwP 2: *""*
		PwP 3: "*I've now also asked the neurologist: "Do you seriously believe, with the amount of medication you prescribe, that people without medical expertise really take their medication as they should and must?" "No," he says, "we don't. We don't do that. We assume that it doesn't work that way." Yes, I said, "Why are you doing that?". Well, I can't understand that."*
		PwP 4: *""*
		PwP 5: *""*
	Openness towards new experiences (also towards new technology)	PwP 1: "*Yes, I want to do whatever is possible. I've already parachuted twice, for example. Parachuting, paragliding. I think it's brilliant."*
		PwP 2: *""*
		PwP 3: *"Yes, I mean, I was already used to it, we went to the theatre (...). And cooked and tried things out and made things fancy."*
		PwP 4: *"Do you know the app? It's so beautiful. They do it for the holidays. It's an app, they put photos and reports in it."*
		PwP 5: *"Yes, we were all over the world. My husband was a physicist. He often had contracts abroad. I lived two years in America..." "But as I said, I might need this article (travelling). I need a lot then... I get together with people, I see or get to know new things. That's also important."*
		"I don't need (outpatient nursing service) to get me out of bed. My bed does that now."
Psychosocial factors	**Helpfulness & asking for help**	*PwP 1: "I once gave a lecture about resilience in this form."*
		PwP 2: "One of them can also make an effort. I also do everything for them. Because if I'm driving again, then "Here, Grandma, can you pick this up for me?", "Grandma, I've got something there.""
		PwP 3: "So sometimes in summer I have 5 keys because the others are all gone, or the hallway is full of boxes because they all order online but are working and of course aren't there when they arrive late in the morning or evening. That works quite well."
		PwP 4: "Then we'll go for a walk tonight so that my husband can get some exercise too."
		PwP 5: "I've kept them and whenever I play the music for others, I say: "Oh, you're sitting there so bored. Let's do something, let's listen to some music.""
		"On the other hand, it's also a pleasure when I've spoken to people who have a problem and they thank you umpteen times because I've encouraged them a little to dare to do it (surgery for DBS).""

Table S11 Continued.

Themes	Subthemes	Quotations from interview participants
	Life-affirmation	*PwP 1: "If you have Parkinson's you're not healthy, that's clear, but I can go on living, it's not a death sentence for me with Parkinson's."*
		PwP 2: "I always make a quick recovery."
		PwP 3: "I'm also happy about small things and I'm happy that way."
		PwP 4: "I mean, I've always been a positive person. Satisfied. I am satisfied."
		PwP 5: "No matter what happens. I'm always like a stand-up guy."
	Self-efficacy	*PwP 1: "And I think I have it in my hands. Only I have it in my hands HOW it goes on. It only goes on for me if I want to stay mobile as long as possible. That's what I think, isn't it?"*
		PwP 2: "I get myself arranged for everything."
		PwP 3: I asked once, went to a patient group, asked all the doctors: "What is that?" Until I thought to myself: "These are pills that haven't been digested."
		PwP 4: ""
		PwP 5: "And if you do something for it (mobility), that means I have to pull myself together and then I have to want to make an effort. Then I can improve the curve so much."
Psychosocial factors	**Adapt expectations, accept limits**	*PwP 1: "I mean, I'm someone who has done a lot of sport and always danced passionately and all sorts of things and when you have restrictions like that, you have to work with yourself, it takes time and understanding and a lot of patience and a lot of nerves."*
		PwP 2: ""
		PwP 3: "I mean, the great thing is that I have learnt... to say no sometimes or not to feel guilty when I haven't achieved something."
		PwP 4: ""
		PwP 5: "That (sport) played an important role and it wasn't easy for me when it was no longer possible."

Table S11 Continued.

Themes	Subthemes	Quotations from interview participants
	Sociable attitude	*PwP 1: "I also go out on my own, then I meet someone and we go for a drink. I do that too. I usually take an active part in life."* *PwP 2: "My sister always says: "Are you going out again? Do you know (someone)?" and I say: "Well, then I'll get to know them. You won't meet anyone at home." "* *PwP 3: "We had a large circle of friends. We celebrated parties and were invited to lots of them and I loved doing that."* *PwP 4: "I meet up with my friends and on Thursday mornings with half the family, my sister, her daughter and grandchild and great-granddaughter come for (coffee) and then we sit there at a big table. It's always great."* *PwP 5: "I would love to go out and mingle with people again."*
	Physically active lifestyle (self-care)	*PwP 1: "Usually I work full-time and I'm in the office at home. I'm often sitting or standing and don't get much exercise. I then try to run around the flat or hang up the laundry. It's just not the same as starting to move early in the morning. I just think that if you start moving early in the morning, basically getting the engine going that you boosted earlier, then the day is a completely different one. When I get up in the morning and sit down at the table or go straight to the office, then somehow the day is not like elsewhere, where you've already moved a bit in the morning. I realise all that, that's a big factor for me, where I say I have to go to the gym early in the morning so that I'm better oiled and lubricated for the day."* *PwP 2: "I always had to accompany them to all sporting events when she (grandchildren) was young. The other two then ran the race and I was the luggage carrier."* *PwP 3: "Yes, I've actually always done sport... I had a husband who was also sporty. I've always played tennis in a team and I've actually done everything. I've surfed in the Mediterranean and I've done Nordic skiing and now I only play table tennis (laughs). But I enjoy that too."* *PwP 4: "I've always enjoyed doing sport. I've always enjoyed gymnastics. I went to gymnastics competitions."* *PwP 5: "I've always done a lot of sport myself, which means I know what I can expect of myself and which joints I need to lift myself."*
Chronic inflammatory comorbidity (& treatment)	**Chronic inflammatory bowel disease**	*PwP 1: "I had previously taken the L-Dopa tablet and he changed it to capsules. And because I have Crohn's disease (since 1986), the capsules are much better for me." (Therapy: unknown)* *PwP 3: "I've had bowel disease since I was 17 years old. It's part of my life. I have eaten accordingly. I've always been slim because I learnt as an adolescent that if I don't eat anything, my bowel is at rest. As soon as it gets something, as soon as I eat something, the intestines work and then it is obviously unable to function. That's why I always held back on eating. I also tried to live healthily because I was ill." (Therapy: Olsalazin - Intestinal antiphlogistic)*

Table S11 Continued.

Themes	Subthemes	Quotations from interview participants
	Arthritis	*PwP 2:*
		"I now have a joint prosthesis here (points to left shoulder). But this is from polyarthritis, these prostheses. Fingers and there (points to shoulder)."
		"I'm going for my treatment on Tuesday. I go to Dr (name) every month for an intravenous infusion (Therapy: Tocilizuman - immunosuppressant) (...). It will be almost 15 years that I've been going for intravenous treatment every month."

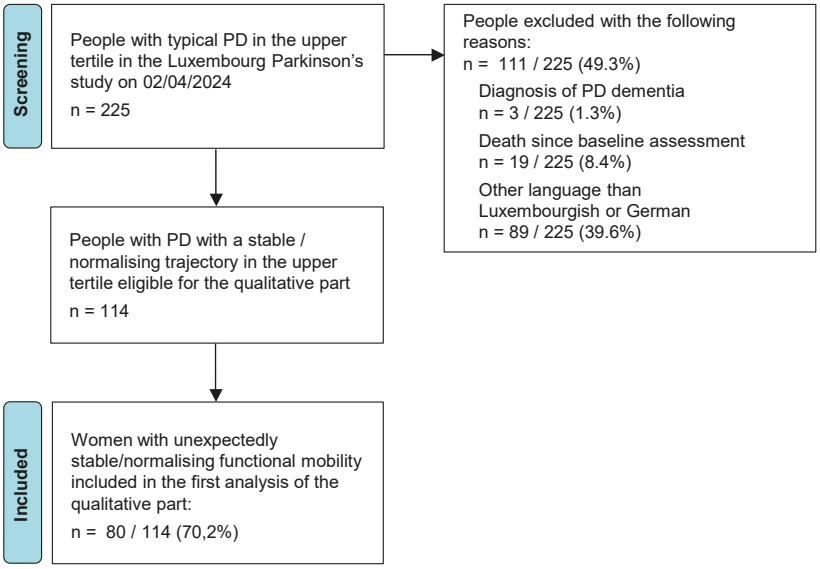


Figure S1 Flowchart of patient recruitment into the qualitative part

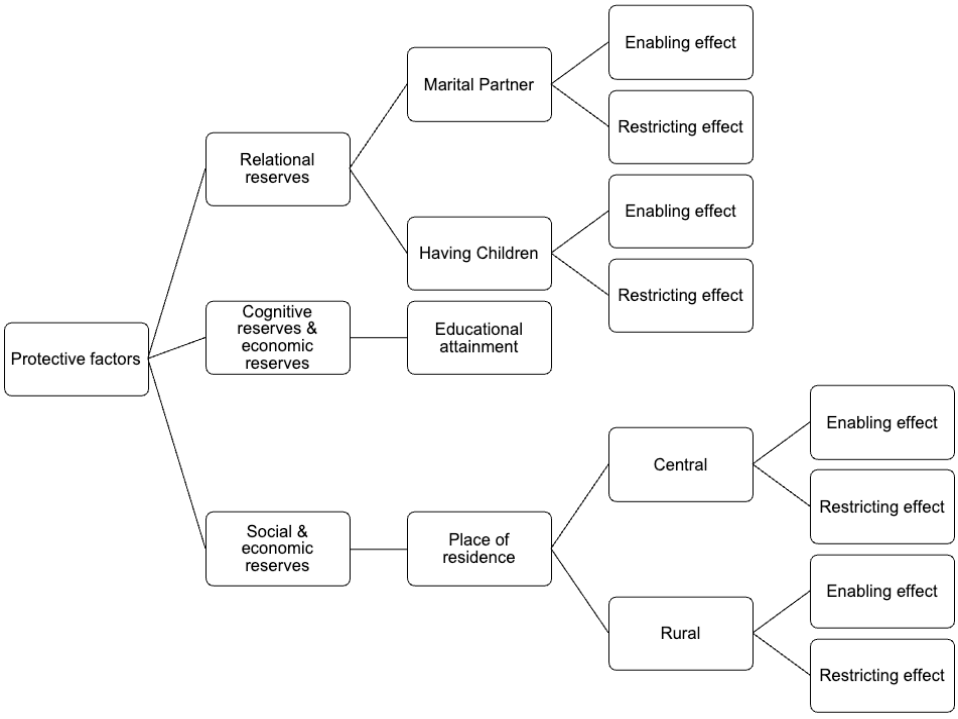


Figure S2 Coding tree and unconstrained data matrix of unexpectedly stable/normalising functional mobility by handling the progression of mobility impairment

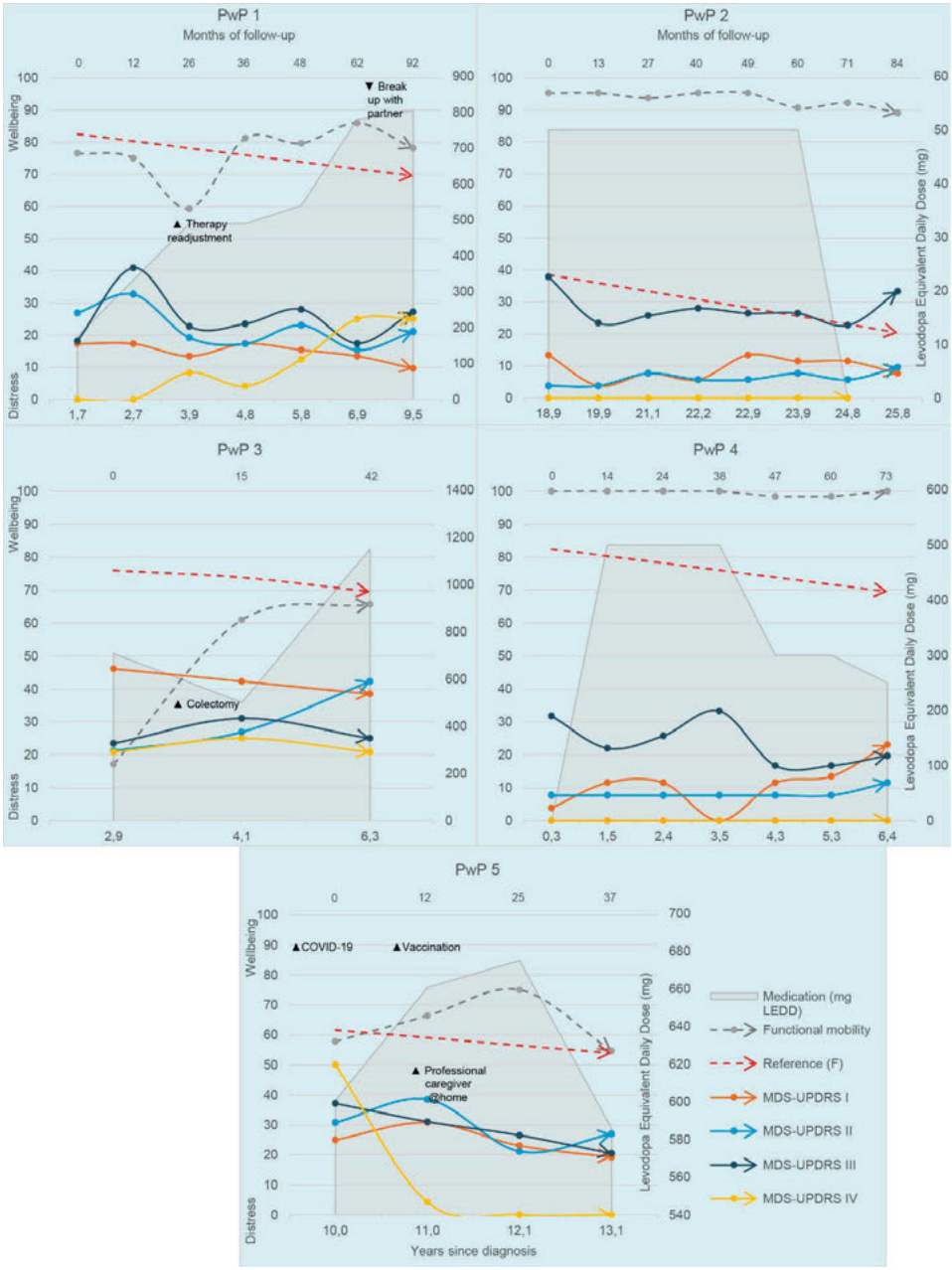


Figure S3 Trajectories of patient-reported and clinician-assessed motor and nonmotor symptoms
Red doted: Marginal means of functional mobility in women with the same years since diagnosis
Abbreviations: MDS: Movement Disorders Society, UPDRS: Unified Parkinson's Disease Rating Scale

