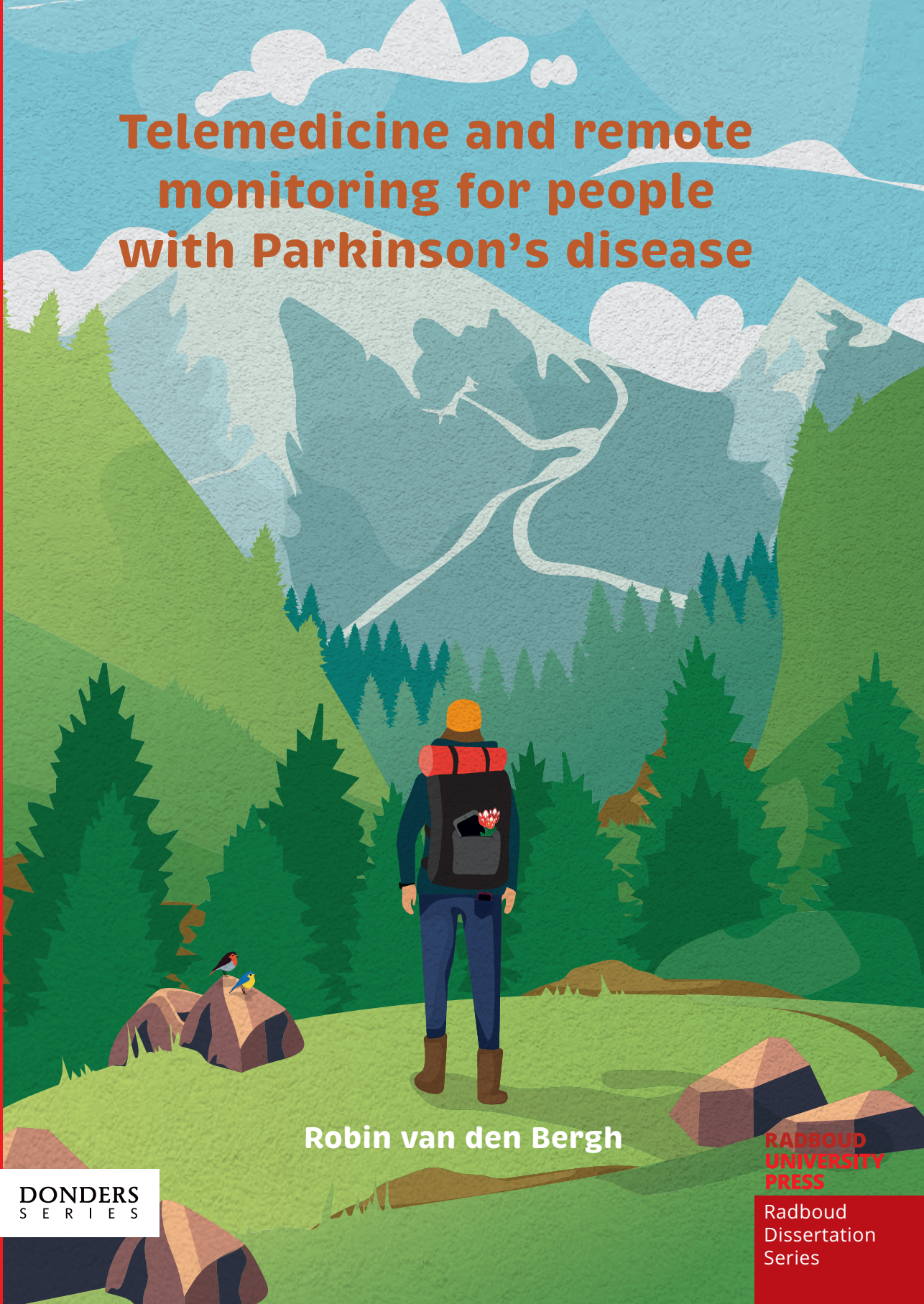
Telemedicine and remote monitoring for people with Parkinson's disease



Robin van den Bergh

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Telemedicine and remote monitoring for people with Parkinson's disease

Robin van den Bergh

The research presented in this thesis was conducted at the Center of Expertise for Parkinson and Movement Disorders, Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, the Netherlands.

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Telemedicine and remote monitoring for people with Parkinson's disease

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geboren op 30 oktober 1996
te Roosendaal en Nispen

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Dissertation

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Het monitoren van je Parkinson kan je helpen te blijven doen wat je belangrijk vindt. Voor mij is dat wandelen in de bergen.

Inge van den Broek

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1

General introduction

Why we should study telemedicine and remote monitoring for persons with Parkinson's disease

Globally, Parkinson's disease (PD) affects over 7 million people, and these numbers are projected to increase to 12 million before 2040.[1] PD has become the world's fastest growing neurological disease due to ageing of our population and environmental exposures.[1,2] In the Netherlands, the neurological hospital care for the approximately 63.500 persons with Parkinson's disease or atypical parkinsonism (**box 1**) is typically organized as follows. Every 3 to 12 months (depending on disease severity and for example anxiety levels), a person with PD and their care partner travel, sometimes quite far, to the outpatient clinic of a hospital. They take place in the waiting room and wait for their appointment with the movement disorder specialist, a specialized PD nurse, or both. Their appointment typically lasts about 15 minutes, although some experts insist on seeing patients for longer. The healthcare professional, the person with PD and often their care partner discuss how the past period has been. In addition to this conversation, the movement disorder specialist or PD nurse may conduct various tests to assess current motor or non-motor (mainly cognitive) functions. This appointment and such a conversation can be quite nerve-wrecking: in an unfamiliar environment, and under certain time constraints, you are asked to talk about a deeply personal and private matter, namely your own health. If necessary, the medication prescription is changed and referrals can be made to other healthcare professionals for additional non-pharmacological interventions. Then, the person with PD returns home where they will resort to self-care for the upcoming months (**figure 1**).

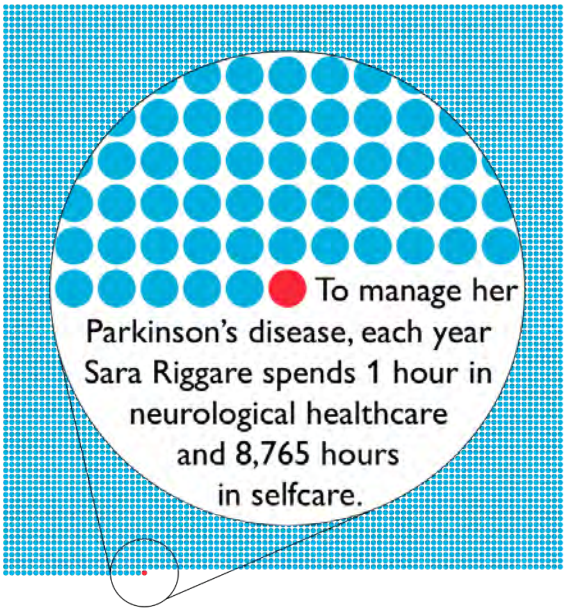

Figure 1. Sara Riggare, a researcher with Parkinson's disease, illustrates how much time she spends each year in self-care at home.

Box 1. Parkinson's disease and atypical parkinsonism

Parkinson's disease is a progressive neurological disorder.[3] The clinical diagnosis can be made if a person presents with the typical motor features including bradykinesia (this is required) plus either a resting tremor, rigidity or both, and, in case pharmacological treatment is initiated, if the symptoms respond well to dopaminergic medication.[3] The manifestation of PD is highly heterogeneous between people, with a broad range of possible motor and non-motor features.[4] Besides those necessary for diagnosis, prominent motor features include postural instability, gait disturbances, dysphagia and dysarthria. Examples of non-motor features include cognitive impairments, autonomic dysfunction, sleep disorders and neuropsychiatric changes such as depression, anxiety and hallucinations. Most people are diagnosed when they are in their early- to mid-sixties, although some persons with PD develop the disease before the age of 40.[5] Disease progression varies considerably between persons, but most affected individuals ultimately face considerable disability in the later disease stages. Survival is somewhat diminished, and more so for people with a younger age at onset, but most people generally live with the disease for over a decade.[4,6]

The term atypical parkinsonism collectively refers to a group of neurodegenerative diseases that all share some clinical features with PD, but that are characterised by a different pathophysiology, a much more aggressive disease course and a generally poor to absent response to oral pharmacotherapy. The clinical phenotype is also more complex, involving manifestations beyond the hypokinetic rigid syndrome that is characteristic of PD. Survival is also typically considerably reduced, unlike the situation in PD. Examples of atypical parkinsonism include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies (DLB) and vascular parkinsonism. In this thesis, I will consistently refer to and focus on individuals living with PD, but all the considerations and recommendations offered throughout this dissertation equally apply to individuals living with atypical parkinsonism. In fact, due to their generally greater disability and faster disease progression, telemedicine approaches are arguably even more important for this specific population.

For many persons with PD, the first-line management of the disease consists of dopaminergic medication, levodopa being the first choice in most individuals. Levodopa is used to restore the dopamine levels in the brain, but maintaining the right dose of dopamine in the body throughout the day becomes increasingly difficult as the disease progresses. Without sufficient central dopaminergic stimulation, someone's symptoms will worsen, for example, movements will slow down and decrease in amplitude (greater bradykinesia). When the central dopaminergic stimulation exceeds its therapeutic goals, many of the symptoms will

be suppressed, but someone will concurrently develop involuntary and excessive movements (these are generally referred to as dyskinesias). Besides a shortage of dopamine, other neurotransmitter deficits also occur in PD including a lack of norepinephrine, acetylcholine and serotonin.

Due to the heterogenous and multifaceted manifestation of PD, optimal disease management requires strong collaboration between and integration of services from various specialized healthcare professionals.[7,8] The movement disorder specialist and PD specialized nurse can accurately diagnose, prescribe and adjust medication, inform people about the disease and its treatment options and can facilitate connections with other healthcare professionals. Other important healthcare disciplines include the physiotherapist for training strength, balance, and overall physical functioning, the speech therapist to maintain speech and intelligibility and train safe swallowing, and the occupational therapist to overcome issues in daily life. Also, the general practitioner can coordinate care services, the dietician can advise about food intake, the psychologist can help to deal with the mental aspects of PD and the social worker can help to sustain social connections. Overall, no less than 30 different professional disciplines can theoretically offer support to people living with PD (**figure 2**). These healthcare professionals can all contribute to improving the person with PD's functioning in daily life and reduce the risk of medical complications such as falls and pneumonias.[9]

Challenges in healthcare for persons with PD

The care for persons with PD has advanced considerably since the first documentation of the disease by James Parkinson in 1817.[10] Despite these tremendous improvements, the current PD healthcare system is challenged in various ways. I will highlight three challenges in particular.

Challenge I. Maintaining access to care

For effective disease management, people should be monitored regularly to know if any new issues have arisen that may require treatment. However, gaining and maintaining access to medical specialists remains challenging for many persons with PD for various reasons.[11,12] First, the motor features of the disease decrease their mobility. For example, bradykinesia, balance impairments and freezing of gait can hamper traveling to the outpatient clinic as walking, biking and driving a car become increasingly difficult. Furthermore, these features can make people afraid to leave their house, making the visit to the hospital energy-draining at the least and, even worse, force people to cancel appointments altogether. Second, persons with PD become more reliant on other people to bring them to the clinic

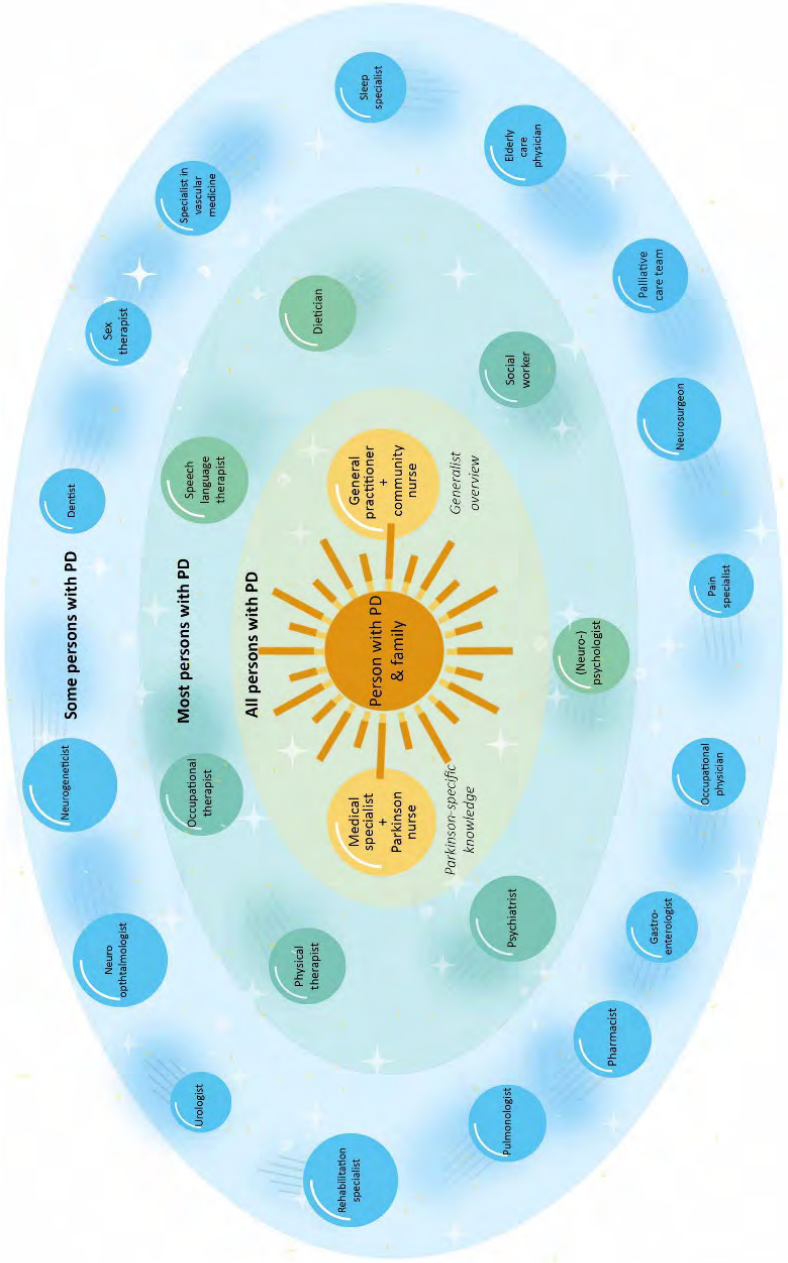

Figure 2. Professional disciplines involved in the multidisciplinary care for people with Parkinson's disease. As published in.[3]

as their disease progresses, for example because driving is no longer safe.[13] Even when support is present, this puts additional strain on already overburdened caregivers.[14] Third, healthcare professionals are not always available close by.[15,16] In many countries in the world, the coverage of specialized healthcare professionals is limited and persons with PD must travel far (100+ kilometre) or through rough landscapes such as mountains to get from their home to the hospital. Taken together, this difficulty in maintaining access to care negatively affects the quality and continuity of care.

Challenge II. Capturing objective data at home

This issue is compounded by the fact that when people do make it to the hospital, then their clinical presentation is often not at all representative of their actual performance at home. Indeed, the tests conducted by the movement disorder specialist or PD nurse in the hospital provide them with at best a snapshot of someone's functioning. For example, freezing of gait can be severely debilitating at home, but it is notoriously difficult to elicit this phenomenon during visits to the clinic, much to everyone's frustration. Conversely, tremor is typically worse during hospital visits. The response fluctuations to oral pharmacotherapy are complex and take hours to evolve, so it will be very difficult to capture the full spectrum of response fluctuations during brief hospital visits. Classic motor performance tests conducted in the hospital include assessments of bradykinesia such as finger tapping, assessment of rigidity and a retropulsion test (e.g.[17]). Although they assess a relevant aspect of the disease, these in-clinic assessments fail to capture day-to-day and even hour-to-hour changes.[18,19] Certainly for individuals with more advanced disease, PD features fluctuate considerably throughout the day in response to timing of intake of the medication. Someone could have severe problems getting out of bed, only to walk fluently 30 minutes later when the medication starts working. Finally, many important elements of PD are difficult to assess during in-clinic visits simply because these by definition take place in the person's own home. Examples include the night-time issues (the many reasons for a disturbed sleep) and falling incidents.[20] This lack of insight in accurate, every day, at home functioning makes the healthcare professional's job difficult, as they need to rely on a proxy of someone's real functioning to provide the best possible treatment. It has been said that the hospital is the perfect place to get the wrong impression about a person living with PD.