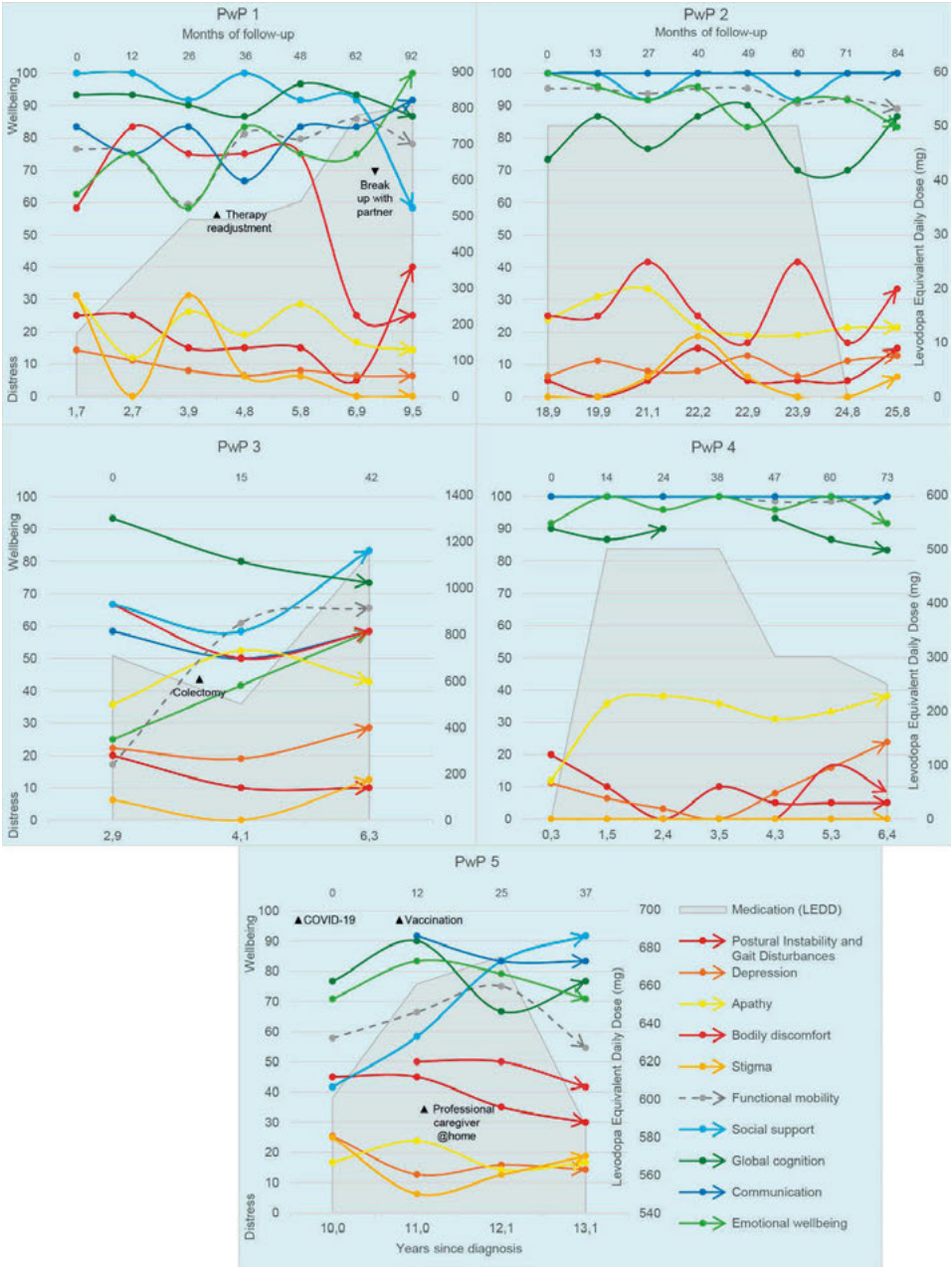


Figure S4 Trajectories of distress and wellbeing in female interview participants

Assumptions of mixed models

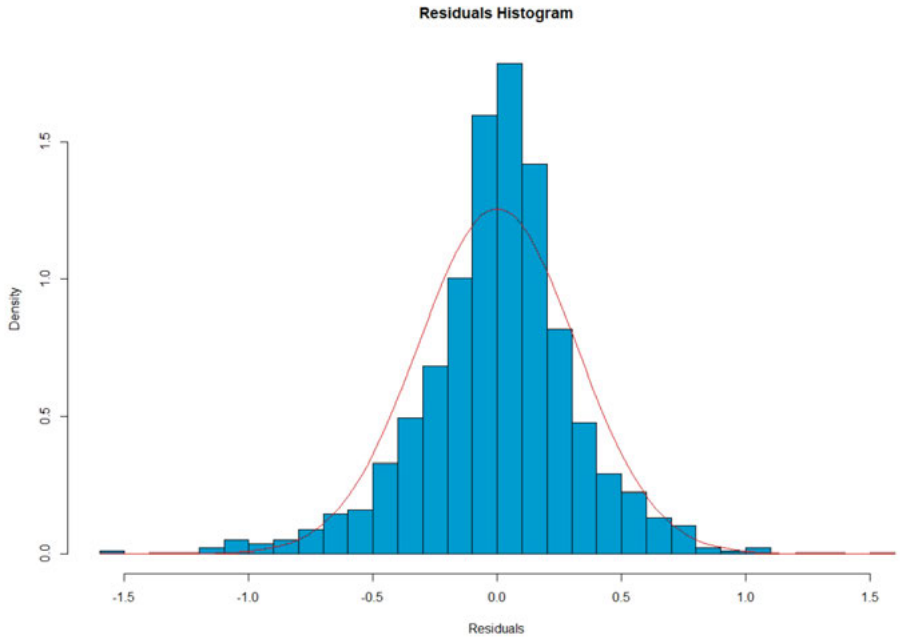


Figure S5 Residuals Histogram

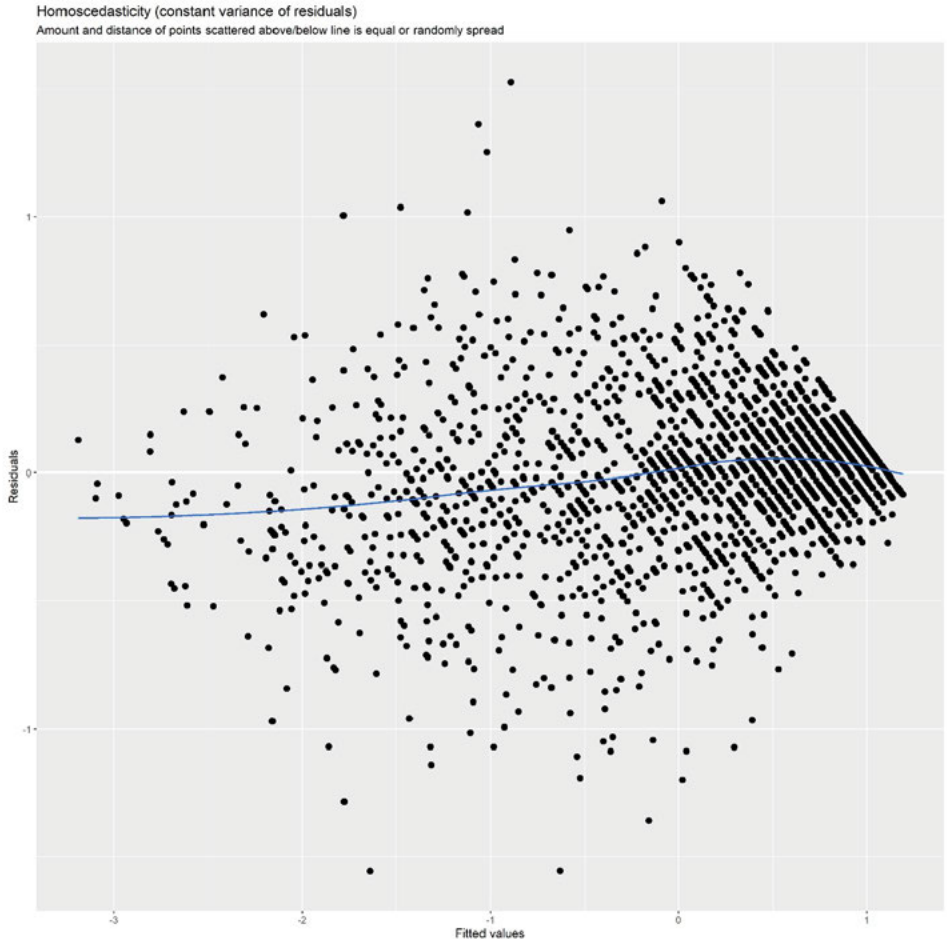


Figure S6 Residuals VS fitted values plot

Figure S7 Scatterplot of cohort effect. FMCS

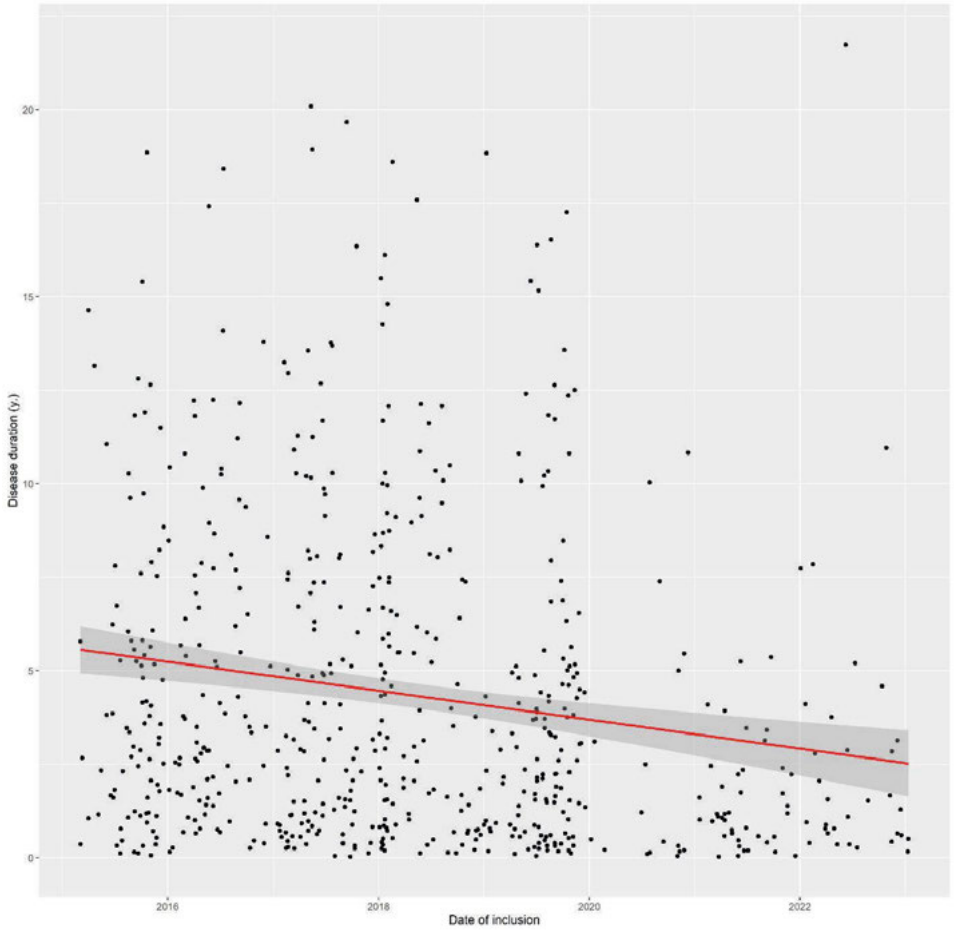


Figure S8 Scatterplot of cohort effect. Years since diagnosis (y.)

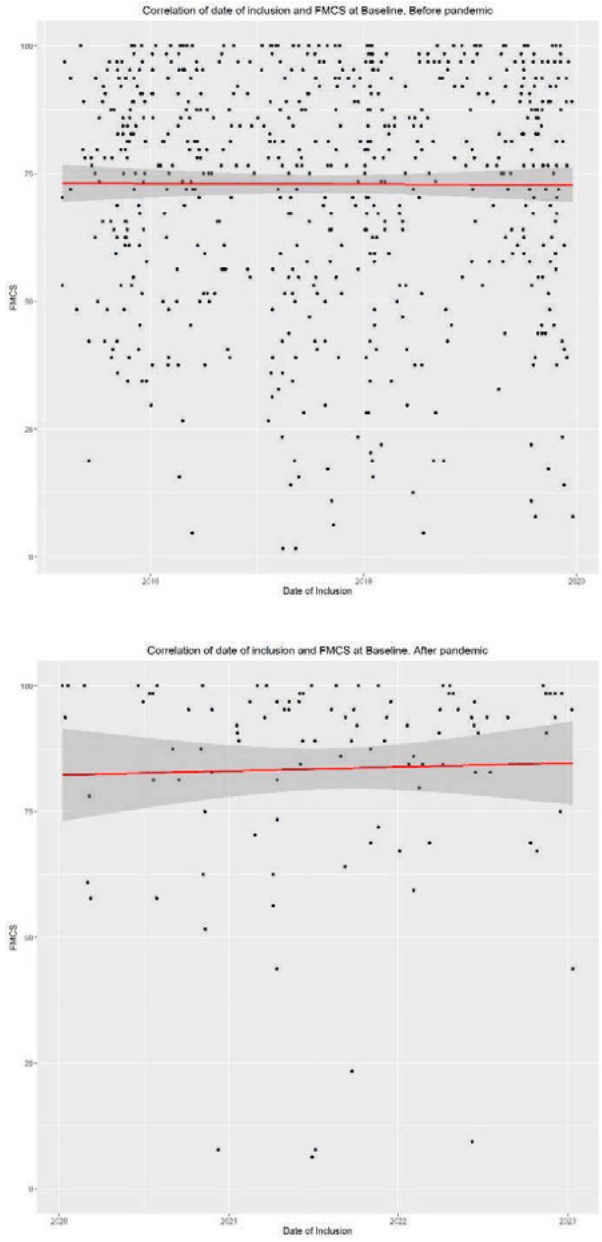


Figure S9 Scatterplot of cohort effect. Before and after the pandemic

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AKL, MZ: Conceptualization, Methodology, Supervision, Writing – review & editing.
RK: Conceptualization, Methodology, Funding, Resources, Supervision, Writing – review & editing.
All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CHAPTER 8

General discussion

“Parkinson’s doesn’t tell me what to do,
I tell Parkinson’s what I WANT to do.

- PwP 1

8.1 SUMMARY AND INTERPRETATION OF THE MAIN FINDINGS

In this dissertation, I conceptualised functional mobility as the ability to move independently to accomplish functional activities or tasks and to participate in activities of daily living in line with the definition by Bouca-Machado et al. (2018). I chose to focus on a patient-reported outcome to ensure that changes were relevant from the perspective of the individuals living with PD (FDA, 2009). Patient-reported functional mobility was measured by the validated PDQ-39-based patient-reported functional mobility composite score (FMCS) (Chapter 2). The systematic review of the determinants of patient-reported functional mobility (Chapter 3) concluded that future research on patient-reported functional mobility should focus on environmental factors as determinants. Thus, we investigated the moderation of contextual reserves and investigated the phenomenon of unexpectedly stable functional mobility in people with PD. While the *educational attainment* of 10 to 16 years was associated on a nominal significance level with a slower decline of patient-reported functional mobility in men, we did not detect a moderation by the *partner, children* or *place of residence*. The subsequent qualitative interviews with individuals with unexpectedly stable trajectories of functional mobility helped to understand unexpectedly stable/normalising trajectories of functional mobility. Factors perceived as enablers of functional mobility included the presence of a person with a driving license living in the same household, psychosocial factors like self-efficacy and self-care in the form of a physically active lifestyle. Additionally we identified the co-occurrence and treatment of chronic inflammatory diseases as a potentially protective factor (Chapter 7). In preparation for this analysis, we described the progression of motor- and non-motor symptoms in men and women and found that compared to men, women showed an overall slower disease progression. These findings confirmed previous longitudinal findings (Picillo et al., 2022, Iwaki et al., 2021) and highlighted the need for stratified analyses. Moreover, we expanded an established and well-accepted illustration of PD progression (Poewe et al., 2017) by providing a comprehensive empirical description and illustration of the progression of motor- and non-motor symptoms (Chapter 5). In addition, we investigated the modification of the trajectory of functional mobility by different *GBA1*-variants. The results show an association of the PD-risk variants with a more rapid progression of non-motor symptoms, but not functional mobility (Chapter 6).

Across all Chapters, I tried to integrate the perspective of men and women with PD and to maximise the impact and translation of the doctoral research for the care of people with PD. Involving people with PD helped to set the right priorities and do research that matters to them (Bowring et al., 2022). In addition, I promoted patient-public involvement by sharing interpretations with the Luxembourg Parkinson's Association, so that its members could evaluate whether the analyses were consistent with their personal experiences. Furthermore, the dissertation provided usable tools and thus promoted the translation of

research into practice by accompanying our article (Hanff et al., 2023b), i.e., Chapter 2 by a freely accessible online Functional Mobility Composite Score (FMCS) spreadsheet calculator in the form of an R-shiny app (https://tq9t3h-ahanff.shinyapps.io/FMCS_calculator/). I provided scores and estimated (marginal) means given 0, 10, 20, 30 and 40 years since diagnosis by various subgroups and illustrated the trajectories in detailed figures as shown in Chapters 5, 6 and 7. Finally, I provided evidence for, and theoretical explanations of, how the choice of statistical method may influence research outcomes (Chapter 4) for educational purposes related to the statistical methodology. In the following paragraphs, I will discuss methodological considerations, implications and future directions more in detail.

8.2 METHODOLOGICAL CONSIDERATIONS

Causal inferences in longitudinal data analysis

Causal considerations

The linear mixed effects models are the best attempt to understand the phenomenon of unexpectedly stable/normalising trajectories of functional mobility. While randomised controlled trials (RCT) study designs are more suited to establishing causality, RCTs are impossible in environmental, social, and personal research questions like ours. Thus, this dissertation focussed on effect moderation acknowledging that probably no direct causal effects could be established. In longitudinal studies, the individual development of a certain outcome variable can be related to the individual development of other variables (Twisk, 2013). In Chapters 5 and 7, we analysed the association of sex/gender, *GBA1*-variants and reserves (educational attainment, partner, children, place of residence) with a slower decline of patient-reported functional mobility. Those reserves are potential means that can be used to overcome adverse life events or that are involved in delaying or modifying the decline (Cullati et al., 2018). We assumed those reserves were time invariant as they probably did not change during the observation period. The association was the strongest for the educational attainment in men (Chapter 7). However, the findings were not consistent across sex/gender and under different circumstances (sensitivity analyses in individuals with advanced disease stages and baseline data). Unexpectedly stable patient-reported functional mobility may have different causes as no specific event, condition or characteristic would be sufficient by itself to produce an unexpectedly stable/normalizing trajectory of patient-reported functional mobility (Rothmann et al., 2008). Specifically, the fixed effects for the moderation by contextual reserves *educational attainment*, *partner, children* and *place of residence* (Chapters 7) suggest a limited moderation of the included fixed effects. Consequently, there may be other causes by which a person could show an unexpectedly high patient-reported functional mobility (Rothmann et al., 2008), e.g., the psychosocial characteristics found in the inductive analysis of the qualitative interviews with people experiencing stable/normalizing trajectories of functional mobility (Chapter 7). In the

present dissertation, we investigated different components, i.e., sex/gender (Chapter 5), genetic components (Chapter 6) or different environmental reserves (Chapter 7) and cannot conclude that our findings are specific (i.e., one cause leading to a single effect). Moreover, the results indicate, that the protective effect of the reserves might change across sex/gender and this requires further investigation.

Best practice to handle longitudinal data

In longitudinal data, it is common to create "change scores" by subtracting baseline from follow-up measurements (Lindh-Rengifo et al., 2021). This statistical method has some limitations (Tennant et al., 2022). In the analyses in Chapters 5 to 7, we used the linear mixed effects models, a statistical method that uses more data points and accounts for the typical pattern of variances and correlations among the repeated measures (Long, 2012). In the educational article described in Chapter 4, I tried to raise interest of the clinical research community in linear mixed effects models for longitudinal data analysis by illustrating the results of the paired t-test, regression and linear mixed methods on the same data and the same research question. According to Long (2012), observed scores with shorter intervals of the visits tend to have higher correlations with each other than observations with longer intervals. This might be due to intervening factors that affect responses, such as life events. Thus, timing of the observations influences the correlations (Long, 2012) and could account for the inconclusive statistical results described in Chapter 7.

A common challenge in longitudinal studies is missing data. Twisk et al. (2013) illustrated that mixed-model analysis with or without multiple imputations do not lead to valid results. Specifically, both approaches, i.e., with and without multiple imputation behaved equally unsatisfactorily when the results were compared with the results of the analysis on the complete data set. Consequently, we applied the mixed-models on the original dataset and provided a detailed description of our study population, analysed the extent to which those other variables predict subsequent participation (Table 2) and provided sensitivity analyses with baseline data of the extent to which bias might distort estimates (Munafo et al., 2018) in line with best practice in clinical observational research designs. Those preliminary analyses indicated the missingness was related to observed characteristics rather than unobserved values and thus missing at random (Twisk et al., 2013). Consequently, in Chapters 5 – 7, we assumed that if data were missing, they were missing at random, and the results are only valid under this assumption. Moreover, we used the directed acyclic graphs (DAGs) (Figure 9) with the web-based DAGitty (Textor et al., 2016) to identify confounding variables requiring conditioning when estimating the protective effect of the reserves on the decline of patient-reported functional mobility.

Selective enrolment and attrition

The determinants (*place of residence, children, partner, educational attainment*) and

outcome (patient-reported functional mobility) partly determined the subsequent participation in the follow-up visits. Specifically, when testing if the 328 participants with missing data at follow-up were inherently significantly different compared to the 350 participants with complete data trough inferential testing (Kruskal-Wallis and chi-square tests (using "missing compare"-function of the "finalfit"-package (Ewen Harrison et al., 2021)), the participants with missing data at the 3rd follow-up had a worse functional mobility, were older, had less years of education, were more often widowed or divorced, reported less social support, lower global cognition and higher levels of symptoms like apathy and depression. Consequently, we could make the results more generalisable to the subgroup with complete data (e.g., younger individuals with better functional mobility at baseline). To avoid collider-conditioning bias, we did not include the collider "subsequent participation" in the model (Digitale et al., 2023). Additionally, the more frequent missing data at follow-up in individuals with lower educational attainment might explain the unconfirmed moderation by *educational attainment* in the sensitivity analysis with the baseline data in men and women (Table 3). Moreover, most of the identified factors associated with missing data at follow-up can be related to functional impairments in advanced disease stages. According to the missing data analysis in the subgroup of individuals with PD in early disease stages (H&Y ≤ 2), symptoms of apathy instead of the functional impairments were significantly higher in the group with missing data at follow up (Pauly et al., 2022). Consequently, the risk of a collider bias might be lower in the early disease stages-subgroup. A sensitivity analysis in this subgroup (Table 4) confirmed the moderation by 10 to 16 years of education in men. Thus, the results seem more applicable to individuals in early disease stages. Moreover, as in early disease stages functional mobility is less impaired and did not yet worry individuals with PD (Bouca-Machado et al., 2020b), this might explain the inconclusive statistical results described in Chapter 7. Finally, the significant better patient-reported functional mobility at baseline in people recruited after than those recruited before the pandemic (+9.4, 95%CI: 4.7, 12.5, $p < 0.001$), illustrated the impact of the pandemic on the recruitment of the more vulnerable individuals with PD. Identified cohort effects suggested the functional mobility of recruited participants increased over the years indicating a probable underestimation of the decline of functional mobility.

Table 2 Compare baseline characteristics of people with and without missing primary outcome at third follow-up (n = 678)

Variables at baseline		Not missing n = 350 Mean (SD) n (%)	Missing n = 328 Mean (SD) n (%)	p
FMCS (0 – 100)[b]		78.3 (19.0)	67.2 (25.4)	<0.001*
Years since diagnosis		5.2 (5.0)	5.5 (5.3)	0.376
Country of residence	Luxembourg	210 (51.5)	198 (48.5)	0.985
	Outside Luxembourg	140 (51.9)	130 (48.1)	
Age (y)		65.6 (9.7)	69.3 (11.5)	<0.001*
Generation	Generation X (1965 - 1980)	44 (59.5)	30 (40.5)	<0.001*
	Baby boomers (1946 - 1964)	205 (58.2)	147 (41.8)	
	Silent generation (1928 - 1945)	101 (40.2)	150 (59.8)	
Sex/gender	Male	233 (52.1)	214 (47.9)	0.777
	Female	117 (50.6)	114 (49.4)	
Years of Education		13.4 (3.9)	12.4 (4.3)	0.002*
Marital status	Single	22 (61.1)	14 (38.9)	0.002*
	Divorced / Widowed	48 (37.8)	79 (62.2)	
	Married / Partnered	278 (54.2)	235 (45.8)	
Children	No	55 (55.0)	45 (45.0)	0.523
	Yes	293 (51.0)	282 (49.0)	
Living area	Rural area	128 (46.9)	145 (53.1)	0.051
	Central area	222 (54.8)	183 (45.2)	
PDQ-39 subscale social support (0 - 100)[b]		89.0 (15.2)	84.3 (20.4)	0.001*
MoCA (0 – 30)[b]		25.3 (3.7)	23.5 (4.7)	<0.001*
SAS (0 - 42)[a]		13.2 (5.5)	15.3 (6.1)	<0.001*
BDI-I (0 – 63)[a]		9.1 (6.8)	11.0 (7.2)	<0.001*
Motivation to participate	General interest in research	59 (51.8)	55 (48.2)	1.000
	To support Parkinson's research	248 (54.7)	205 (45.3)	0.026
	To get more information about the disease	96 (48.7)	101 (51.3)	0.379

Abbreviations Categorical variables: counts (%), numerical variables: mean (SD), a : Greater = worse, b : Greater = better, * = p-values significant after Bonferroni-adjustment (p-value * 14 comparisons ≤ 0.05), Abbreviations: BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, SAS: Starkstein Apathy Scale

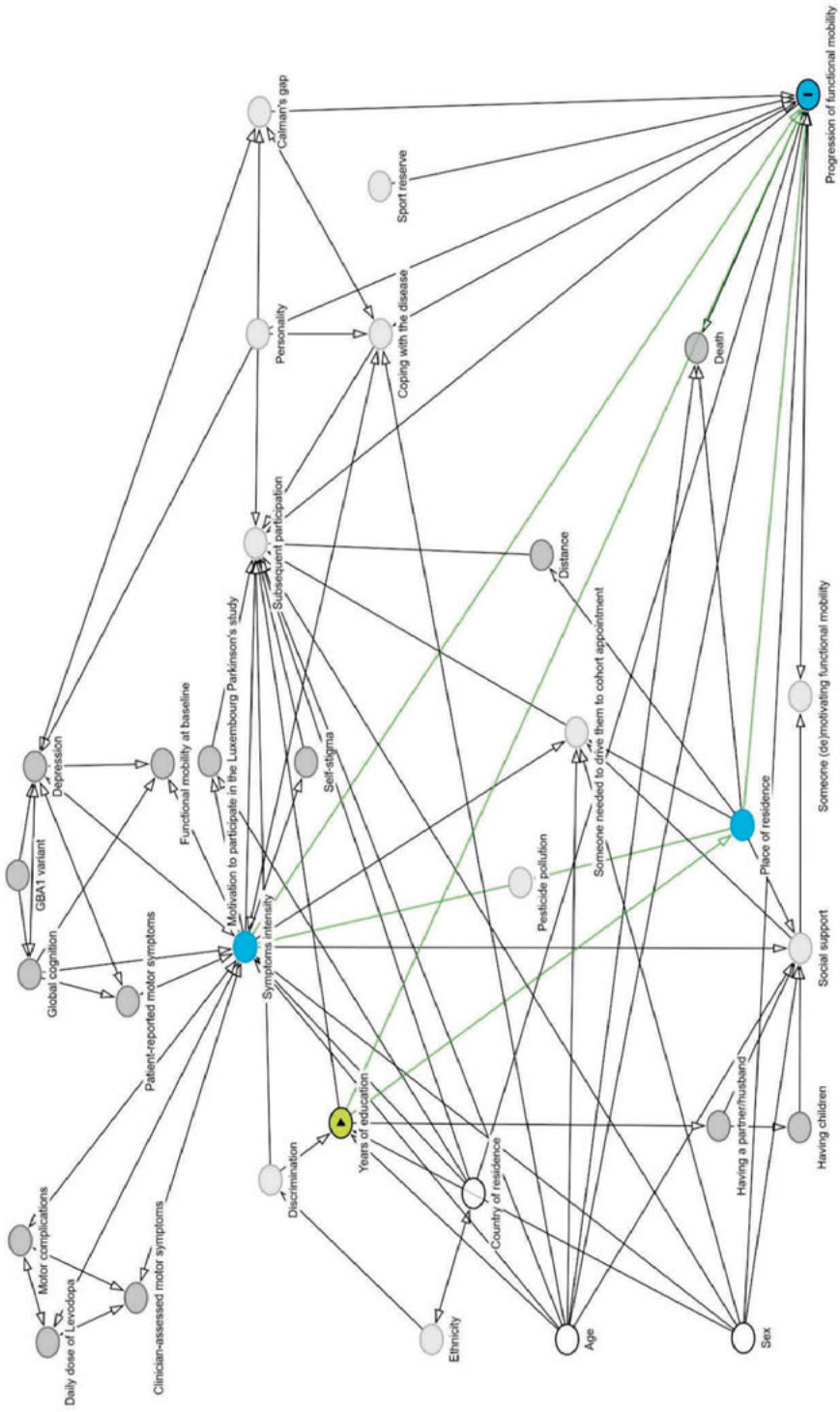

Figure 9 Directed Acyclic Graph illustrating the research question investigating the potential moderation of the trajectory of patient-reported functional mobility by educational attainment

Table 3 Moderation by reserves in men and women - Sensitivity analysis with baseline data

	Men					
	Educational attainment			Have a partner		
Predictors	**stand. B (CI 95%)**	**P-Value**	**df**	**stand. B (CI 95%)**	**P-Value**	**df**
(Intercept)	0.042 (-0.162 – 0.246)	0.687	469.000	-0.016 (-0.218 – 0.186)	0.876	467.000
Years since diagnosis	-0.465 (-0.631 – -0.299)	<0.001	469.000	-0.357 (-0.538 – -0.175)	<0.001	467.000
Fixed effect: Age (years)	-0.171 (-0.254 – -0.088)	<0.001	469.000	-0.182 (-0.267 – -0.096)	<0.001	467.000
Fixed effect: Country of residence [Outside Luxembourg]	-0.156 (-0.327 – 0.014)	0.072	469.000	-0.185 (-0.357 – -0.014)	0.034	467.000
Fixed effect: Years of education				0.063 (-0.019 – 0.144)	0.132	467.000
Fixed effect: Years of education [10 - 16 y of education]	-0.069 (-0.295 – 0.157)	0.546	469.000			
Fixed effect: Years of education [>16 y of education]	0.100 (-0.142 – 0.343)	0.418	469.000			
Moderation: years since diagnosis × [10 - 16 y of education]	-0.006 (-0.208 – 0.196)	0.954	469.000			
Moderation: years since diagnosis × [> 16 y of education]	0.086 (-0.130 – 0.302)	0.435	469.000			
Fixed effect: Have a partner [Yes]				0.078 (-0.137 – 0.292)	0.479	467.000
Moderation: years since diagnosis × Have a partner [Yes]				-0.097 (-0.300 – 0.106)	0.347	467.000
Observations	477			474		
R2 / Adjusted R2	0.251 / 0.240			0.254 / 0.244		

	Women					
	Educational attainment			Have a partner		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
	0.096 (-0.169 – 0.360)	0.477	231.000	0.110 (-0.115 – 0.336)	0.335	232.000
	-0.164 (-0.415 – 0.087)	0.200	231.000	-0.365 (-0.537 – -0.192)	<0.001	232.000
	-0.097 (-0.228 – 0.035)	0.149	231.000	-0.123 (-0.255 – 0.009)	0.068	232.000
	-0.067 (-0.320 – 0.186)	0.603	231.000	-0.108 (-0.358 – 0.142)	0.397	232.000
				0.006 (-0.116 – 0.128)	0.922	232.000
	-0.157 (-0.458 – 0.145)	0.307	231.000			
	-0.016 (-0.395 – 0.362)	0.933	231.000			
	-0.224 (-0.520 – 0.073)	0.138	231.000			
	-0.363 (-0.763 – 0.038)	0.076	231.000			
				-0.139 (-0.385 – 0.106)	0.265	232.000
				-0.009 (-0.250 – 0.233)	0.942	232.000
	239			239		
	0.174 / 0.149			0.160 / 0.138		

Table 3 Continued.