Challenge III. Providing proactive care

Current care for persons with PD is mainly reactive, i.e., problems are solved when they arise.[7,21] In the relatively long timeframe in between visits, new problems may

arise that would ideally require proactive medical attention. Examples include near-fall incidents which may precede an actual fall, possibly accompanied by fall-related injuries, or progressing swallowing impairments which can accommodate into an aspiration pneumonia. Currently, persons with PD must rely on their own proactive attitude to bring the appointment with their healthcare professional forward.[22] Such a reactive healthcare system might detect issues too late, causing avoidable disease burden and preventable hospital admissions.[23,24] Preferably, the PD healthcare system detects and manages upcoming issues earlier and more proactively to prevent disability and costs, without creating additional work for the healthcare professionals or persons with PD.[21,25]

Telemedicine and remote monitoring for Parkinson's disease

Rapid technological advancements allow for the extension and remote delivery of healthcare, also referred to as telemedicine (from Greek *tele-* meaning "far off, afar, at or to a distance"; **figure 3**).[26,27] In all forms of telemedicine, there is no physical contact between a healthcare professional and person with PD, but their interaction and communication are mediated through technology. Telemedicine is an important pillar of the overarching concept *eHealth*, which, besides telemedicine, also encompasses the use of technology for supporting care management (e.g. electronic patient records) and supporting public health (e.g., monitoring the population health through healthcare claims data).[28] Telemedicine is a broad container term, making it difficult to discuss if and how it should be useful for healthcare. To further our discussion, I divide telemedicine in three categories. First, remote consultations in which the regular consultation takes place through, e.g., a video conferencing software.[29] Second, remote monitoring, which is the repeated measurement of a symptom or variable through time to track changes in its severity, e.g., wearing a smartwatch to track fluctuations in tremor and bradykinesia.[30] Third, remote treatments, which are regular treatments provided remotely through technology such as telephone based psychotherapy[31], video based speech therapy[32], website based care partner support[33] or a multitude of apps to track exercise plans.[34]

In my thesis, I study telemedicine in general, but I also zoom in on remote monitoring in particular. Remote monitoring, or tracking, can take many forms and shapes. Broadly speaking, monitoring tools can be divided into active and passive systems. Active monitoring requires input from the user such as a self-report questionnaire or e-diary. For example, women with PD could manually track the impact of their hormonal cycle on their PD symptoms in a smartphone app.[35] Passive tracking requires no input from the user and relies on sensors to continuously collect data

in the background. For PD, most passive monitoring systems use wearable sensors such as a smartwatch or mobile phone with embedded accelerometers and gyroscopes to detect movements.[36,37]

Already, remote monitoring is finding its way to research settings and to daily clinical practice. In research, remote monitoring data plays an important role in detecting fine-grained symptom changes over time to track disease progression and to capture even small improvements in response to symptomatic or putative disease modifying interventions. Detailed disease progression measures are necessary for PD prevention trials and disease modification efforts, as they are able to detect small differences across time unobservable by a human assessor.[38–40] In clinical practice, remote monitoring is most commonly used to supplement clinical judgment by tracking the effect of medication on motor symptoms by using commercially available wearable sensor systems[41] such as the Personal KinetiGraph[42,43] or PD_Monitor.[44] Some persons with PD also self-track, i.e., they use various tools to track their own symptoms or signs.[45,46] In all instances, the monitoring system is a tool, a means to ultimately enhance the understanding and management of a person's PD.

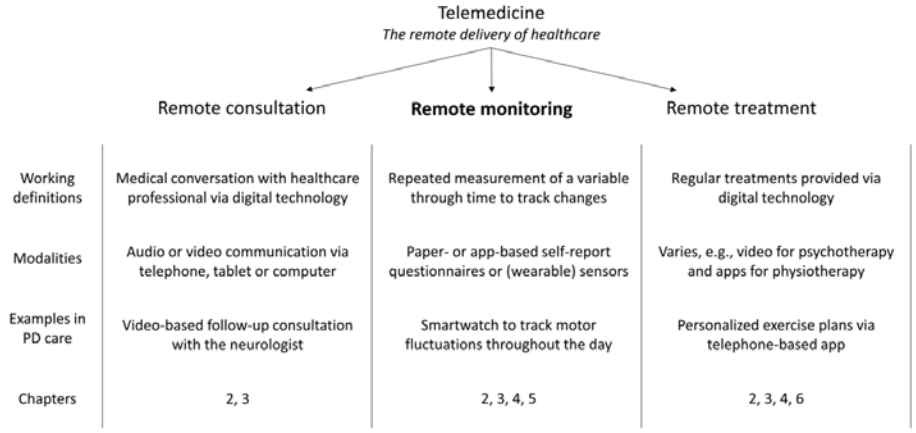

Figure 3. Schematic overview of telemedicine and its components.

Using telemedicine and remote monitoring to overcome PD healthcare challenges

The COVID-19 pandemic, including the national lock-downs, has served as a powerful catalyst that stimulated the development and implementation of telemedicine and remote monitoring in PD healthcare.[47,48] We have seen an

incredible surge in the uptake of telemedicine during the pandemic, because telemedicine was the only option to safely stay in contact with others.[49,50] Quickly, physical rating scales were translated into digital versions[51] and video-consultation software was implemented in many hospitals.[52] At first, videoconferencing was new and uncomfortable for many, but people quickly adjusted and experienced both the benefits and the burdens of telemedicine.[53–55] Using the lessons learned during the COVID-19 pandemic, I state that telemedicine can contribute significantly to the challenges of the PD healthcare system outlined above.

Contribution I. Telemedicine to maintain access to care

Remote video consultations could help to stay in contact with healthcare professionals from within the comfort of your own home, despite increasing (motor) symptoms.[53] Already, 'virtual clinics' exist in which physical follow-up appointments are replaced by a combination of wearable symptom trackers and telephone consultations to discuss necessary changes.[56] Another example is the proactive reaching out to persons with PD during COVID. Persons with PD who were most at risk of being alone, without medication or required medical attention were proactively called by a team of healthcare professionals to identify and address any needs.[57] However, despite promising examples, many communication and monitoring tools have been developed for and tested with persons with early and mid-stage PD. People in a more advanced disease stage are often overlooked in research and development studies[58] and are at risk of losing access to care when technology is too rapidly implemented.[59,60] Yet, especially the persons with more advanced PD have a high disease burden[61] and a large need for access to specialized healthcare professionals.[62] Therefore, in **chapter 2 and 3**, I describe for *whom* telemedicine is applicable. In **chapter 2,** I review the current state of telemedicine for persons with PD and highlight promising developments and continuous challenges. In **chapter 3**, I present interviews with persons with PD and healthcare professionals to evaluate whether telemedicine can be of use in the delivery of palliative care for persons with PD and under what conditions.

Contribution II. Telemedicine to capture objective data at home

Remote monitoring can objectively capture data from everyday life about topics relevant for the person with PD. The data provide better insight in real-life motor and non-motor symptoms, including sporadic and fluctuating events, all in the environment of the person. Thereby, remote monitoring enhances the quality of knowledge available for making treatment decisions.[63,64] Despite an ever increasing number of existing monitoring systems, few tools explicitly address *how* we can

design monitoring tools relevant to their users.[65] Therefore, we investigate *how* remote monitoring tools can be developed and designed so that they become more person-centred and usable in everyday practice. In **chapter 4**, I use a mixed methods approach to evaluate the usability and utility of a remote monitoring system for physiotherapy practice and explored user profiles of remote monitoring.

Contribution III. Telemedicine to provide proactive care

Continuous remote monitoring information could fuel online dashboards regarding a person with PD's status and can help to signal early warning signs of worsening. Such information can be combined with built-in videoconferencing software to enable quick communication and treatment updates, making healthcare proactive instead of reactive.[7,21] Already, some studies have shown the cost-effectiveness of questionnaire-based proactive screening[66] and have employed a monitoring tool to detect fall incidents.[67] However, proactive management of issues through continuous symptom monitoring requires a stronger causal framework to understand what should be monitored and where preventive efforts would have an effect. Monitoring preferences vary widely for good reasons[45,46,65], so we need to specify targets for effective prevention to avoid overburdening persons with PD with all sorts of monitoring technology. Therefore, in **chapter 5**, I describe a mixed methods study in which we draft causal pathways for frequently occurring complications and define *what* symptoms should be monitored for proactive care. In **chapter 6**, I present an epidemiological evaluation of the validity of an innovative healthcare infrastructure *where* remote monitoring technology could be implemented in clinical practice to enable proactive healthcare.