Predictors	Men					
	Children			Place of residence		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
(Intercept)	0.015 (-0.231 – 0.262)	0.903	468.000	0.004 (-0.137 – 0.146)	0.951	463.000
Years since diagnosis	-0.372 (-0.602 – -0.143)	0.002	468.000	-0.475 (-0.594 – -0.357)	<0.001	463.000
Fixed effect: Age (y)	-0.168 (-0.252 – -0.084)	<0.001	468.000	-0.174 (-0.258 – -0.089)	<0.001	463.000
Fixed effect: Country of residence [Outside Luxembourg]	-0.180 (-0.351 – -0.010)	0.038	468.000	-0.185 (-0.356 – -0.015)	0.033	463.000
Fixed effect: Years of education	0.064 (-0.017 – 0.146)	0.123	468.000	0.056 (-0.027 – 0.139)	0.189	463.000
Fixed effect: Children [Yes]	0.034 (-0.217 – 0.286)	0.790	468.000			
Moderation: Children [Yes]	-0.074 (-0.317 – 0.169)	0.550	468.000			
Fixed effect: Place of residence [Central]				0.067 (-0.098 – 0.232)	0.424	463.000
Moderation: Place of residence [Central]				0.076 (-0.083 – 0.235)	0.347	463.000
Random effects						
σ2	0.16			0.16		
τ00	0.74 ND			0.73 ND		
τ11	0.44 ND.disease_duration			0.45 ND.disease_duration		
ρ01	0.65 ND			0.65 ND		
ICC	0.87			0.87		
N	479 ND			476 ND		
Observations	1789			1778		
Marginal R2 / Conditional R2	0.207 / 0.894			0.200 / 0.893		

Note *Nominal significance

	Women					
	Children			Place of residence		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
	-0.083 (-0.370 – 0.203)	0.568	231.000	-0.081 (-0.321 – 0.160)	0.510	226.000
	-0.443 (-0.766 – -0.120)	0.007	231.000	-0.377 (-0.630 – -0.124)	0.004	226.000
	-0.122 (-0.255 – 0.010)	0.071	231.000	-0.123 (-0.261 – 0.015)	0.080	226.000
	-0.119 (-0.372 – 0.134)	0.356	231.000	-0.114 (-0.371 – 0.143)	0.383	226.000
	0.009 (-0.113 – 0.132)	0.880	231.000	-0.006 (-0.133 – 0.121)	0.923	226.000
	0.135 (-0.168 – 0.439)	0.380	231.000			
	0.086 (-0.262 – 0.434)	0.627	231.000			
				0.146 (-0.122 – 0.413)	0.285	226.000
				0.017 (-0.273 – 0.306)	0.910	226.000
	0.14			0.14		
	0.63 ND			0.64 ND		
	0.14 ND.disease_duration			0.14 ND.disease_duration		
	0.34 ND			0.35 ND		
	0.85			0.85		
	241 ND			241 ND		
	880			880		
	0.167 / 0.872			0.157 / 0.871		

Table 4 Moderation by reserves in men and women - Sensitivity analysis in the subgroup with an early disease stage (H&Y ≤ 2)

	Men					
	Educational attainment			Have a partner		
Predictors	**stand. B (CI 95%)**	**P-Value**	**df**	**stand. B (CI 95%)**	**P-Value**	**df**
(Intercept)	-0.312 (-0.570 – -0.055)	0.018	441.954	-0.247 (-0.479 – -0.015)	0.037	424.264
Years since diagnosis	-0.814 (-1.057 – -0.572)	<0.001	433.076	-0.618 (-0.846 – -0.389)	<0.001	407.090
Fixed effect: Age (years)	-0.116 (-0.186 – -0.046)	0.001	466.438	-0.123 (-0.195 – -0.052)	0.001	462.274
Fixed effect: Country of residence [Outside Luxembourg]	-0.165 (-0.319 – -0.010)	0.037	458.532	-0.181 (-0.334 – -0.027)	0.021	454.700
Fixed effect: Years of education				0.060 (-0.010 – 0.130)	0.093	453.116
Fixed effect: Years of education [10 - 16 y of education]	0.317 (0.035 – 0.599)	0.028	425.949			
Fixed effect: Years of education [>16 y of education]	0.322 (0.024 – 0.620)	0.034	424.774			
Moderation: years since diagnosis × [10 - 16 y of education]	0.342 (0.070 – 0.613)	0.014*	405.792			
Moderation: years since diagnosis × [> 16 years of education]	0.227 (-0.061 – 0.515)	0.122	411.452			
Fixed effect: Have a partner [Yes]				0.261 (0.014 – 0.508)	0.038	406.212
Moderation: years since diagnosis × Have a partner [Yes]				0.080 (-0.168 – 0.328)	0.527	393.191
Random effects						
σ2	0.16			0.16		
τ00	0.74 ND			0.73 ND		
τ11	0.44 ND.disease_duration			0.45 ND.disease_duration		
ρ01	0.65 ND			0.65 ND		
ICC	0.87			0.87		
N	479 ND			476 ND		
Observations	1789			1778		
Marginal R2 / Conditional R2	0.207 / 0.894			0.200 / 0.893		

Note *Nominal significance

	Women					
	Educational attainment			Have a partner		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
	-0.261 (-0.528 – 0.005)	0.055	251.976	-0.060 (-0.281 – 0.161)	0.595	249.236
	-0.447 (-0.662 – -0.233)	<0.001	187.553	-0.393 (-0.554 – -0.232)	<0.001	191.686
	-0.030 (-0.144 – 0.085)	0.612	248.762	-0.048 (-0.163 – 0.067)	0.413	250.673
	-0.033 (-0.268 – 0.201)	0.779	240.002	-0.031 (-0.264 – 0.203)	0.796	243.336
				0.042 (-0.065 – 0.148)	0.444	238.477
	0.157 (-0.142 – 0.456)	0.302	239.896			
	0.335 (-0.028 – 0.699)	0.071	240.006			
	0.043 (-0.202 – 0.288)	0.729	174.018			
	0.048 (-0.243 – 0.339)	0.745	158.680			
				-0.055 (-0.296 – 0.187)	0.656	232.433
				-0.018 (-0.213 – 0.176)	0.853	164.773
	0.14			0.14		
	0.63 ND			0.64 ND		
	0.14 ND.disease_duration			0.14 ND.disease_duration		
	0.34 ND			0.35 ND		
	0.85			0.85		
	241 ND			241 ND		
	880			880		
	0.167 / 0.872			0.157 / 0.871		

Table 4 Continued.

Predictors	Men					
	Children			Place of residence		
	stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
(Intercept)	0.025 (-0.259 – 0.309)	0.861	444.994	-0.040 (-0.200 – 0.120)	0.624	459.029
Years since diagnosis	-0.420 (-0.698 – -0.141)	0.003	439.717	-0.547 (-0.694 – -0.400)	<0.001	369.596
Fixed effect: Age (y)	-0.114 (-0.184 – -0.043)	0.002	466.217	-0.119 (-0.190 – -0.048)	0.001	458.833
Fixed effect: Country of residence [Outside Luxembourg]	-0.163 (-0.318 – -0.008)	0.039	457.959	-0.169 (-0.324 – -0.014)	0.033	453.109
Fixed effect: Years of education	0.056 (-0.014 – 0.127)	0.119	453.709	0.055 (-0.017 – 0.126)	0.134	452.235
Fixed effect: Children [Yes]	-0.078 (-0.371 – 0.215)	0.602	418.756			
Moderation: Children [Yes]	-0.158 (-0.451 – 0.134)	0.288	419.321			
Fixed effect: Place of residence [Central]				-0.002 (-0.194 – 0.190)	0.983	419.875
Moderation: Place of residence [Central]				-0.013 (-0.199 – 0.173)	0.893	355.672
Random effects						
σ2	0.16			0.16		
τ00	0.75 ND			0.75 ND		
τ11	0.45 ND.disease_duration			0.45 ND.disease_duration		
ρ01	0.66 ND			0.65 ND		
ICC	0.87			0.87		
N	477 ND			472 ND		
Observations	1779			1782		
Marginal R2 / Conditional R2	0.201 / 0.894			0.194 / 0.893		

Women					
Children			Place of residence		
stand. B (CI 95%)	P-Value	df	stand. B (CI 95%)	P-Value	df
-0.253 (-0.528 – 0.022)	0.071	232.463	-0.105 (-0.339 – 0.129)	0.379	248.102
-0.548 (-0.756 – -0.340)	<0.001	185.626	-0.361 (-0.541 – -0.182)	<0.001	201.316
-0.048 (-0.163 – 0.067)	0.410	248.749	-0.047 (-0.168 – 0.074)	0.446	247.710
-0.044 (-0.279 – 0.191)	0.713	243.482	-0.036 (-0.276 – 0.204)	0.769	237.517
0.047 (-0.060 – 0.154)	0.384	238.807	0.035 (-0.076 – 0.146)	0.537	236.082
0.207 (-0.085 – 0.499)	0.164	225.484			
0.184 (-0.044 – 0.411)	0.113	163.878			
			0.015 (-0.247 – 0.276)	0.912	232.910
			-0.059 (-0.265 – 0.147)	0.573	166.082
0.14			0.14		
0.64 ND			0.65 ND		
0.13 ND.disease_duration			0.14 ND.disease_duration		
0.34 ND			0.32 ND		
0.84			0.85		
240 ND			235 ND		
876			874		
0.153 / 0.868			0.154 / 0.873		

Representativeness

In our statistical analyses, we included all participants from the Luxembourg Parkinson's study with typical PD or PDD across all disease stages while for the qualitative interviews we prioritised individuals without PDD. Thus, we enabled the interview participants to engage in discussions without the additional challenges posed by cognitive impairments. Consequently, the results from the interviews are representative for individuals without PDD. We enhanced the generalisability of our findings by analysing data of all participants (with PD and PDD) from varying settings, environments and disease stages. Recruitment started in 2015 with annual follow-ups when the estimated prevalence of PD in Luxembourg was 565 – 1356 (Hipp et al., 2018). As 486 of the participants lived in Luxembourg, we might have captured 35.8 to 86.0% of the population with PD. New data indicate an even higher prevalence in line with the increasing numbers reported by Dorsey et al. (2018). The nonresponse to the study invitation may be related to the endpoints under study through factors, such as functional mobility, social conditions, age, type of education, number of working hours, altruistic attitudes towards research, etc. Unfortunately, no information was available about the characteristics of all people who were asked to participate in the cohort, and bias due to selective attrition may have influenced the findings. Nonetheless, these limitations apply to many longitudinal cohort datasets.

Ensure Clinical and Statistical Significance

In the longitudinal data analyses (Chapters 5 – 7) we raised multiple related questions within the framework of a single study to provide a comprehensive overview of the progression of motor- and non-motor symptoms across different groups. Thus, the control of the increased type 1 error was an important aspect. We provided the nominal p-values and indicated the significant p-values after adjustment for multiple comparisons (Hochberg and Benjamini, 1990) for full transparency and to allow readers to interpret the results at the error rate appropriate for their own purposes.

With increasing emphasis on evidence-based practice (van Meijel et al., 2004, Dicenso et al., 2005, Chalmers and Glasziou, 2009, Alper and Haynes, 2016, Polit and Beck Tatano, 2017, Skivington et al., 2021, Lima et al., 2023), health professionals need to base their practice on evidence that is not only "real" (statistical significance) but also clinically important (Polit, 2017, Dicenso et al., 2005, Yaddanapudi, 2016). To enable health professionals' clinical interpretation (Polit, 2017), I specified the clinical significance of a change for the developed composite score. Clinical significance was defined as: "the smallest difference in score in the domain of interest which patients perceive as beneficial" (Jaeschke et al., 1989). Specifically, I converted previously communicated benchmarks for the clinical significance of the PDQ-39 to the PDQ-39-based Functional Mobility Composite Score (FMCS) as described in Chapter 2 (Peto et al., 2001, Fitzpatrick et al., 2004, Hanff et al., 2023b). Consequently, a change of 3.67 - 4.72 points on the FMCS was the threshold for interpreting an improvement

or worsening in functional mobility as clinically meaningful. Future research systematically reviewing and summarising the clinical significance of instruments recommended by the Movement Disorders Society could support researchers and health professionals in the interpretation of clinical significance. However, the interpretation of clinical significance as a threshold has limitations (Tenan et al., 2021, Tenan and Simon, 2022, Tenan and Boyer, 2023). While clinical significance can be a useful concept for power calculations, men and women with PD still need to decide what change is meaningful to them and what personal effort they are willing to invest.

Mix perspectives by mixing methods

The mixed methods study (Chapter 7) aimed to investigate the reserves moderating the trajectory of patient-reported functional mobility and to understand their daily experience by people with PD. Also, we aimed to describe the characteristics of individuals with unexpectedly stable/normalising trajectories of functional mobility. The methodology in the mixed methods research design incorporated different methods to collect, analyse and interpret the data. While first the prospective dynamic cohort data was quantitatively analysed by linear mixed effects models in Chapters 5 - 7, the subsequent qualitative semi-structured interviews presented in Chapter 7 were analysed by qualitative content analysis (Elo and Kyngas, 2008) helping to understand under what circumstances the reserves affected the trajectories of functional mobility. Thus, the integration of qualitative and quantitative data in the mixed methods design helped to develop a causal explanation and generate further hypotheses (Bazeley, 2018). An exploratory mixed methods research design, first exploring the phenomenon of stable trajectories of patient-reported functional mobility despite increasing years since diagnosis in the qualitative part and assessing the emerging important variables in the subsequent quantitative part, would have been an alternative design. However, this dissertation capitalised on the unique longitudinal data collected over eight years from over 800 people with PD and PDD, an endeavour that could not have been achieved within the limited time frame of a single doctoral research project (Creswell and Plano Clark, 2018).

The problem-centred pragmatism was chosen as the overarching philosophical tool. This approach focuses on the consequences of research, on the primary importance of the question asked rather than methods, and on the use of multiple methods of data collection to inform the problem(s) under study (Creswell and Plano Clark, 2018). In addition to the mix and respect of different perspectives, the mixed methods design helped to push the boundaries of qualitative and qualitative research. Specifically, I applied some strategies of the complexity-informed approach (Greenhalgh and Papoutsi, 2018) by integrating contextual and subjective experiences with linear mixed models to generate new insights to produce a rich, nuanced picture of the effect of the different reserves and the underlying reasons. In addition, this approach lead to unexpected results. For example, three of the five

interview participants with unexpectedly stable trajectories of functional mobility reported a co-existing chronic inflammatory comorbidity and treatments (antibody treatment, intestinal antiphlogistic). These findings align with the molecular pathogenesis of PD involving neuroinflammation (Moehle and West, 2015, Poewe et al., 2017, Castillo-Rangel et al., 2023). This neuroinflammation could potentially be mitigated by treatment (Pinel Rios et al., 2019). In addition, the incidence of chronic inflammatory bowel diseases is increased in individuals with PD and genetic variants in leucine-rich repeat kinase 2 (LRRK2) (Herrick and Tansey, 2021) indicating a potential genetic factor. Such insights can help to refine approaches to PD management. In this context, measuring the impact of interventions on functional mobility from a patient-perspective becomes increasingly important.

Patient-centred measurement of patient-reported functional mobility

According to a recent systematic review of measurement instruments for assessing functional mobility in individuals with PD, no established instrument specifically assessed functional mobility through patient reports (Bouca-Machado et al., 2020a). Similarly, most studies were excluded in our systematic review as they did not assess patient-reported functional mobility (Chapter 3), although patient-reported outcomes have a critical role in assessing clinical significance as they ensure that changes have an impact from the perspective of the individuals living with PD (FDA, 2009). I chose to validate a composite score based on the subscales of mobility and activities of daily living of a measurement of health-related quality of life (PDQ-39) (Chapter 2) since developing, translating and validating an entirely new instrument is a long-lasting process, especially as the multilingual context of Luxembourg requires an instrument to be validated in several languages. The focus on patient-reported functional mobility instead of gait parameters was more in line with our main focus, i.e., the perspective of individuals with PD. Specifically, according to Ferreira et al. (2015), their perspectives on important outcomes differ from those of clinicians. While individuals with PD and their caregivers highlighted the capability of performing activities of daily living as the most important parameter, for clinicians, time spent for specific tasks was the most useful parameter (Ferreira et al., 2015). This is also in line with the notions that individuals move with intentionality (Zegelin, 2008) and that mobility is fundamental to independently meet life-maintenance needs (Maslow, 1943, Carp, 1988). In addition, quality of life and health are very individual. This was illustrated in Chapter 7 by the heterogenous trajectories of non-motor symptoms and the associated level of distress across people with PD. While some reported no distress due to urinary incontinence, other individuals reported this as severely distressing (Hurt et al., 2019). Thus, using measures that are not patient-centred (not covering domains that are of importance to individuals) may not be valid for those patients. Moreover, standardised measures with fixed, common items for all respondents independent of the sociodemographic and health-related characteristics, may not capture the phenomenon they intend to and thus be unresponsive to change after treatments (Carr and Higginson, 2001).

In addition to the individuality of quality of life and health, attempts to quantify them using standardised generic measures have been confounded by the "disability paradox" (Albrecht and Devlieger, 1999). Individuals with significant health and functional problems or intrusive symptoms did not necessarily report impaired quality of life scores (Albrecht and Devlieger, 1999). Similarly, shared characteristics of the interview participants emerging from the inductive analysis (Chapter 7), were life affirmation, the adaption of their expectations and acceptance of the limits. This can also be related to the Calman's gap. According to Calman (1984), quality of life (and thus also functional mobility) are subjective and can be poor when expectations do not match the experiences. Thus, the stable trajectories of patient-reported functional mobility might also reflect the stable Calman's gap. However, this needs to be further investigated.

In the dissertation, patient-reported functional mobility was the main interest. Similarly, according to the pragmatic worldview (Creswell and Plano Clark, 2018), studies focusing on the experience of, and the compensatory mechanism by people with PD in their daily life, then the reality as experienced by the people living with the disease, e.g., a patient-reported outcome, might be the best. Moreover, I assumed the terms "patient-reported functional mobility" and "functional mobility as reported by the patient" do not mean the same. While the first accepts the patient-reported functional mobility as its own concept, the second term highlights the deviation from the "real truth". Thus, for the dissertation I chose the term "patient-reported functional mobility". However, if the objective is to answer a biological question by measuring the biological progression of PD with new biological markers (Simuni et al., 2024, Höglinger et al., 2024), then the "reality" as stated by the objective measure might suit the best according to this overreaching worldview (Creswell and Plano Clark, 2018).

8.3 IMPLICATIONS

Understanding individual changes over time by illustrating individual symptoms' trajectories

Designing reliable healthcare systems might best build upon the time course and nature of the service needs of people with PD, rather than conventional differentiation by care setting or diagnosis (Algase et al., 1996). Individuals often ask doctors at the time of diagnosis about their prognosis (Sanders et al., 2022) and in this situation, the trajectories across sex/gender and genetic variants for different symptoms as illustrated in our figures (Chapters 5 – 6) might be helpful for clinicians in their support of individuals in the different dimensions of illness progression in PD. Specifically, they can offer conceptual maps of the archetypical patient journey and facilitate timely identification and assessment (Murray et al., 2024). This strategic overview of the needs on the "mean" trajectories (marginal means) combined with available services, may help policies and services to be better conceptualised, formulated, and developed (Murray et al., 2005).

However, this trajectory approach also bears the risk of oversimplifying a single individual's journey as they may experience multiple trajectories as illustrated in the individual trajectories in Chapter 7. Consequently, the "mean" trajectories are applicable on a population level but may evolve atypically for individuals (Geijteman et al., 2024). Thus, although those "mean" trajectories for men and women as described in Chapter 5 give a conceptual overview, individuals should not be categorised into a trajectory group without regular assessment (Murray et al., 2005).

From disease prevention to health promotion

Health promotion and disease prevention can focus on individual behaviour changes or aim at modifying the broader social, economic, or environmental conditions (Gerhardus et al., 2015). Although background factors (sex/gender, age, genetics, partner and children, educational attainment, place of residence) cannot be easily or directly influenced, they can help to identify risk profiles and develop targeted interventions on the population level (Algase et al., 1996). A higher age and age at diagnosis, lower global cognition, higher symptoms of depression, motor- and non-motor symptoms and postural instability and gait disturbances characterised individuals with a decreasing trajectory of patient-reported functional mobility (Chapter 7). Thus, health professionals should identify those individuals as they require specific attention in phases of vulnerability. However, these characteristics are not specific and those symptoms become increasingly prevalent over the course of PD. Consequently, further research could integrate our results in the development of a vulnerability risk-profile for unstable trajectories of patient-reported functional mobility and evaluate its predictive validity. As the *GBA1*-variants moderated the effect of time since diagnosis on non-motor symptoms and not on functional mobility (Chapter 6), their role in such a risk profile is yet to be determined.

In addition, to counterbalance the limitations of pharmacological therapy, applying a holistic approach including non-pharmacological interventions (Kalbe et al., 2024), health professionals could promote the characteristics of individuals with stable trajectories of patient-reported functional mobility, i.e., global cognition and address symptoms of depression, motor- and non-motor symptoms and postural instability and gait disturbances and thus enhance patient-reported functional mobility. Specifically, self-care in the form of a physically active lifestyle emerged from our qualitative analysis as a facilitator of space betwen reported & functional mobility (Chapter 7). Similarly, another recent Cochrane review highlighting the importance of physical exerice for people with PD or PDD in general and recommended to give special consideration to the personal preferences of people with PD or PDD (Ernst et al., 2023). This supports the findings of our qualitative interviews. Specifically, the experienced importance of autonomy in switching between places to accomplish and participate in activities of daily living (Chapter 7) supports a goal-oriented approach to increase the engagement of individuals with PD in exercise therapy (Zegelin, 2008, Adlbrecht and Mayer, 2018, Maslow,

1943). Our systematic review (Chapter 3) found inconclusive results about the association of depression (Rantakokko et al., 2019, Dutra et al., 2022) with patient-reported functional mobility. However, lower symptoms of depression characterised people with unexpectedly stable trajectories of functional mobility (Chapter 7), which aligns with the protective role of self-efficacy in maintaining functional mobility, as reported in the qualitative interviews. Also, while these interviews highlighted the role of self-efficacy in the management of the impact of PD on the daily life, one study (Dutra et al., 2022) explored the cross-sectional relationship between functional mobility and self-efficacy, specifically related to balance (i.e., Activity-specifc Balance Confidence scale - ABC). Although this scale was recommended by MDS for evaluating gait and stability among individuals with PD (Bloem et al., 2016), its use is limited when specifically measuring self-efficacy. Also, a recent study found that cognitive training, a treatment option to enhance and maintain cognitive function, can increase physical activity (Bode et al., 2023). However, a Cochrane review concluded there is a need for more robust, adequately powered studies of cognitive training (Orgeta et al., 2020). According to our systematic review (Chapter 3), previous research evaluating the cross-sectional association of global cognition (Lindh-Rengifo et al., 2021, Dutra et al., 2022, Rantakokko et al., 2019) with patient-reported functional mobility has been inconclusive. In addition, we didn't identify a clear moderating role of the educational attainment in our mixed-methods analyses reported in Chapter 7. Finally, according to the deductive analysis of the qualitative interviews (Chapter 7), individuals without a driving license and without a partner required individual transport alternatives to the car. For instance, those could be accessible, affordable, available and accepted vehicles with a design adapted to the requirements of (older) individuals with PD and PDD providing a safe and comfortable transport alternative to the car (Cirella et al., 2019).

We want to emphasise that while health promotion and disease prevention both aim to improve overall health, it is essential for nurses and the healthcare system to go beyond primary and secondary disease prevention (such as avoiding specific actions or complications or responding to a decrease in functional mobility) by adopting a health promotion approach. Specifically, in collaboration with the interdisciplinary team, the nurse can proactively strengthen reserves (e.g. self-efficacy, self-care, transport service) in a goal-oriented approach and thus empower individuals with PD to overcome phases of vulnerability (Spini et al., 2013), e.g. fall or another negative life event. Although this dissertation did not specifically address falls, a recent Cochrane review (Allen et al., 2022) suggests that exercise interventions likely reduce the rate of falls in people with PD. Furthermore, in falls prevention, nurses often prioritise safety, which can sometimes lead to unintended negative consequences (Clancy and Mahler, 2016), such as physical restraints or a reduction in autonomy and mobility. This reinforces the decision to adopt a health promotion approach that emphasises mobility promotion rather than solely focusing on disease prevention, such as preventing falls.

Finally, health promotion demands coordinated action involving the different sectors as individuals, families and communities and nurses have a major responsibility to mediate between differing interests in society to enhance health (World Health Organisation, 1986). Consequently, I recommend efficient health promotion interventions to be organised on population-level promoting the broader environmental and social conditions for mental health helping people with chronic conditions to actively shape their illness trajectory despite an unfavourable environment, until the age- and Parkinson's friendly ecosystem is widely implemented.

Age- and Parkinson's friendly ecosystem

As illustrated above, compared to the individual behavioural approaches, a modification of the broader social, economic, or environmental conditions seems more effective (Gerhardus et al., 2015). The qualitative study supports the potential of transport as a core element of a smart, age-friendly ecosystem (van Hoof and Marston, 2021) in age-friendly cities (World Health Organisation, 2007) to enable functionality despite PD or older age. Moreover, promoting green and active means of transport (e.g., public transport, and active trips) may lead to environmental benefits, as well as health benefits via increased physical activity (Giménez-Nadal et al., 2022) - one self-care characteristic of the interviewed group. Importantly, local amenities should be provided within walking distance (reachable within a 10 or 20-minutes walk from home) to foster older adults' walking for transport in smaller communities and to enable active and healthy ageing in place (Hasselder et al., 2022). The qualitative findings illustrate how the environment is hindering functional mobility in people with PD. Among others due to functional limitations (e.g., restricted functional mobility), public transport was less accessible to people with PD. Politics need to further incentivise cities and rural areas to adapt their design to the functional capacities (Iwarsson and Stahl, 2003) of men and women with PD and thus equally enabling the whole population to use the environment and to participate in daily life tasks like grocery shopping (Nilsson et al., 2013). The qualitative study (Chapter 7) and previous research (Mason et al., 2016) found people with PD experience changes in symptoms as an effect of age. Health professionals can help individuals with PD to advocate for adequate health care by familiarising individuals with the possibilities and raising realistic expectations of health. Thus, they prevent individuals from setting low expectations leading to a tolerance of restricted autonomy. Additionally, the role of biological age (Pavelka et al., 2022b), the age at diagnosis and the various effects of ageing in moderating the effect of years since diagnosis on functional mobility needs to be further investigated. Also, a phenomenon covering similar aspects to vulnerability (Spini et al., 2013) as used in this dissertation is frailty. Frailty is defined as: "a clinical state in which there is an increase in an individual's vulnerability for developing increased dependency and/or mortality when exposed to a stressor" (Morley et al., 2013). PD is a contributing factor to frailty and its characteristics (McMillan et al., 2021, Tenison and Henderson, 2020). Similar to our dissertation, future research projects could investigate the reasons

why some individuals with PD become frail while others don't and the role of biological age. Finally, investigations of frailty across generations in individuals with an unexpectedly stable/normalising trajectory of functional mobility could provide further insights while the specificities of functional mobility trajectories in individuals with an early onset PD also need to be further explored.

Functionality despite disability through empowerment of people with Parkinson's disease

Despite the presence of an unfavourable context (rural place of residence, no driving license, no partner, no children, low educational attainment), the interviewed women maintained a stable trajectory of functional mobility leading to the conclusion that other factors than the reserves might be key for a stable trajectory of functional mobility. The phenomenon of functionality (functional mobility) despite disability (years since diagnosis) is a key aspect of the International Classification of Functioning, disability and health (ICF) (World Health Organisation, 2001). Similar to the ICF, here I demonstrate that people with disabilities can still have a high level of functioning and participation and that their disability does not necessarily define their overall functioning.

In addition to the previously mentioned environmental factors linked to the place of residence, this dissertation investigated to what extent personal contextual factors shape the ability of individuals with PD to stay functionally mobile, despite increasing years since diagnosis. The trajectories of the interview participants (Chapter 7) experiencing different stressors (other co-morbidities or other adverse life events) illustrate the successful overcoming of vulnerability with different coping strategies (Lazarus and Folkman, 1984) such as self-efficacy or self-care. Also, our inductive analysis (Chapter 7) suggests the psychosocial factors and personal attributes (Zegelin, 2008) might reinforce the ability to cope with and recover from stressors and thus reduce vulnerability (Cullati et al., 2018). Moreover, all interview participants expressed life affirmation and the importance of expectation management (Chapter 7). Thus, to improve quality of life and patient-reported functional mobility, health professionals might help individuals with PD to narrow the gap between expectations and experiences (Calman, 1984) by visualising the individual trajectories compared to the "mean" progression in their reference group.

As previously illustrated by Riggare (2022), individuals with PD spend most of their time providing self-care rather than receiving medical attention. Moroever, in study by Scott Duncan et al. (2022) exploring self-management in individuals with chronic diseases, their participants expressed a desire to be more actively involved in their own care. They also expressed a desire for better support for activities imposed by health care professionals (Scott Duncan et al., 2022). The concept of the trajectory nurse, as described by Grypdonck (2005), could potentially address these needs. Thus, the implementation into health care

of self-management approaches integrating the perspective of the individual with PD is required to better support self-empowering behaviour in individuals with PD (Scott Duncan et al., 2022). Moreover, as the goals of mobility of the interviewed individuals with PD were mainly related to autonomous decision-making (Zegelin, 2008) to perform activities of daily living (Ferreira et al., 2015), the approach to increase quality of life and functional mobility and related interventions by health professionals should be goal-oriented (Calman, 1984).
Participants with an unexpectedly stable trajectory experienced high self-efficacy beliefs (Chapter 7) motivating behaviour and performance (Bandura, 1986). In a study aiming to identify factors associated with better self-management in people with PD following an acute event, self-efficacy was the only characteristic that influenced self-management (Chenoweth et al., 2008). Moreover, married individuals with PD with the support of their spouse or others have better self-efficacy and a sense of coherence (Chenoweth et al., 2008). Thus, marital status might indirectly influence self-care via an increase in self-efficacy. In this dissertation, the experienced self-efficacy increasing self-care emerged from the inductive analyses only. Our qualitative findings describe some of the factors affecting self-care from the middle-range theory of self-care for chronic illnesses, e.g., resilience in the face of social confrontations, openness towards new experiences (also towards new technology), provide and ask for support, life-affirming and sociable attitude, high self-efficacy beliefs, adaption of expectations, acception of limits. Also our interview participants refered to self-care activities promoting a physically active lifestyle. In the theory of self-care, self-care refers to maintaining health by pursuing healthy behaviours and managing disease (Riegel et al., 2012). The theory described the following factors affecting self-care: Previous experiences and skill, motivation, cultural beliefs and values, confidence, habits, functional and cognitive abilities, support from others and access to care. Those could be further investigated in individuals with unexpectedly stable trajectories of functional mobility. Finally, the unexpectedly stable trajectories of functional mobility could be seen as an indicator of effective maintenance of health through self-care, similar to the biographical, illness-related and everyday life work of the individual as previously described (Corbin and Strauss, 2010, Corbin, 1991).