References

1. Feigin, V. L. *et al.* Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* **18**, 459–480 (2019).
2. Dorsey, E. R., Sherer, T., Okun, M. S. & Bloem, B. R. The Emerging Evidence of the Parkinson Pandemic. *JPD* **8**, S3–S8 (2018).
3. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* **397**, 2284–2303 (2021).
4. Armstrong, M. J. & Okun, M. S. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA* **323**, 548 (2020).
5. Post, B. *et al.* Young Onset Parkinson's Disease: A Modern and Tailored Approach. *JPD* **10**, S29–S36 (2020).
6. Williams-Gray, C. H. *et al.* The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry* **84**, 1258–1264 (2013).
7. Bloem, B. R. *et al.* Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology* **19**, 623–634 (2020).
8. Goodwin, N. Understanding Integrated Care. *International Journal of Integrated Care* **16**, 6 (2016).
9. Talebi, A. H. *et al.* Specialized Versus Generic Allied Health Therapy and the Risk of Parkinson's Disease Complications. *Movement Disorders* **38**, 223–231 (2023).
10. Parkinson, J. An Essay on the Shaking Palsy. *J Neuropsychiatry Clin Neurosci* (2002).
11. Willis, A. W., Schootman, M. & Evanoff, B. A. Neurologist care in Parkinson disease. (2011).
12. Dorsey, E. R. & Willis, A. W. Caring for the majority. *Mov Disord.* **28**, 261–262 (2013).
13. Crizzle, A. M., Classen, S. & Uc, E. Y. Parkinson disease and driving: An evidence-based review. *Neurology* **79**, 2067–2074 (2012).
14. Geerlings, A. D. *et al.* Caregiver burden in Parkinson's disease: a mixed-methods study. *BMC Med* **21**, 247 (2023).
15. Williams, U., Bandmann, O. & Walker, R. Parkinson's Disease in Sub-Saharan Africa: A Review of Epidemiology, Genetics and Access to Care. *JMD* **11**, 53–64 (2018).
16. Dorsey, E. R. *et al.* Moving Parkinson care to the home. *Mov Disord.* **31**, 1258–1262 (2016).
17. Goetz, C. G. *et al.* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results: MDS-UPDRS: Clinimetric Assessment. *Mov. Disord.* **23**, 2129–2170 (2008).
18. Warmerdam, E. *et al.* Long-term unsupervised mobility assessment in movement disorders. *The Lancet Neurology* **19**, 462–470 (2020).
19. Evers, L. J. W., Krijthe, J. H., Meinders, M. J., Bloem, B. R. & Heskes, T. M. Measuring Parkinson's disease over time: The real-world within-subject reliability of the MDS-UPDRS. *Movement Disorders* **34**, 1480–1487 (2019).
20. Fasano, A., Canning, C. G., Hausdorff, J. M., Lord, S. & Rochester, L. Falls in Parkinson's disease: A complex and evolving picture: Falls and PD. *Mov Disord.* **32**, 1524–1536 (2017).
21. Lithander, F. E. *et al.* Proactive and Integrated Management and Empowerment in Parkinson's Disease protocol for a randomised controlled trial (PRIME-UK) to evaluate a new model of care. *Trials* **24**, 147 (2023).

22. Prins, E. M. *et al.* Determinants of coping styles of people with Parkinson's Disease. *NPJ Parkinsons Dis* **9**, 99 (2023).
23. Low, V. *et al.* Measuring the burden and mortality of hospitalisation in Parkinson's disease: A cross-sectional analysis of the English Hospital Episodes Statistics database 2009–2013. *Parkinsonism & Related Disorders* **21**, 449–454 (2015).
24. Hassan, A. *et al.* High rates and the risk factors for emergency room visits and hospitalization in Parkinson's disease. *Parkinsonism & Related Disorders* **19**, 949–954 (2013).
25. Ypinga, J. H. L. *et al.* Rationale and design to evaluate the PRIME Parkinson care model: a prospective observational evaluation of proactive, integrated and patient-centred Parkinson care in The Netherlands (PRIME-NL). *BMC Neurol* **21**, 286 (2021).
26. World Health Organization. *Classification of Digital Health Interventions*. https://www.who.int/publications/i/item/WHO-RHR-18.06 (2018).
27. Achey, M. *et al.* The past, present, and future of telemedicine for Parkinson's disease. *Movement Disorders* **29**, 871–883 (2014).
28. Raad voor de Volksgezondheid en Zorg. *E-Health in Zicht*. https://www.raadrvs.nl/documenten/publicaties/2002/04/25/e-health-in-zicht (2002).
29. Beck, C. A. *et al.* National randomized controlled trial of virtual house calls for Parkinson disease. *Neurology* **89**, 1152–1161 (2017).
30. Powers, R. *et al.* Smartwatch inertial sensors continuously monitor real-world motor fluctuations in Parkinson's disease. *Sci. Transl. Med.* **13**, eabd7865 (2021).
31. Dobkin, R. D. *et al.* Telephone-based cognitive behavioral therapy for depression in Parkinson disease: A randomized controlled trial. *Neurology* **94**, e1764–e1773 (2020).
32. Maas, J. J. L., De Vries, N. M., Bloem, B. R. & Kalf, J. G. Design of the PERSPECTIVE study: PERsonalized SPEeCh Therapy for actIVE conversation in Parkinson's disease (randomized controlled trial). *Trials* **23**, 274 (2022).
33. Duits, A. A., Boots, L. M. M., Mulders, A. E. P., Moonen, A. J. H. & Vugt, M. E. Covid Proof Self-Management Training for Caregivers of Patients with Parkinson's Disease. *Movement Disorders* **36**, 529–530 (2021).
34. Willemse, I. H. J. *et al.* Smartphone applications for Movement Disorders: Towards collaboration and re-use. *Parkinsonism & Related Disorders* **0**, (2024).
35. Subramanian, I. *et al.* Unmet Needs of Women Living with Parkinson's Disease: Gaps and Controversies. *Movement Disorders* **37**, 444–455 (2022).
36. Del Din, S., Godfrey, A., Mazzà, C., Lord, S. & Rochester, L. Free-living monitoring of Parkinson's disease: Lessons from the field: Wearable Technology for Parkinson'S Disease. *Mov Disord.* **31**, 1293–1313 (2016).
37. Ancona, S. *et al.* Wearables in the home-based assessment of abnormal movements in Parkinson's disease: a systematic review of the literature. *J Neurol* **269**, 100–110 (2022).
38. Schootemeijer, S. *et al.* The STEPWISE study: study protocol for a smartphone-based exercise solution for people with Parkinson's Disease (randomized controlled trial). *BMC Neurol* **23**, 323 (2023).
39. Pagano, G. *et al.* Trial of Prasinezumab in Early-Stage Parkinson's Disease. *N Engl J Med* **387**, 421–432 (2022).
40. Janssen Daalen, J. M., Oosterhof, T. H., Bloem, B. R. & Darweesh, S. K. L. Wearables for Parkinson's: Fast-Paced toward Novel Outcome Measures. *Movement Disorders* mds.29608 (2023).

41. Deb, R., An, S., Bhat, G., Shill, H. & Ogras, U. Y. A Systematic Survey of Research Trends in Technology Usage for Parkinson's Disease. *Sensors* **22**, 5491 (2022).
42. Krause, E., Randhawa, J. & Mehanna, R. Comparing subjective and objective response to medications in Parkinson's disease patients using the Personal KinetiGraph™. *Parkinsonism & Related Disorders* **87**, 105–110 (2021).
43. Woodrow, H. *et al.* A blinded, controlled trial of objective measurement in Parkinson's disease. *npj Parkinsons Dis.* **6**, 35 (2020).
44. Antonini, A. *et al.* Toward objective monitoring of Parkinson's disease motor symptoms using a wearable device: wearability and performance evaluation of PDMonitor®. *Front. Neurol.* **14**, 1080752 (2023).
45. Riggare, S., Scott Duncan, T., Hvitfeldt, H. & Hägglund, M. "You have to know why you're doing this": a mixed methods study of the benefits and burdens of self-tracking in Parkinson's disease. *BMC Med Inform Decis Mak* **19**, 175 (2019).
46. Evers, L. J. W., Peeters, J. M., Bloem, B. R. & Meinders, M. J. Need for personalized monitoring of Parkinson's disease: the perspectives of patients and specialized healthcare providers. *Front Neurol* **14**, 1150634 (2023).
47. Bloem, B. R., Dorsey, E. R. & Okun, M. S. The Coronavirus Disease 2019 Crisis as Catalyst for Telemedicine for Chronic Neurological Disorders. *JAMA Neurol* **77**, 927 (2020).
48. Shalash, A., Spindler, M. & Cubo, E. Global Perspective on Telemedicine for Parkinson's Disease. *JPD* **11**, S11–S18 (2021).
49. Hassan, A. *et al.* Global Survey on Telemedicine Utilization for Movement Disorders During the COVID -19 Pandemic. *Movement Disorders* **35**, 1701–1711 (2020).
50. Fasano, A. *et al.* Management of Advanced Therapies in Parkinson's Disease Patients in Times of Humanitarian Crisis: The COVID -19 Experience. *Movement Disord Clin Pract* **7**, 361–372 (2020).
51. Schneider, R. B. *et al.* Remote Administration of the MDS-UPDRS in the Time of COVID-19 and Beyond. *JPD* **10**, 1379–1382 (2020).
52. Falconer, D., Gow, S., Whitney, D., Walters, H. & Rogers, S. The Power of Access in Parkinson's Disease Care: A Retrospective Review of Telehealth Uptake During the COVID-19 Pandemic. *Front. Neurol.* **13**, 830196 (2022).
53. Dorsey, E. R., Okun, M. S. & Bloem, B. R. Care, Convenience, Comfort, Confidentiality, and Contagion: The 5 C's that Will Shape the Future of Telemedicine. *JPD* **10**, 893–897 (2020).
54. Dorsey, E. R., Bloem, B. R. & Okun, M. S. A New Day: The Role of Telemedicine in Reshaping Care for Persons With Movement Disorders. *Movement Disorders* **35**, 1897–1902 (2020).
55. Mulroy, E. *et al.* Reply to: "A New Day: The Role of Telemedicine in Reshaping Care for Persons With Movement Disorders". *Movement Disorders* **35**, 1903–1904 (2020).
56. Evans, L., Mohamed, B. & Thomas, E. C. Using telemedicine and wearable technology to establish a virtual clinic for people with Parkinson's disease. *BMJ Open Qual* **9**, e001000 (2020).
57. Sennott, B. *et al.* Novel Outreach Program and Practical Strategies for Patients with Parkinsonism in the COVID-19 Pandemic. *JPD* **10**, 1383–1388 (2020).
58. Maas, B. R. *et al.* Time trends in demographic characteristics of participants and outcome measures in Parkinson's disease research: A 19-year single-center experience. *Clinical Parkinsonism & Related Disorders* **8**, 100185 (2023).
59. Nouri, S., Khoong, E. C., Lyles, C. R. & Karliner, L. Addressing Equity in Telemedicine for Chronic Disease Management During the Covid-19 Pandemic. *NEJM Catalyst* **1**, 1–13 (2020).
60. Hughes, H. K., Hasselfeld, B. W. & Greene, J. A. Health Care Access on the Line - Audio-Only Visits and Digitally Inclusive Care. *N Engl J Med* **387**, 1823–1826 (2022).