8.4 FUTURE DIRECTIONS

I would like to conclude this discussion chapter by exploring future directions addressed to men and women with PD, health professionals, researchers, the healthcare system and society.

First, research aiming to develop an effective intervention to promote functional mobility must assess its efficiency as experienced by the persons living with the disease. Quality of life and health are very individual experiences (Carr and Higginson, 2001).

Consequently, instead of using standardised measures with fixed items that apply uniformly to all respondents regardless of their characteristics, the development of a personalised assessment of functional mobility could be more effective. Such an approach, e.g., integrating the individual rating of importance, could provide a more accurate assessment from the perspective of individuals with PD (Carr and Higginson, 2001), without suggesting an expectation of complete well-being. This expectational aspect was criticised 45 years ago by Antonovsky (1979) in the World Health Organisations' definition of health[7] (World Health Organisation, 2006). As this state of complete well-being is rarely achievable for individuals with a chronic illness, the focus on integrity in healthcare and assessment instruments can lead to unrealistically high expectations of people with chronic illnesses like PD and thus create dissatisfaction and a low quality of life (Prell et al., 2020, Calman, 1984).

Secondly, the visualisation of the different symptom trajectories in softwares of the electronic health record (e.g. fever curve) and digital tools, could support healthcare providers to get an overview of the longitudinal symptoms progression. Specifically, clinical practice would profit from a tool, helping them to calculate and predict the individual risk of vulnerability and a subsequent decreasing trajectory of functional mobility. Identification of individuals at risk of vulnerability could be enhanced with a traffic light system monitoring longitudinal trajectories of functional mobility and switching to orange in phases of vulnerability. Thus, they could anticipate phases of vulnerability and plan for deteriorating health and thus reduce distress (Murray et al., 2017). The data analysed in the present work was prospectively collected at an annual interval. Patient-centred data from self-tracking[8], a mass phenomenon through omnipresent smartphones (Heyen, 2020) could potentially be used to get a better understanding of the changes over time and thus systematically improve health-care and research enabling personalised medicine (Riggare et al., 2019). However, this must not lead to an increase in the tracking burden for individuals with PD. Importantly, Riggare and colleagues (2019) suggest an increase in the benefits and reduction of the burden of self-tracking through improved tools and increased use of self-tracking results in the dialogue with healthcare. Specifically, tools for self-tracking should be accurate and adaptable to the needs and interests of the users (Riggare et al., 2019).

Thirdly, as it has been pointed out that creative lateral thinking has led to important advances in understanding (Horrobin, 1990), the research environment must allow researchers to explore unfamiliar paths. With the mixed-methods design I investigated

7 "WHO's definition of health: "A state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity." WORLD HEALTH ORGANISATION 2006. Constitution of the World Health Organization. In: HEADQUARTERS, W. (ed.). https://www.who.int/publications/m/item/constitution-of-the-world-health-organization..

8 Digital self-tracking: "the permanent gathering and evaluation of self-related data in one's daily life" by using digital technologies (Heyen, 2020).

the “positive anomalies”, i.e., the phenomenon of unexpectedly high functional mobility using mixed methods, which encouragely lead to unexpected results (co-existing chronic inflammatory comorbidity and treatments (antibody treatment, intestinal antiphlogistic)) and felt akin to a clinical investigation. A comprehensive, multi-faceted and interdisciplinary case description involving neurologists and rheumatologists could lead to new insights. Also, the investigation of the adaptation of individuals with PD to another co-occuring chronic disease, the prioritisation of the one taking up the largest effort (Murray et al., 2024) and the role of the previously discussed “disability paradox” (Albrecht and Devlieger, 1999) could help to further explain these findings. This dissertation focussed on the context (environmental and personal factors) and did not investigate the role of the body structures and functions (e.g., freezing of gait), activities and participation (e.g., health interventions) (Figure 8) in the trajectory of patient-reported functional mobility. Future studies co-creating an intervention to promote stable trajectories or focussing on understanding the “positive anomalies” in individuals with freezing of gait could be considered.

Finally, PD is the fastest-growing neurodegenerative condition (Dorsey and Bloem, 2018, Dorsey et al., 2007). To face this challenge, society and the healthcare system must recognise the central role of individuals with PD and their families in shaping the trajectory of the disease (Corbin and Strauss, 2010). Also, an efficient health system requires the use of the full potential and expertise of the nurses to help men and women with PD to better adjust their daily lifes to the challenges caused by the disease. Importantly, they can also help to adapt their treatment(s) to their daily routines (Grypdonck, 2005). More than twenty years ago in the UK, the specialist nurses already complemented the multidisciplinary team by supporting individuals with PD among others in setting realistic and achievable goals (MacMahon and Thomas, 1998). The contribution of self-care to health in individuals with chronic conditions is increasingly acknowledged with nurses playing an important role (Tenison et al., 2020, Bloem et al., 2020). Recently, the nurses were included as partners in the multidisciplinary ParkinsonNet Luxembourg (ParkinsonNet Luxembourg, 2023) and will support individuals to self-monitor and self-manage, provide information and ensure that they know how to access the right help at the right time. In order to strengthen the links across disciplines and settings (incl. communities) and the transversal impact of research, I suggest to set up an interdisciplinary health services research department at Parkinson’s research clinics or in the form of a health-clinic at the University of Luxembourg to pilot and evaluate interdisciplinary innovations including but not limited to electronic solutions for improving support of individuals living with PD in Luxembourg. Nurses are well positioned to help improve trajectories of patient-reported functional mobility in men and women with PD as their unique perspective on health enables nurses to see possibilities for people to experience wellness in the presence of a chronic disease (Lyon, 2012) and thus to promote unexpectedly stable trajectories of functional mobility.

8.5 CONCLUSION

The research conducted in this dissertation aimed to improve our understanding of factors protecting functional mobility, the phenomenon of unexpectedly stable functional mobility and how these are experienced by individuals with PD, ensuring changes were understood from the perspective of the individuals living with PD. Taking the results of the individual chapters of this dissertation together, a number of conclusions related to this overall aim can be made.

Using data from the Luxembourg Parkinson's study, a nationwide, observational, longitudinal-prospective and dynamic cohort, I validated the patient-reported Functional Mobility Composite Score (FMCS), a tool based on the PDQ-39 questionnaire available in different languages helping to assess patient-reported functional mobility until a patient-centred assessment is developed (Chapter 2). The systematic review concluded that future research on patient-reported functional mobility should shift the focus towards the environmental factors determining patient-reported functional mobility (Chapter 3). To increase awareness of clinical researchers and future PhD students for the statistical methods of longitudinal data analysis, I demonstrated in a comparative analysis, how the choice of statistical method may influence research outcomes (Chapter 4). While single studies previously assessed the association of different *GBA1*-variants or sex/gender with the progression of PD, I expanded an established and well-accepted illustration of PD progression (Poewe et al., 2017) by providing a comprehensive empirical description and illustration of the progression of motor- and non-motor symptoms (Chapter 5 – 6). Finally, the mixed-methods study concluded that the driving license or the 24h-availability of a person with a driving license and the characteristics of individuals with unexpectedly stable trajectories of patient-reported functional mobility (psychosocial factors similar to self-efficacy, self-care activities promoting a physically active lifestyle and chronic inflammatory diseases) facilitate stable trajectories of patient-reported functional mobility (Chapter 7).

Unexpectedly stable trajectories of functional mobility in men and women with PD have clinical and care relevance for the affected individuals, but seem in quantitative analyses to be multifactorial in nature, with little evidence for general determinants of patient-reported functional mobility over time. Although I could not detect a significant moderation of the trajectories of patient-reported functional mobility by the different reserves (i.e., educational attainment, partner, children, place of residence), the qualitative study helped to gain some potential explanations, context and insights in the barriers and facilitators of functional mobility as perceived by women with PD. Thus, the experience of individuals with PD and their context could be adequately valued. I believe that this research design will help health sciences to find new solutions to complex problems. This dissertation presented several analyses of data of the extensive dataset of the Luxembourg Parkinson's study and adds

new knowledge to a topic that is a priority according to people with PD (Bowring et al., 2022). The evolving methods over the chapters illustrate my continuous learning process starting with the well-known method, i.e., the systematic review (Chapter 3) over to the cross-sectional analyses with R (Chapter 2), to the longitudinal analyses (Chapter 5 – 7) and the mixed-methods (Chapter 7). The description of the trajectories of the different motor- and non-motor symptoms (Chapter 5) was an important step toward understanding the dynamics of the parallel trajectories in preparation for the investigation of potential moderators (Chapter 6 and 7). This dissertation was a first step in transversal translational research. The interdisciplinary exchange with the supervisors and the members of the National Centre for Excellence in Research in PD enabled new insights. Specifically, the combination of the clinical point of view with geneticists allowed me to explore another scientific discipline (Chapter 6). Similarly, the collaboration with a Prof. of applied statistics helped to translate statistical methodology for educational purposes (Chapter 4).

In conclusion, the call for an accessible and usable environment for people with PD remains relevant. This thesis suggests, that an age- (and PD) friendly ecosystem as requested almost twenty years ago by the World Health Organisation (2007) could solve the main barrier of functional mobility as experienced by men and women with PD: An environment that is not adapted to their functional capacities and thus unable them to participate in life. To counterbalance this barriers, men and women with PD might benefit from further flexible alternatives to the car as means of transportation independent of their place of residence, as well as housing arrangements with better support structures. Interestingly, despite a challenging environment the interview partners experienced factors enabling functional mobility, among others the self-efficacy enabling them to take control of their own life leading to self-care interventions, e.g., physically active lifestyle. Complex population wide interventions aiming to empower those reserves and characteristics of people with chronic diseases (and the general population) can promote stable trajectories of functional mobility and a self-determined life. Through their unique perspective on health, nurses can assume their role as advocates for the men and women with PD by promoting the respect towards and value of their point of views through patient-centred measurements and care. Thus, they can support men and women to learn to live autonomously with PD, in their preferred manner and environment.

CHAPTER 9

Summaries and Valorisation

English Summary

Nederlandse Samenvatting

Deutsche Zusammenfassung

Résumé en français

Impact paragraph

SUMMARIES

English Summary

Functional mobility is one of the disease-related features most relevant to people with PD (Bowring et al., 2022). It worsens as the disease progresses (Lindh-Rengifo et al., 2021, Mirelman et al., 2019) resulting in increasing professional care and nursing home costs (Chaudhuri et al., 2024). A promotion of mobility and functionality could help to delay institutionalisation and respect the desire of people with PD to remain in their homes (Habermann and Shin, 2017). This dissertation aimed to understand determinants of functional mobility, the phenomenon of unexpectedly stable trajectories for functional mobility and their experience in people with PD.

CHAPTER ONE introduces the impaired functional mobility in Parkinson's disease, life with a chronic disease, longitudinal data analysis of the Luxembourg Parkinson's Study, the mixed-methods design and the involvement of individuals with PD in the dissertation. Using data from the Luxembourg Parkinson's study, a nationwide, observational, longitudinal-prospective and dynamic cohort, CHAPTER TWO reports the assessment of convergent and discriminative validity of the Functional Mobility Composite Score (FMCS). The FMCS is an algorithm based on the Parkinson's Disease Questionnaire-39 (PDQ-39) to assess patient-reported functional mobility in a multilingual context of Luxembourg. To get an overview of the current state of research, CHAPTER THREE reports a systematic review concluding future research on patient-reported functional mobility should focus among other on environmental factors as determinants. In preparation of the longitudinal analyses, CHAPTER FOUR demonstrates in a comparative analysis, how the choice of statistical method may influence research outcomes. Using the previously established and validated methodology, CHAPTER FIVE applies linear mixed-effects models to deal with the differential trajectories of patient-reported functional mobility and the motor- and non-motor symptoms in men and women with PD. An overall slower disease progression was observed in women compared to men. As the development of Parkinson's disease (PD) is influenced by genetic and environmental factors and the role of PD-risk *GBA1* variants is not yet well understood, CHAPTER SIX compares the progression of patient-reported functional mobility and other symptoms in individuals with different genetic *GBA1* variants (Gaucher-related or PD-risk *GBA1* variants) and the non-carriers. The *GBA1*-variants were not associated with a slower decline of patient-reported functional mobility. Nevertheless, a reevaluation of their pathologic relevance would be warranted if these findings are confirmed in an independent cohort due to the described effect modification of the non-motor symptoms. To better understand the phenomenon of unexpectedly stable trajectories of functional mobility and the protective factors involved, CHAPTER SEVEN reports a sequential explanatory mixed-methods study. First mixed effects models investigated the effect modification of relational (partner, children), cognitive (educational attainment), and

socioeconomic (place of residence) reserves on the trajectory of patient-reported functional mobility. Then qualitative semi-structured interviews with participants experiencing an unexpectedly stable trajectory of functional mobility explored their perceptions of barriers and facilitators related to those reserves. Characteristics of individuals with unexpectedly stable trajectories of patient-reported functional mobility that emerged from the inductive analysis were psychosocial factors similar to self-efficacy, chronic inflammatory diseases and self-care activities promoting a physically active lifestyle. Finally, CHAPTER EIGHT of this dissertation synthesises and discusses the results of all chapters, the methodological considerations and presents future directions and the overall conclusions of this dissertation.

Nederlandse Samenvatting

Functionele mobiliteit is een van de ziekte-gerelateerde kenmerken die het meest relevant zijn voor mensen met de ziekte van Parkinson (Bowring et al., 2022). Dit verslechtert naarmate de ziekte vordert (Lindh-Rengifo et al., 2021a, Mirelman et al., 2019), wat resulteert in toenemende professionele zorg- en verpleeghuiskosten (Chaudhuri et al., 2024). Het bevorderen van mobiliteit en functionaliteit zou kunnen helpen om institutionalisatie te vertragen en de wens van mensen met de ziekte van Parkinson om in hun eigen huis te blijven, te respecteren (Habermann en Shin, 2017). Dit proefschrift had als doel de determinanten en het fenomeen van onverwachte stabiele trajecten in functionele mobiliteit te begrijpen, evenals de bijbehorende ervaringen van mensen met de ziekte van Parkinson.