61. Kluger, B. M. *et al.* Defining Palliative Care Needs in Parkinson's Disease. *Mov Disord Clin Pract* **6**, 125–131 (2019).

62. Katz, M. Telehealth increases access to palliative care for people with Parkinson's disease and related disorders. *Ann Palliat Med* **9**, S75–S79 (2020).

63. Isaacson, S. H. *et al.* Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting transdermal rotigotine patch: A pilot study. *Parkinsonism & Related Disorders* **64**, 132–137 (2019).

64. Omberg, L. *et al.* Remote smartphone monitoring of Parkinson's disease and individual response to therapy. *Nat Biotechnol* **40**, 480–487 (2022).

65. Kenny, L. *et al.* The Views and Needs of People With Parkinson Disease Regarding Wearable Devices for Disease Monitoring: Mixed Methods Exploration. *JMIR Form Res* **6**, e27418 (2022).

66. Wijers, A., Hochstenbach, L. & Tissingh, G. Telemonitoring via Questionnaires Reduces Outpatient Healthcare Consumption in Parkinson's Disease. *Movement Disord Clin Pract* **8**, 1075–1082 (2021).

67. Silva de Lima, A. L. *et al.* Feasibility of large-scale deployment of multiple wearable sensors in Parkinson's disease. *PLoS ONE* **12**, e0189161 (2017).

2

The state of telemedicine for people with Parkinson's disease

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Abstract

Purpose of review

The COVID-pandemic has facilitated the implementation of telemedicine in both clinical practice and research. We highlight recent developments in three promising areas of telemedicine: teleconsultation, telemonitoring, and teletreatment. We illustrate this using Parkinson's disease as a model for other chronic neurological disorders.

Recent findings

Teleconsultations can reliably administer parts of the neurological examination remotely, but are typically not useful for establishing a reliable diagnosis. For follow-ups, teleconsultations can provide enhanced comfort and convenience to patients, and provide opportunities for blended and proactive care models. Barriers include technological challenges, limited clinician confidence, and a suboptimal clinician-patient relationship. *Telemonitoring* using wearable sensors and smartphone-based apps can support clinical decision making, but we lack large-scale RCT's to prove effectiveness on clinical outcomes. Increasingly many trials are now incorporating telemonitoring as an exploratory outcome, but more work remains needed to demonstrate its clinical meaningfulness. Finding a balance between benefits and burden for individual patients remains vital. Recent work emphasised the promise of various *teletreatment* solutions, such as remotely adjustable deep brain stimulation parameters, virtual reality enhanced exercise programs, and telephone-based cognitive behavioural therapy. Personal contact remains essential to ascertain adherence to teletreatment.

Summary

The availability of different telemedicine tools for remote consultation, monitoring and treatment is increasing. Future research should establish whether telemedicine improves outcomes in routine clinical care, and further underpin its merits both as intervention and outcome in research settings.

Introduction

Telemedicine is defined as the delivery of healthcare at a distance.[1] Spurred by the COVID-19 pandemic, telemedicine in its various forms has become a widely debated topic. Arguments in favour include the expanded access to multidisciplinary care, reduced travel burden, and convenience of in-home assessments.[1,2] Telemedicine also holds promise to deliver interventions remotely and to measure outcomes at home in the framework of clinical trials.[3] Counterarguments include concerns that implementation of telemedicine might interfere with the intimacy of the clinician-patient relationship, limit diagnostic accuracy, and enlarge inequalities in access to healthcare.[4,5,6]

As the use of telemedicine increases rapidly worldwide to prevent COVID-19 transmission [7], it is crucial to critically delineate the current state of telemedicine. Here, we discuss recent developments in the various fields of telemedicine, covering a period from approximately January 2019 to February 2021. In doing so, we focus on Parkinson's disease (PD) as a model disease for other chronic neurological disorders. Specifically, we will cover three telemedicine approaches: teleconsultation, telemonitoring, and teletreatment. For each area, recent advances are highlighted and placed within a broader context. Pressing limitations and future research avenues will also be discussed.

Teleconsultation

Teleconsultation means that the consultation between patient and clinician takes place remotely, e.g. through telephone or video conferencing (for a step-by-step guide, see [8]). In this section, we discuss the reliability and feasibility of remote neurological examinations, the experiences of patients and healthcare providers, and the opportunities for novel care models (**figure 1**).

Parts of neurological examinations can be administered during teleconsultations [9], and this provides comparable results to in-person evaluations for upper limb functioning [10] and evaluation of deep brain stimulation candidacy.[11] However, remote consultations remain limited in their scope because specific assessments–such as rigidity and balance–cannot be performed remotely, and because subtle features such as bradykinesia or tremor are prone to be underdetected by video-based ratings compared to in-person ratings.[12] Indeed, a qualitative study showed that neurologists experienced a reduced confidence in their decisions because of these limitations, and additional in-person examinations were often necessary to verify the remote observations.[13] Therefore, teleconsultations seem only suitable

when the medical history or a partial neurological examination is sufficient for the neurologist to adjust the treatment plan. When a diagnosis must be newly established during a very first contact, it remains preferable to see the patient physically to allow for a thorough examination. A caveat here is that in many parts of the world, access to physical care remains restricted, e.g. due to long travel distances and limited provider capacity.[14] Under such circumstances, it is possible to perform at least a part of the neurological examination remotely, which is arguably better than no examination at all.

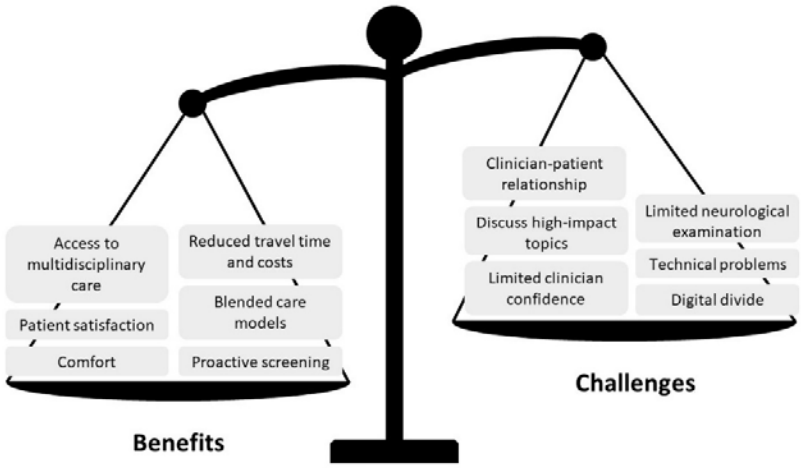

Figure 1. Benefits and challenges of teleconsultations compared to in-person consultations mentioned in recent studies on teleconsultations. The scale's position reflects the authors' opinion on the overall readiness of teleconsultations for deployment in clinical practice.

Overall, patients were satisfied with the delivery of remote consultations.[15-18] The most commonly mentioned advantages include enhanced convenience [15,18,19], greater comfort [15,18], and reduced travel time and costs. [11,13,16,19,20] Furthermore, teleconsultations enable enhanced access to specialist care [1,19,] especially for patients living in rural areas [20,21] and homebound patients with severe disability requiring palliative care.[22] Common disadvantages mentioned by both patients and clinicians include technical difficulties [13,15,16,19], lack of hands-on examinations [13,19], and reduced quality of the doctor-patient contact.[13,19] In particular, neurologists had difficulties breaking bad news to patients through telephone or video consultations.[13] Taken together, teleconsultations can benefit both patients and professionals in specific situations, such as reducing travel burden for stable patients. However, teleconsultations are not suitable when clinicians must address high-impact topics,

or when patients themselves prefer an in-person contact [5] or have no access to technology.[6] Therefore, these experiences of both patients and clinicians suggest that teleconsultations cannot replace all in-person care, but should rather be regarded as an adjunct or additional service that clinicians can use in specific situations.[2,4]

Teleconsultations also offer unique possibilities to extend hospital-based care into blended care models, i.e. combining hospital- and home-based care.[23] A remarkable example was implemented in northern Italy where, during the peak of the COVID crisis in early 2020, Parkinson patients had limited access to in-person care by their own neurologist. These patients were offered remote access to a telenursing service via videoconferencing. Although this Parkinson nurse was a complete newcomer for the patients and could only be seen remotely, the nurse resolved over 60% of incoming requests from patients at a distance, thereby preventing unnecessary travel to the hospital.[24] When more specialized medical care was required, a teleconsultation with a specialist(s) or multidisciplinary team was scheduled during which most issues could be resolved remotely. If needed, subsequent in-person contacts or even hospital admissions were arranged.

Teleconsultations also offer opportunities to provide proactive care, i.e. aiming to identify new medical issues early on so these can be managed timely, thereby preventing avoidable disability and reducing unnecessary costs. An illustrative example is a proactive outreach program that targeted homebound and vulnerable patients with advanced PD and related disorders.[25] A nurse or social worker proactively called these patients to discuss topics such as home safety, physical and mental wellbeing, medical care provisions, and also lockdown restrictions or scheduling of healthcare appointments. Patients and caregivers reported that the program made them feel safe and supported.[25] Whether this proactive approach actually avoids medical deterioration and prevents e.g. costly admissions remains to be determined. Similarly, a case report illustrated how intense but completely remotely delivered patient contact could reduce the frequency of falls, which may have prevented fractures or other injuries.[26] The cost-effectiveness of proactive and blended care models must be evaluated in future research.

Telemonitoring

Telemonitoring is the remote gathering of information about a patient which is used to inform healthcare providers (in a clinical setting) or researchers (in the framework of a trial). A wide and expanding spectrum of tools can be used for telemonitoring, including body-worn sensors [27,28], home sensors [29], specific apps for the smartphone [30,31], digital diaries [32], or analysis of common appliances such as computer keyboards [33]

(only several selected high-quality references are given here). The promise of remote monitoring is to offer objective, continuous measures of relevant symptoms while patients are at home. This is important because hospital-based assessments can deviate considerably from daily living assessments.[34] Moreover, during in-person visits to the hospital, it remains difficult to reliably ascertain complex fluctuating events (such as response fluctuations to dopaminergic medication), rare events (such as falls [35]) or gradually developing events (such as a slowly progressive decline in physical activities, or disease progression itself).[36] In this section, we discuss whether telemonitoring tools are ready for use in trials and clinical practice, and what patients think about telemonitoring (**figure 2**).

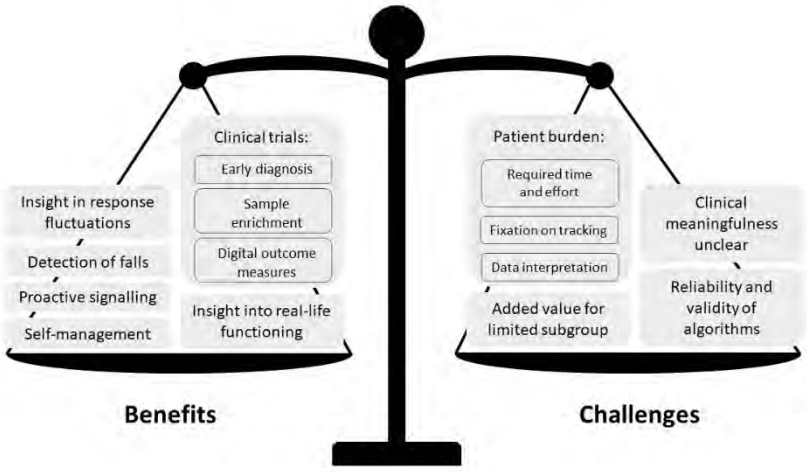

Figure 2. Benefits and challenges of telemonitoring compared to in-hospital measures mentioned in recent studies on telemonitoring. The scale's position reflects the authors' opinion on the overall readiness of telemonitoring for deployment in clinical practice and trials.

Perhaps the most immediate application for telemonitoring is its deployment in clinical trials. Recognition is growing that the currently available clinical rating scales may be insufficiently sensitive and accurate to detect meaningful changes in patient functioning; this is particularly problematic in the setting of clinical trials where new experimental interventions are being tested. For that reason, many ongoing and planned studies are incorporating some form of telemonitoring into the overall repertoire of assessments, for now as surrogate, exploratory outcome measures. Recent examples of such studies include a phase 3 study assessing continuous subcutaneous infusion of levodopa/carbidopa [37], and a phase 2 study assessing co-administration of two compounds (CST-103

and CST-107) [38], which both use a wearable sensor to measure at home functioning as secondary outcome. A clear advantage is that telemonitoring, by virtue of the objective and longitudinal assessment in the patient's own home environment, may offer a very sensitive indication of therapeutic benefits. An important challenge is how to interpret such telemonitoring outcomes in terms of their clinical meaningfulness, even when statistically significant.[39] The increasing adoption of telemonitoring in clinical trials, alongside existing measures for patient functioning and quality of life, will help to further refine the reliability and validity of telemonitoring outcomes and support its acceptance by regulatory bodies.

In addition, telemonitoring tools could assist with subject enrolment in clinical trials by enabling early identification of people with PD or prodromal stages of PD. In a 6-year longitudinal study of prodromal individuals, specific gait characteristics such as step velocity and length were predictive of conversion to PD, even when measured as early as up to 4 years prior to the clinical diagnosis.[40] Other technologies suitable for early disease detection encompass touchscreen typing [31] or voice analysis.[41] However, voice studies often relied on high-quality data collected in controlled environments, making it difficult to apply such tools for large-scale screening based on less standardized real-life recordings. One study addressed this issue by collecting telephone-quality voice data from 1483 people with PD and 8300 healthy controls across seven countries.[42] Although using these real-life data reduced the classification accuracy, this study represents an important step towards analysing data as they would be captured in everyday life.

Incorporating telemonitoring into regular clinical practice faces similar challenges. Recent work indicates that it is feasible and informative to employ telemonitoring tools such as wrist-worn sensors and smartphone applications in clinical practice.[43–46,47] However, conclusive evidence of their actual impact on clinical outcomes is lacking. Telemonitoring tools often consist of a dashboard for clinicians that presents the remotely collected data. Pilot studies show positive experiences of clinicians who used such tools in clinical practice. Specifically, the information on symptom severity and medication intake displayed in these dashboards was in line with in-clinic assessments [43], enabled a clinician to make treatment decisions that were comparable to in-person evaluations in most cases [47], and resulted in more medication adjustments and higher medication doses.[45] Despite these encouraging initial findings, we lack large-scale RCTs assessing the effect of such dashboards on clinically relevant outcomes. A recent controlled trial showed improved scores on the MDS-UPDRS part III and IV in the ON state when the patient's case management was supported by a telemonitoring tool.[48] However, since no

effects were observed on the MDS-UPDRS part II and PDQ-39, more research is needed to verify whether the benefits translate into an improved patient functioning in daily life. Furthermore, for only few patients, the dashboard provided the clinician with usable information beyond that obtained during the regular clinical evaluation.[46,49] These patients had symptoms that strongly fluctuated [46] or that changed very subtly [49], or who experienced unexpected effects of multiple medications.[49] Therefore, future studies should further identify specific patient populations that may benefit most from telemonitoring tools. Finally, we note that most published work was conducted by groups that also originally developed the monitoring tools under examination. We encourage independent research groups to conduct RCTs to further test the effectiveness of such tools, which will be essential to persuade both the clinical and scientific community about the merits of telemonitoring.