HOOFDSTUK ÉÉN introduceert de verstoorde functionele mobiliteit bij de ziekte van Parkinson, het leven met een chronische ziekte, de longitudinale data-analyse van de Luxemburgse Parkinson Studie en het mixed-methods ontwerp dat de betrokkenheid van individuen met Parkinson in het proefschrift omvat. Met behulp van gegevens uit de Luxemburgse Parkinson-studie, een landelijke, observationele, longitudinale-prospectieve en dynamische cohortstudie, rapporteert HOOFDSTUK TWEE de beoordeling van de convergente en discriminatieve validiteit van de Functionele Mobiliteit Composite Score (FMCS). De FMCS is een algoritme gebaseerd op de Parkinson's Disease Questionnaire-39 (PDQ-39) om door patiënten gerapporteerde functionele mobiliteit te beoordelen in de meertalige context van Luxemburg. Om een overzicht te krijgen van de huidige stand van onderzoek, rapporteert HOOFDSTUK DRIE een systematisch overzicht en concludeert dat toekomstig onderzoek naar door patiënten gerapporteerde functionele mobiliteit zich onder andere zou moeten richten op omgevingsfactoren als determinanten. Ter voorbereiding op de longitudinale analyses demonstreert HOOFDSTUK VIER in een vergelijkende analyse hoe de keuze van statistische methode de onderzoeksresultaten kan beïnvloeden. Met behulp van de eerder vastgestelde en gevalideerde methodologie past HOOFDSTUK VIJF lineaire gemengde-effectenmodellen toe om de verschillende trajecten van door patiënten gerapporteerde functionele mobiliteit en de motorische en niet-motorische symptomen bij mannen en vrouwen met Parkinson te onderzoeken. Een algemeen langzamere ziekteprogressie werd waargenomen bij vrouwen in vergelijking met mannen. Aangezien de ontwikkeling van de ziekte van Parkinson (PD) wordt beïnvloed door genetische en omgevingsfactoren en de rol van PD-risico GBA1-varianten nog niet goed wordt begrepen, vergelijkt HOOFDSTUK ZES de progressie van door patiënten gerapporteerde functionele mobiliteit en andere symptomen bij dragers van verschillende genetische GBA1-varianten (Gaucher-gerelateerde of PD-risico GBA1-varianten) met de niet-dragers. De GBA1-varianten werden niet met een langzamere achteruitgang van door patiënten gerapporteerde functionele mobiliteit in verbinding gebracht. Desalniettemin zou een herwaardering van hun pathologische relevantie gerechtvaardigd zijn indien deze bevindingen worden bevestigd in een onafhankelijke cohortstudie vanwege de effectmodificatie van de niet-

motorische symptomen in de huidige studie. Om het fenomeen van onverwacht stabiele trajecten van functionele mobiliteit en de betrokken beschermende factoren beter te begrijpen, rapporteert HOOFDSTUK ZEVEN een sequentiële verklarende mixed-methods studie. Eerst onderzochten we de effectmodificatie van relationele (partner en kinderen), cognitieve (schoolonderwijs) en sociaaleconomische (woonplaats) reserves op het verloop van door patiënten gerapporteerde functionele mobiliteit. Vervolgens werden kwalitatieve semi-gestructureerde interviews gehouden met deelnemers die een onverwacht stabiel traject van functionele mobiliteit ervaren, om hun percepties van barrières en facilitatoren met betrekking tot deze reserves te verkennen. Kenmerken van individuen met onverwacht stabiele trajecten van door patiënten gerapporteerde functionele mobiliteit die voortkwamen uit de inductieve analyse waren psychosociale factoren vergelijkbaar met zelfeffectiviteit, chronische ontstekingsziekten en zelfzorgactiviteiten die een fysiek actieve levensstijl bevorderen. Ten slotte synthetiseert en bespreekt HOOFDSTUK ACHT van dit proefschrift de resultaten van alle hoofdstukken en de methodologische overwegingen, en presenteert het de toekomstige richtingen en de algemene conclusies van dit proefschrift.

Deutsche Zusammenfassung

Das Management der funktionellen Mobilität stellt für Menschen mit Parkinson eine Priorität dar (Bowring et al., 2022). Sie verschlechtert sich im Krankheitsverlauf (Lindh-Rengifo et al., 2021a, Mirelman et al., 2019) und führt zu einem erhöhten Pflegebedarf und steigenden Kosten (Chaudhuri et al., 2024). Eine Förderung der Mobilität und Funktionalität könnte dazu beitragen, die Institutionalisierung zu verzögern und somit den Wunsch von Menschen mit Parkinson zu respektieren, in ihrem Zuhause zu bleiben (Habermann und Shin, 2017). Diese Dissertation zielte darauf ab, die Determinanten der funktionellen Mobilität, das Phänomen unerwartet stabiler Verläufe der funktionellen Mobilität und deren Erfahrungen bei Menschen mit Parkinson zu verstehen.

Die Einleitung in KAPITEL EINS behandelt die beeinträchtigte funktionelle Mobilität bei Parkinson-Krankheit, das Leben mit einer chronischen Erkrankung, die longitudinale Datenanalyse der Luxemburger Parkinson-Studie und das Mixed-Methods-Design, welches die Einbeziehung von Personen mit Parkinson in die Dissertation umfasst. Unter Verwendung von Daten aus der Luxemburger Parkinson-Studie, einer landesweiten, beobachtenden, longitudinal-prospektiven und dynamischen Kohorte, berichtet KAPITEL ZWEI über die Bewertung Untersuchung der konvergenten und diskriminierenden Validität des *Functional Mobility Composite Score (FMCS)*. Der FMCS ist ein Algorithmus, der auf dem Parkinson's Disease Questionnaire-39 (PDQ-39) basiert, um die von Menschen mit Parkinson berichtete funktionelle Mobilität im mehrsprachigen Kontext Luxemburgs zu erfassen. Um einen Überblick über den aktuellen Stand der Forschung zu erhalten, berichtet KAPITEL DREI über einen systematischen Review welches schlussfolgert, dass sich zukünftige Forschung zur von Menschen mit Parkinson berichteten funktionellen Mobilität unter anderem auf Umweltfaktoren als Determinanten konzentrieren sollte. Zur Vorbereitung der Längsschnittanalysen zeigt KAPITEL VIER in einer vergleichenden Analyse, wie die Wahl der statistischen Methode die Forschungsergebnisse beeinflussen kann. Unter Verwendung der zuvor etablierten und validierten Methodik wendet KAPITEL FÜNF lineare gemischte Modelle an, um die unterschiedlichen Verläufe funktionellen Mobilität sowie der motorischen und nicht-motorischen Symptome bei Männern und Frauen mit Parkinson zu untersuchen. Insgesamt wurde bei Frauen im Vergleich zu Männern ein langsameres Fortschreiten der Krankheit beobachtet. Da die Entwicklung der Parkinson-Krankheit (PD) von genetischen und Umweltfaktoren beeinflusst wird und die Rolle der PD-Risiko-*GBA1*-Varianten noch nicht gut verstanden wird, vergleicht KAPITEL SECHS den Verlauf der von Patienten berichteten funktionellen Mobilität und anderer Symptome bei Personen mit und ohne genetische *GBA1*-Varianten (Gaucher-bezogene oder PD-Risiko-*GBA1*-Varianten). Die *GBA1*-Varianten wurden nicht mit einem langsameren Rückgang funktioneller Mobilität in Verbindung gebracht. Allerdings wäre eine Neubewertung ihrer pathologischen Relevanz gerechtfertigt aufgrund der Effektmodifikation der nicht-motorischen Symptome nach Bestätigung dieser Ergebnisse in einer unabhängigen

Kohorte. Um das Phänomen unerwartet stabiler Verläufe der funktionellen Mobilität und die beteiligten schützenden Faktoren besser zu verstehen, berichtet KAPITEL SIEBEN über eine sequenzielle erklärende Mixed-Methods-Studie. Zunächst untersuchten wir die statistische Effektmodifikation von relationalen (Partner, Kinder), kognitiven (Schulbildung) und sozioökonomischen (Wohnort) Reserven auf den Verlauf der funktionellen Mobilität. Anschließend wurden qualitative, halbstrukturierte Interviews mit Teilnehmenden geführt, die einen unerwartet stabilen Verlauf der funktionellen Mobilität erlebten, um deren Wahrnehmungen von Barrieren und fördernden Faktoren im Zusammenhang mit diesen Reserven zu erforschen. Merkmale von Individuen mit unerwartet stabilen Verläufen der funktionellen Mobilität, die aus der induktiven Analyse hervorgingen, waren psychosoziale Faktoren ähnlich der Selbstwirksamkeit, Selbstpflegeaktivitäten, die einen körperlich aktiven Lebensstil fördern sowie chronische entzündliche Erkrankungen. Schließlich vereint und diskutiert KAPITEL ACHT dieser Dissertation die Ergebnisse aller Kapitel, die methodischen Überlegungen und stellt zukünftige Richtungen und die allgemeinen Schlussfolgerungen dieser Dissertation vor.

Résumé en français

La mobilité fonctionnelle est l'une des caractéristiques les plus importantes pour les personnes atteintes de la maladie de Parkinson (Bowring et al., 2022). Elle se détériore au fur et à mesure que la maladie progresse (Lindh-Rengifo et al., 2021a, Mirelman et al., 2019), ce qui entraîne une augmentation des coûts des soins (Chaudhuri et al., 2024). La promotion de la mobilité fonctionnelle pourrait aider à retarder l'institutionnalisation et, par conséquent, à respecter le désir des personnes atteintes de rester à domicile (Habermann et Shin, 2017). Cette thèse vise à comprendre les déterminants et le phénomène des « trajectoires étonnamment stables » de la mobilité fonctionnelle ainsi que l'expérience des personnes atteintes de la maladie de Parkinson.

CHAPITRE UN introduit la mobilité fonctionnelle altérée dans la maladie de Parkinson, la vie avec une maladie chronique, l'analyse des données longitudinales de l'étude Parkinson de Luxembourg et le design de la méthode mixte qui inclut la participation des individus atteints de Parkinson dans la dissertation. En utilisant les données d'une étude de cohorte observationnelle, longitudinale-prospective et dynamique menée au Luxembourg, le CHAPITRE DEUX rapporte l'évaluation de la validité convergente et discriminante du Functional Mobility Composite Score (FMCS). Le FMCS est un algorithme basé sur le questionnaire PDQ-39 qui a pour but d'évaluer la mobilité fonctionnelle vécue par les personnes atteintesde la maladie de Parkinson dans un contexte multilingue au Luxembourg. Le CHAPITRE TROIS présente une revue systématique des déterminants concluant que les futures recherches devraient, entre autres, se centrer sur les facteurs environnementaux en tant que déterminants de la mobilité fonctionnellevécue par les personnes vivant avec la maladie de Parkinson. En guise de préparation aux analyses longitudinales, le CHAPITRE QUATRE montre, grâce à une analyse comparative, en quoi le choix d'une méthode statistique peut influencer les résultats de la recherche. En utilisant l'algorithme préalablement validée, le CHAPITRE CINQ présente une application de modèles linéaires à effets mixtes afin d'analyse les trajectoires différentielles de la mobilité fonctionnelle et des symptômes moteurs et non moteurs chez des hommes et des femmes atteints de la maladie de Parkinson. Cette analyse a montré une progression plus lente de la maladie a été observée chez les femmes que chez les hommes. Etant donné que le développement de la maladie de Parkinson est influencé par des facteurs génétiques et environnementaux et que le rôle des variantes *GBA1* à risque de PD n'est pas encore bien connus, le CHAPITRE SIX compare la progression de la mobilité fonctionnelle et d'autres symptômes entre les individus avec différentes variantes génétiques *GBA1* (variantes *GBA1* liés à la maladie de Gaucher ou à risque de la maladie de Parkinson) et des individus non-porteurs. Bien que les variantes *GBA1* n'aient pas été associés à une diminution plus lente de la mobilité fonctionnelle, si ces résultats sont confirmés dans une étude de cohorte indépendante, une réévaluation de leur pertinence pathologique serait justifiée en raison de la modification des effets des symptômes non moteurs. Pour mieux comprendre

le phénomène des « trajectoires étonnamment stable » de la mobilité fonctionnelle ainsi que les facteurs protecteurs impliqués, le CHAPITRE SEPT rapporte une étude mixte séquentielle explicative. Les modèles à effets mixtes ont d'abord étudié la modification des effets des réserves relationnelles (partenaire, enfants), cognitives (éducation) et socio-économiques (lieu de résidence) sur la trajectoire de la mobilité fonctionnelle vécue par les patients. Ensuite, des entretiens qualitatifs semi-structurés avec des participants présentant une « trajectoire étonnamment stable » de la mobilité fonctionnelle ont exploré leurs perceptions des obstacles et des facilitateurs liés à ces réserves. L'analyse inductive a montré que les personnes avec des « trajectoires étonnamment stables » de la mobilité fonctionnelle avaient les caractéristiques suivantes : des facteurs psychosociaux similaires à l'auto-efficacité, des activités d'auto-soins favorisant un mode de vie physiquement actif ainsi que des maladies inflammatoires chroniques. Enfin, le CHAPITRE HUIT de cette thèse synthétise et discute les résultats de tous les chapitres, les considérations méthodologiques, et présente les orientations futures ainsi que les conclusions générales de cette thèse.

IMPACT PARAGRAPH

The research described in this dissertation had the general aim to enhance our understanding of trajectories of functional mobility in people with Parkinson's disease (PD). The relevance of this dissertation will be outlined below in the context of its impact on science, society, the economy and groups outside the scientific community.

Scientific impact

One important component of this dissertation is the insight that psychosocial factors, particularly self-efficacy, enabled individuals to remain functionally mobile, even in challenging environments, such as living in rural areas without the support of a partner or children. This better understanding of unexpectedly stable trajectories in patient-reported functional mobility can guide researchers and health professionals to focus on promoting self-efficacy and thus lead to the development and implementation of effective interventions. Secondly, this dissertation helps to advance the patient-centred measurement of functional mobility by validating an openly available algorithm to calculate the PDQ-39-based patient-reported functional mobility composite score (FMCS) from an existing questionnaire used by health professionals and researchers to assess health-related quality of life (PDQ-39) in individuals with PD (Peto et al., 1998). Also, this dissertation serves as an example for researchers interested in learning from individuals with unexpectedly stable symptom trajectories. Specifically, this dissertation demonstrates the selection of individuals for qualitative interviews based on their stable trajectories with an advanced statistical method (random effects that capture differences that are not directly visible through basic descriptive statistics) allowing the combination of quantitative (numbers) and qualitative (experiences) data.

Thirdly, the methodological article and the public sharing of the statistical code for the open-source tool R used in this thesis contribute to an improved understanding and application of statistical methods for longitudinal data analysis by clinical researchers and students. Reproducible, responsible research was promoted by providing information required for reproduction according to the reporting guidelines and through the publication of among others the preprints and the statistical code on the project page from the open science framework (DOI: https://www.doi.org/10.17605/OSF.IO/4VKNP). The resulting publications are freely accessible (open-access), providing researchers with unrestricted access to the findings. Moreover, the comprehensive empirical description and illustration of the progression of motor- and non-motor symptoms in men and women with different genetic variants can be integrated in the education of health professionals and serve as a starting point for further research projects.

Finally, some parts of this dissertation already had a scientific impact. The BMJ Open Editor's picks blog 2022 featured an international study (CENTRE-PD Top 10), the preparatory work of this dissertation, updating the research priorities for the management of Parkinson's disease (Bowring et al., 2022). Moreover, the dissertation contributes to discussions within the field of Parkinson's disease. Specifically, in 2022, the faculty of the Movement Disorders Society selected the poster contribution on unexpectedly high functional mobility as a high-scoring abstract for the guided poster tour (Hanff et al., 2022a). Recently, the systematic review of determinants of patient-reported functional mobility was discussed in an editorial of the Journal of Parkinson's disease on non-pharmacological interventions for people with PD (Kalbe et al., 2024), indicating that it is gaining attention and being integrated into ongoing discussions in the field.

Societal and Economic Relevance

As a result of demographic change, the proportion of the working population paying into health insurance is decreasing, while the proportion of older people in need of care is increasing. At the same time, the world is facing a nursing shortage and family members are increasingly struggling to ensure the care of their relatives. In addition, PD is the fastest-growing neurodegenerative condition (prevalence is expected to double from 6.9 million in 2015 to 14.2 million in 2040 worldwide (Dorsey and Bloem, 2018)). The average annual cost per individual with Parkinson's disease in Luxembourg in 2016 was €22,673 with the highest costs (69%) being associated with long-term care (Schmitz et al., 2022). This dissertation helps to address those societal and economic challenges through health promotion and thus contributes to the ongoing cultural change of research and health care towards health promotion. Specifically, the promotion of self-efficacy in people with PD could enable them to maintain stable trajectories of functional mobility and thus decrease the need of professional care, delay institutionalisations, reduce nursing home costs and respect the desire of people with PD to remain in their homes.