Many patients are motivated to monitor their symptoms, as long as there is a clear goal. [50,51] However, a mixed-methods study into the patient's perspectives on self-tracking showed that, even for the most highly motivated patients, it remains necessary to strike a balance between the perceived benefits and the inevitable burden of self-tracking.[50] Specifically, patients reported that self-tracking of e.g. their medication intake or exercise regimes helped them to better understand and manage their PD and to better inform their treating clinician. As a potential burden they mentioned difficulties understanding connections between variables, and getting too fixated on tracking. This balance between benefits and burden could explain the large differences in retention rates between studies. For example, when patients were given (multiple) wearable sensors and were asked to actively provide information using a smartphone-based application, compliance was excellent for up to two weeks [44,52], but decreased steeply after three months.[43] However, when the balance between burden and benefits for patients was improved, e.g., by using only a single tool, by focussing on passive monitoring, and by providing highly personal contact (such as a readily accessible helpdesk), dropout rates could be minimized to 3% after six months in one study [49] or even only 1% after one year in another.[53] Future research should further improve the balance between benefits and burdens by tailoring the implementation of the monitoring tools to the individual patient's context, measuring only those variables that are relevant and meaningful to both patient and clinician.[54,55]

Teletreatment

The development of technological devices has enabled numerous treatments to be delivered remotely. Here, we review the benefits and challenges of remotely

delivered device-assisted therapies, exercise programs, and cognitive behavioural therapy (CBT) (**figure 3**).

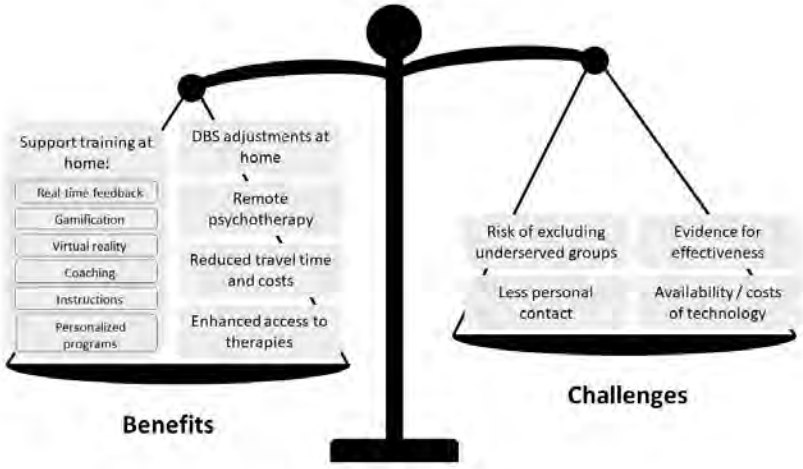

Figure 3. Benefits and challenges of teletreatments compared to in-person treatments mentioned in recent studies on teletreatments. The scale's position reflects the authors' opinion on the overall readiness of teletreatments for deployment in clinical practice.

During the COVID-pandemic, parameters for device-assisted therapies such as deep brain stimulation (DBS) were successfully adjusted remotely.[56,57] Patients completed self-rated questionnaires about symptom severity and uploaded a video of their motor functioning at home, which were assessed by the hospital-based clinician. Then, whilst video-calling with the patient, the clinician remotely adjusted the parameters of the DBS electrodes during an online therapeutic session. Comparing their condition before and after the parameter adjustments, patients reported a decrease in symptom severity.[56] The patient satisfaction rates with the remote adjustment sessions were comparable to in-clinic adjustments.[56,57] Although patients reported some difficulty learning how to use the program, these observational results highlight the potential of teletreatment to continue care within the patient's home, even for quite markedly affected patients, and thereby prevent unnecessary travel to the hospital.

For patients with PD, it would be very helpful to be able to perform various non-pharmacological interventions at home, such as physical exercises, speech therapy, or cognitive training. Recent work has shown the feasibility and merits of home-based physical exercise programs which typically included a smartphone-based

application or website that showed a personalized training program to patients, with instruction videos explaining which exercises had to be performed and what precautions should be taken.[58–60] A continued contact with a tele-coach using telephone or video calls remained important so patients could ask questions, check whether they were exercising correctly, and could be motivated and supported.[59,61] A double-blind RCT exemplified how technology can further improve home-based physical exercise programs.[62] Specifically, in this study, patients used a home-trainer augmented with virtual reality software and gamified elements to perform aerobic exercises at home, three times a week for six months. The results showed a stabilisation of UPDRS motor scores and an improvement in VO2 max scores, as compared to an active control group that performed only stretching exercises. Another technology-supported exercise program also appeared to be effective, but only in a more sedentary subgroup of patients.[58] Therefore, future research efforts should target specific patient groups, e.g., inactive patients, incorporate methods to facilitate personal contact, and continue to develop methods to enhance training programs with technology.

Remote interventions have also been tested for other allied health treatments, such as speech therapy. Specifically, delivering speech therapy remotely can enhance comfort and considerably reduce costs for patients, with only a slight increase in costs for the healthcare system.[63] Technology offers new methods to possibly augment speech therapy, as is illustrated by an innovative RCT study protocol.[64] This study aims to deliver personalized, home-based, online speech therapy to 215 PD patients. Treatment will be guided online by a speech therapist and, importantly, is supported by a visual feedback application on a smartphone or tablet that shows the patient in real-time whether their pitch is too high or too low.

For various chronic neurological diseases, an online rehabilitation program was designed to strengthen both cognitive and physical skills.[65] The program combines virtual reality with a motion sensor so that patients can see their exercises on a screen and interact with them through bodily movements. The prescribed exercises target memory, dual tasking, executive functions and movement of both upper and lower limbs. Patients received automated feedback on their performance in between exercises, while healthcare professionals personalized the content of each training session. Overall, adherence rates were high and patients reported a positive effect on their daily routine and functioning.[65]

Finally, two studies delivered teletreatments focused on mental health. One study provided patients with various neurological disorders with a 6-week course that

integrated elements from cognitive therapies. Completing the course at home and unsupervised was feasible.[66] An RCT added telephone-based cognitive behavioural therapy to treatment as usual, which led to a stronger reduction in depressive symptoms for PD patients.[67]

Although these studies offer some careful initial evidence that it is feasible and effective to deliver treatments and support training programs remotely, future research should investigate methods to enlarge the effectiveness and boost the patient experience of these treatments through technology.

Conclusion

A growing body of studies published in the last two years has helped to further establish the feasibility and effectiveness of a wide range of different telemedicine tools. Some of the telemedicine tools discussed here are now ready for clinical use in daily practice (e.g., videoconferencing, tools to support exercises), bearing the specific strengths and weaknesses of each approach in mind. Other tools to remotely monitor and treat patients hold great promise, but require further development and independent evaluations to support their use in clinical practice and research. Diversity should be a specific focus of attention in these new studies, making sure that telemedicine approaches can be made widely available to patients with very different clinical and sociodemographic backgrounds. Taken together, the time has come to seriously consider telemedicine as one of many useful tools available in our medical and research armamentarium, alongside with established services such as in-person visits to the hospital. Importantly, rather than regarding telemedicine as a panacea for challenges in research and clinical care, we encourage to consider the use of telemedicine as a supportive tool that can be applied under specific instances, for specific indications and for specific populations of eligible patients.