This dissertation also highlights the importance of an age-friendly ecosystem avoiding car dependency for grocery shopping as requested almost twenty years ago by the World Health Organisation so that individuals with PD, can independently meet vital needs, e.g., nutrition, health care or social relationships. Importantly, individuals with PD experienced the ability to autonomously decide when to go where playing a central role in preserving self-confidence and dignity. Moreover, this dissertation showes that although living in a central area, individuals with PD without a driving license or someone living in the same household can not autonomously decide when to go where. By adding context (personal experiences of individuals with PD) to statistical results, this dissertation can support an emotional engagement of politicians and encourage them to invest in health-promoting interventions and an age- and Parkinson's friendly ecosystem. This brings us to the relevance of our results for individuals with PD and health professionals.

Relevance to Groups other than the Scientific Community

This dissertation addresses one of the highest ranked priorities by individuals with PD, their family and friends and was carried out in continuous collaboration with the members of the Luxembourg Parkinson's Association. In addition, among others, the "Women's Parkinson's Project" (an initiative led by women with PD advocating for improved treatment and research) and its members reshared our preprint on social media (Chapter 5) expressing their gratitude. Moreover, this dissertation demonstrates the potential of mixing perspectives by mixing methods and adopting the perspective of health promotion. Specifically, this dissertation discusses how minimising the gap between the expectations and actual experiences of individuals with PD is crucial for maintaining a good quality of life. Since experiences and expectations are challenging to capture through objective measurements, the dissertation advocates for a healthcare system that places greater emphasis on the experiences of individuals with PD rather than relying solely on biomarkers or physician-assessed measures.

This dissertation also acknowledges the potential of nurses in the empowerment of stable trajectories of functional mobility despite increasing disability and unfavourable environments. Among others, the demonstration of the process of using trajectories to illustrate the change of symptoms over time and the joint discussion with men and women with PD can enhance implementation in health care. As a nurse, I was familiar with the small amount of published research that was useful for daily practice, i.e., "lead to a favourable change in decision-making" (Ioannidis, 2016). Consequently, in this dissertation, I adhered to the recommendations of the Lancet Series on increasing the value of research (Macleod, 2014). Specifically, the previously mentioned preparatory priority setting (Bowring et al., 2022) as a starting point for this dissertation and the involvement of individuals with PD helped to set the right priorities and to ensure the investigations were relevant and meaningful to individuals living with PD. Furthermore, the systematic review of studies reporting previous investigations about determinants of patient-reported functional mobility prior to the start of our data analysis ensured this dissertation adds relevant information to what is already known.

Publications in national journals and public appearances helped to communicate the results in lay language to the public. Since 2018, I have been sharing recent nursing research with the broad public as an independent writer of the "Carte Blanche" at the RTL radio. Moreover, as president of the Luxembourg Nurses Association (ANIL) I promoted a nurse training on the University level and evidence-based policy making based on facts instead of emotions. Consequently, I was selected in 2024 by the National Research Fund (FNR) as participant for the FNR Pairing Scheme "Politics meets research". Recently, I shared my experiences in science communication to researchers and the general public as a panellist in a roundtable organised by the National Research Fund (FNR). In 2023, my contributions

and experiences were featured in the video series of the “Be Brave – Women & Girls in Science” campaign, organised by Research Luxembourg and the Ministry for Equality in Luxembourg. This campaign aimed to tackle gender disparities and promote inclusivity within scientific fields. Finally, this dissertation serves as a positive example paving the way for other nurse researchers interested in doing a PhD in Luxembourg.

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APPENDICES

Similar as investigated in my dissertation, my PhD journey was also a trajectory starting during the COVID-lockdown, navigating through achievments and the loss of family members, and culminating in this final document. Looking back on my journey to this point, it is evident that I could not have reached here without the guidance, support, friendship and care of many.

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HANFF, A.-M., RAUSCHENBERGER, A., AGUAYO, G., LEIST, A., MCCRUM, C., KRÜGER, R., ZEEGERS, M. 2024. Understanding unexpectedly stable trajectories of functional mobility in people with Parkinson's disease: A mixed methods study. *OSF Preprints*. https://doi.org/10.31219/osf.io/a798g_

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National Journals (Selection)

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Public appearances (Selection)

05.2024 National Research Fund (FNR). Panelist in the event "Trends under review – Science Communication in a Changing World." URL: https://www.fnr.lu/trends-under-review-a-forum-for-the-luxembourg-research-community/ (accessed on 30.07.2024)

03.2024 National Research Fund (FNR). Selected participant for the FNR Pairing Scheme "Politics meets research". URL: https://www.fnr.lu/pairing-scheme-politics-meets-research/ (accessed on 30.07.2024)

02.2023 Research Luxembourg & Ministry for Equality in Luxembourg. Selected participant for the video series of the campaign "Be brave – women & girls in science". URL: https://www.researchluxembourg.org/en/women-and-girls-in-science-2023-anne-marie-hanff-phd-candidate-in-transversal-translational-medicine/ (accessed on 30.07.2024)

02.2023 RTL Radio Luxembourg. Interview participant in the Lisa Burke show for the "International Women and Girls in Science Day". URL: https://play.rtl.lu/shows/en/in-conversation-with-lisa-burke/episodes/n/2029129?mediatype=audio (accessed on

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05.2021 RTL Radio Luxembourg. Live interview (Invité vun der Redactioun) discussing how the academisation of nurses can provide perspectives to young people. https://www.rtl.lu/radio/invite-vun-der-redaktioun/a/1728735.html (accessed on 20.08.2024)

11.2020 RTL Radio Luxembourg. Live interview (Invité vun der Redactioun) discussing the training of nurses in Luxembourg. https://www.rtl.lu/radio/invite-vun-der-redaktioun/a/1728735.html (accessed on 20.08.2024)

03.2019 RTL Radio Luxembourg. Live interview (Journal) discussing the training of nurses in Luxembourg. https://www.rtl.lu/radio/invite-vun-der-redaktioun/a/1728735.html (accessed on 20.08.2024)

Since 2018 RTL Radio Luxembourg. Independent writer for the "Carte Blanche" discussing the importance of the academisation for the professionalization of nursing and the society. URL: https://www.rtl.lu/news/carte-blanche/a/1903208.html

Conference Proceedings

HANFF, A.-M., RAUSCHENBERGER, A., AGUAYO, G., LEIST, A., MCCRUM, C., KRÜGER, R. & ZEEGERS, M. 2024. Understand unexpectedly stable trajectories of functional mobility: A mixed-methods study. (Poster presentation at the European Academy of Nursing Sciences summer conference, Turin, Italy, July 2024).

HANFF, A.-M., MCCRUM, C., RAUSCHENBERGER, A., AGUAYO, G., LEIST, A., KRÜGER, R. & ZEEGERS, M. 2023. Factors associated with a slower progression of functional mobility. A longitudinal mixed-models analysis. (Poster presentation at the University of Maastrichts' NUTRIM Symposium Closing the Gap, Maastricht, The Netherlands, November 2023).

HANFF, A.-M. 2023. Progression of Parkinson's in men and women. A longitudinal mixed-methods analysis of the Luxembourg Parkinson's study. (Oral presentation at the University of Luxembourg Life sciences PhD Days, Esch-sur-Alzette, Luxembourg, October 2023).

HANFF, A.-M., MCCRUM, C., RAUSCHENBERGER, A., AGUAYO, G., ZEEGERS, M., LEIST, A. & KRÜGER, R. & MAY, P. 2024. Unexpectedly high functional mobility despite the presence of postural instability and gait disturbances. A longitudinal mixed-models analysis. (Poster presentation at the World Parkinson's conference, Barcelona, Spain, July 2023).

HANFF, A.-M., KIEFFER, A., LECOQ, D. & LEY, C. 2023. *Comment faire bénéficier les soins de santé de la culture des données ? Un héritage de Florence Nightingale, infirmière pionnière.* (**Conference co-organisation** at the University of Luxembourg, Esch-sur-Alzette, Luxembourg, June 2023).

HANFF, A.-M., RAUSCHENBERGER, A., MCCRUM, C., PACHCHEK, S., SAPIENZA, S., AGUAYO, G., ZEEGERS, M., LEIST, A. & KRÜGER, R. 2023. Are pathogenic GBA mutations associated with a decline in patient-reported functional mobility? (Poster presentation at the University of Luxembourg Precision medicine conference, Esch-sur-Alzette, Luxembourg, January 2023).

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HANFF, A.-M., MCCRUM, C., AGUAYO, G., RAUSCHENBERGER, A., LEIST, A., KRÜGER, R. & ZEEGERS, M. 2022. The phenomenon of unexpectedly high functional mobility in people with typical Parkinson's disease. A cross-sectional data analysis. (Poster presentation at the MDS congress, Madrid, Spain, September 2022). **Selected for guided poster tour**

HANFF, A.-M., RAUSCHENBERGER, A., MCCRUM, C., AGUAYO, G., ZEEGERS, M., LEIST, A. & KRÜGER, R. 2022. Validation of a patient-reported Functional Mobility Composite Score (FMCS) in people with Parkinson's disease. (Poster presentation at the MDS congress, Madrid, Spain, September 2022).

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HANFF, A.-M. 2022. Protective factors of patient-reported functional mobility in people with PD. An observational longitudinal mixed-methods study design. (Oral presentation at the CaRe Days, Eindhoven, The Netherlands, May 2022).

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HANFF, A.-M. 2021. Falls in people with Parkinson's disease and the secret of functional mobility. A mixed-method study design. (Oral presentation at the CaRe Days, virtual, May 2021).

HANFF, A.-M., MCCRUM, C., LEIST, A., ZEEGERS, M. & KRÜGER, R. 2021. Falls in people with Parkinson's disease and the secret of functional mobility. A mixed-method study design. (Poster presentation at the MDS congress, virtual, March 2021).

HANFF, A.-M., PAULY, C., PAULY, L., SCHROEDER, V., HANSEN, M., RAMOS MEYERS, G., KAYSEN, A., Hansen, L., Wauters, F. & KRÜGER, R. 2020. Unmet needs of people with Parkinson's disease and their caregivers during COVID-19 related confinement. (Poster presentation at the German Neurology Association (DGN) congress, virtual, November 2020).

HANFF, A.-M., MCCRUM, C., ZEEGERS, KRÜGER, R. & LEIST, A. 2020. Development of a new functional mobility measure in Parkinson's disease. Sample characteristics of the NCER-cohort and exploratory analysis on internal consistency and stability. (Poster presentation at the University of Luxembourg Life sciences PhD Days, virtual, October 2020).

ABOUT THE AUTHOR

Anne-Marie for the Parkinson's Fighters campaign by LCSB Communication Team (2024)

Anne-Marie Hanff was born on the 9th of November 1986 in Luxembourg. Nurse by training in Luxembourg, the only EU country offering no nurse education at the Bachelor level in 2009, she became aware of the importance of evidence-based nursing practice during her professional activity in Switzerland (2009-2011). Consequently, she studied for a Bachelor's and Master's in nursing sciences (2011-2015) in Germany to promote evidence-based nursing practice in Luxembourg. Anne-Marie aimed to create a sustainable pathway for future doctoral students in nursing sciences in Luxembourg. Therefore, Anne-Marie chose to pursue her PhD at the University of Luxembourg with the support of Maastricht University and thus be the first nurse employed as a PhD student at a Luxembourg research institution (Luxembourg Institute of Health). Anne-Marie is eager to further support the setup of academic degrees for nurses at the University of Luxembourg and promote evidence-based nursing practice in an academic position in the care of people with chronic diseases.

Contribution to the wider research community

Anne-Marie recognised the creation of the National Centre for Excellence in Research Parkinson's disease (NCER-PD) in Luxembourg in 2015 as an opportunity to advance nursing research in Luxembourg. Thus, she joined the Parkinson's Research Clinic of Prof Dr Rejko Krüger as a research nurse. Also, her interest in research integrity, sparked by the Lancet Series on "Increasing Value, Reducing Waste," led the young nurse to participate in the World Conference on Research Integrity in 2017. Since then, her guiding principles have become well-founded research designs, conduct and analyses; fully accessible research information and reports; and prioritising research topics that matter to the end-users of the research results. In 2019, Anne-Marie led the Luxembourgish team in the international CENTRE-PD Top 10 project, a collaboration with the Universities of Tübingen and Oxford, aimed at updating research priorities in Parkinson's disease—a project later highlighted in the BMJ Open Editor's Picks blog in 2022. Building on this work, her PhD research focused on patient-reported functional mobility in individuals with Parkinson's disease. Her research topic received attention from the scientific community when, in 2022, the faculty of the Movement Disorders Society selected her poster contribution on unexpectedly high functional mobility as a high-scoring abstract for the guided poster tour (Hanff et al., 2022a). Recently, the systematic review of determinants of patient-reported functional mobility was discussed in an editorial of the Journal of Parkinson's disease on non-pharmacological interventions for people with PD (Kalbe et al., 2024), indicating that it is gaining attention and being integrated into ongoing discussions in the field. When Anne-Marie started her

PhD in 2020 during the COVID-pandemic she adapted by developing an interdisciplinary project analysing semi-structured telephone interviews with people with PD disease during the lockdown to identify the unmet needs of people with PD during confinement. In the same year, she was admitted to the highly competitive 3-year summer school program at the European Academy of Nursing Sciences (EANS), which she completed in 2024.

Contribution to the translation of research into practice

Throughout her studies, Anne-Marie continued to work as a nurse in clinical and research settings, realising how much knowledge (e.g. scientific articles) nurses in Luxembourg can't access due to difficulties in locating, accessing and evaluating scientific literature of central importance in nursing sciences and practice. Given that research is publicly funded and research in a small country such as Luxembourg depends on the population's participation, she's been dedicated to enhancing science communication and patient involvement. Anne-Marie's experience in Germany taught her the central role of translating science into practice, leading her to actively support this translation throughout her career. Anne-Marie has appraised the risk of bias, written lay summaries for health professionals for the Cochrane Nursing Care Field and the Fit-Nursing Care (platform designed to integrate evidence-based practices into nursing care) and serves as editor of the ANIL News (triannual journal published by the Luxembourg Nurses Association (ANIL)). Since 2018, she has been sharing recent nursing research with the broad public as an independent writer of the "Carte Blanche" at RTL radio. In 2021, Anne-Marie founded the Network Clinical Nursing Sciences Luxembourg (NCNSL) to connect health professionals interested in nursing sciences and bridge the research-practice gap. Moreover, in 2023 she organised a conference on statistical literacy for nurses in collaboration with statisticians, mathematicians and nurse scientists at the University of Luxembourg and promoted nursing sciences to the broader public by joining the women in sciences series organized by the national research fund (FNR). Also, she created a hashtag #NursesCanSciences to update the public on nurses' contributions to science in Luxembourg.

Contribution to broader society

Finally, in her additional role as president of the Luxembourg Nurses Association (ANIL) and as a participant in the "Politics meets Research" pairing scheme organised by the National Research Fund (FNR), Anne-Marie advocated for evidence-based policymaking. During meetings with various politicians, including the Prime Minister, Minister of Health, and Minister of Higher Education and Research, the young nurse raised awareness about the importance of university-level nursing education. Consequently, the advocacy of the ANIL contributed to the Luxembourgish government's decision in 2023 to introduce a Bachelor of Nursing degree at the University of Luxembourg.

"Sapere aude" - Immanuel Kant