References

1. Dorsey, E. R., Okun, M. S. & Bloem, B. R. Care, Convenience, Comfort, Confidentiality, and Contagion: The 5 C's that Will Shape the Future of Telemedicine. *Journal of Parkinson's Disease* **10**, 893–897 (2020).
2. Dorsey, E. R., Bloem, B. R. & Okun, M. S. A New Day: The Role of Telemedicine in Reshaping Care for Persons With Movement Disorders. *Movement Disorders* **35**, 1897–1902 (2020).
3. Artusi, C. A. *et al.* Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases. *Parkinsonism & Related Disorders* **46**, S53–S56 (2018).
4. Mulroy, E. *et al.* Reply to: "A New Day: The Role of Telemedicine in Reshaping Care for Persons With Movement Disorders". *Movement Disorders* **35**, 1903–1904 (2020).
5. Mulroy, E. *et al.* Telemedicine in Movement Disorders: Leçons du COVID-19. *Movement Disorders* **35**, 1893–1896 (2020).
6. Nouri, S. S., Khoong, E. C., Lyles, C. R. & Karliner, L. S. Addressing Equity in Telemedicine for Chronic Disease Management During the Covid-19 Pandemic. *NEJM Catalyst* **1**, 1–13 (2020).
7. Hassan, A. *et al.* Global Survey on Telemedicine Utilization for Movement Disorders During the COVID-19 Pandemic. *Movement Disorders* **35**, 1701–1711 (2020).
8. MDS Telemedicine Study Group. Telemedicine in Your Movement Disorders Practice. *April 2020* https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm (2020).
9. Schneider, R. B. *et al.* Remote Administration of the MDS-UPDRS in the Time of COVID-19 and Beyond. *Journal of Parkinson's Disease* **10**, 1379–1382 (2020).
10. Cabrera-Martos, I. *et al.* Agreement Between Face-to-Face and Tele-assessment of Upper Limb Functioning in Patients with Parkinson Disease. *PM&R* **11**, 590–596 (2019).
11. Witek, N., Heath, S. L., Ouyang, B., Tanner, C. M. & Galifianakis, N. B. Remote telemedicine evaluation of deep brain stimulation candidacy. *Neurology: Clinical Practice* **10**, 199–205 (2020).
12. Erb, M. K. *et al.* mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's disease. *npj Digital Medicine* **3**, 6 (2020).
13. Courtney, E., Blackburn, D. & Reuber, M. Neurologists' perceptions of utilising tele-neurology to practice remotely during the COVID-19 pandemic. *Patient Education and Counseling* (2021).
14. Janca, A. *et al.* WHO/WFN Survey of neurological services: A worldwide perspective. *Journal of the Neurological Sciences* **247**, 29–34 (2006).
15. Seritan, A. L., Heiry, M., Iosif, A.-M., Dodge, M. & Ostrem, J. L. Telepsychiatry for patients with movement disorders: a feasibility and patient satisfaction study. *Journal of Clinical Movement Disorders* **6**, 2 (2019).
16. Shalash, A., Fathy, M., Dawood, N. L. & Hamid, E. Adopting Virtual Visits for Parkinson's Disease Patients During the COVID-19 Pandemic in a Developing Country. *Frontiers in Neurology* **11**, 1–8 (2020).
17. Sekimoto, S. *et al.* A Randomized Crossover Pilot Study of Telemedicine Delivered via iPads in Parkinson's Disease. *Parkinson's Disease* **2019**, 1–7 (2019).
18. Tarolli, C. G. *et al.* Video research visits for atypical parkinsonian syndromes among Fox Trial Finder participants. *Neurology: Clinical Practice* **10**, 7–14 (2020).
19. Spear, K. L., Auinger, P., Simone, R., Dorsey, E. R. & Francis, J. Patient Views on Telemedicine for Parkinson Disease. *Journal of Parkinson's Disease* **9**, 401–404 (2019).

20. Singh, R. L., Bush, E. J., Hidecker, M. J. C., Carrico, C. P. & Sundin, S. Considering Health Care Needs in a Rural Parkinson Disease Community. *Progress in Community Health Partnerships: Research, Education, and Action* **14**, 1–1 (2020).
21. Peacock, D. *et al.* Perception of Healthcare Access and Utility of Telehealth Among Parkinson's Disease Patients. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques* **47**, 700–704 (2020).
22. Katz, M. Telehealth increases access to palliative care for people with Parkinson's disease and related disorders. *Annals of Palliative Medicine* **9**, S75–S79 (2020).
23. Bloem, B. R. *et al.* Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology* **19**, 623–634 (2020).
24. Cilia, R., Mancini, F., Bloem, B. R. & Eleopra, R. Telemedicine for parkinsonism: A two-step model based on the COVID-19 experience in Milan, Italy. *Parkinsonism & Related Disorders* **75**, 130–132 (2020).
25. Sennott, B. *et al.* Novel Outreach Program and Practical Strategies for Patients with Parkinsonism in the COVID-19 Pandemic. *Journal of Parkinson's Disease* **10**, 1383–1388 (2020).
26. Mancini, F. *et al.* Personalized care management for persons with Parkinson's disease: A telenursing solution. *Clinical Parkinsonism & Related Disorders* **3**, 100070 (2020).
27. Del Din, S., Kirk, C., Yarnall, A. J., Rochester, L. & Hausdorff, J. M. Body-Worn Sensors for Remote Monitoring of Parkinson's Disease Motor Symptoms: Vision, State of the Art, and Challenges Ahead. *Journal of Parkinson's Disease* 1–13 (2021).
28. Ancona, S. *et al.* Wearables in the home-based assessment of abnormal movements in Parkinson's disease: a systematic review of the literature. *Journal of Neurology* (2021).
29. Tian, Y., Lee, G.-H., He, H., Hsu, C.-Y. & Katabi, D. RF-Based Fall Monitoring Using Convolutional Neural Networks. *Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies* **2**, 1–24 (2018).
30. Lo, C. *et al.* Predicting motor, cognitive & functional impairment in Parkinson's. *Annals of Clinical and Translational Neurology* **6**, 1498–1509 (2019).
31. Iakovakis, D. *et al.* Screening of Parkinsonian subtle fine-motor impairment from touchscreen typing via deep learning. *Scientific Reports* **10**, 12623 (2020).
32. Monje, M. H. G. *et al.* Toward e-Scales: Digital Administration of the International Parkinson and Movement Disorder Society Rating Scales. *Movement Disorders Clinical Practice* **8**, 208–214 (2021).
33. Matarazzo, M. *et al.* Remote Monitoring of Treatment Response in Parkinson's Disease: The Habit of Typing on a Computer. *Movement Disorders* **34**, 1488–1495 (2019).
34. Warmerdam, E. *et al.* Long-term unsupervised mobility assessment in movement disorders. *The Lancet Neurology* **19**, 462–470 (2020).
35. Silva de Lima, A. L. *et al.* Home-Based Monitoring of Falls Using Wearable Sensors in Parkinson's Disease. *Movement Disorders* **35**, 109–115 (2020).
36. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* **397**, 2284–2303 (2021).
37. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04380142, Study Comparing Continuous Subcutaneous Infusion Of ABBV-951 With Oral Carbidopa/Levodopa Tablets For Treatment Of Motor Fluctuations In Adult Participants With Advanced Parkinson's Disease; 2020 May 8 [cited 2021 Mar 7]. Available from: https://clinicaltrials.gov/ct2/show/NCT04380142?recrs=ab&type=Intr&cond=Parkinson+Disease&outc=wearable&phase=12&draw=2&rank=2

38. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04739423, A Study of CST-103 Co-administered With CST-107 in Subjects With Neurodegenerative Disorders (CLIN-011); 2021 Feb 4 [cited 2021 Mar 7]. Available from: https://clinicaltrials.gov/ct2/show/NCT04739423?recrs=ab&type=Intr&cond=Parkinson+Disease&outc=digital&phase=12&draw=2&rank=1
39. Stephenson, D. *et al.* Precompetitive Consensus Building to Facilitate the Use of Digital Health Technologies to Support Parkinson Disease Drug Development through Regulatory Science. *Digital Biomarkers* **4**, 28–49 (2020).
40. Del Din, S. *et al.* Gait analysis with wearables predicts conversion to Parkinson disease. *Annals of Neurology* **86**, 357–367 (2019).
41. Tracy, J. M., Özkanca, Y., Atkins, D. C. & Hosseini Ghomi, R. Investigating voice as a biomarker: Deep phenotyping methods for early detection of Parkinson's disease. *Journal of Biomedical Informatics* **104**, 103362 (2020).
42. Arora, S., Baghai-Ravary, L. & Tsanas, A. Developing a large scale population screening tool for the assessment of Parkinson's disease using telephone-quality voice. *The Journal of the Acoustical Society of America* **145**, 2871–2884 (2019).
43. Elm, J. J. *et al.* Feasibility and utility of a clinician dashboard from wearable and mobile application Parkinson's disease data. *npj Digital Medicine* **2**, 95 (2019).
44. Gatsios, D. *et al.* Feasibility and Utility of mHealth for the Remote Monitoring of Parkinson Disease: Ancillary Study of the PD_manager Randomized Controlled Trial. *JMIR mHealth and uHealth* **8**, e16414 (2020).
45. Isaacson, S. H. *et al.* Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting transdermal rotigotine patch: A pilot study. *Parkinsonism & Related Disorders* **64**, 132–137 (2019).
46. Santiago, A. *et al.* Qualitative Evaluation of the Personal KinetiGraphTM Movement Recording System in a Parkinson's Clinic. *Journal of Parkinson's Disease* **9**, 207–219 (2019).
47. Evans, L., Mohamed, B. & Thomas, E. C. Using telemedicine and wearable technology to establish a virtual clinic for people with Parkinson's disease. *BMJ Open Quality* **9**, e001000 (2020).
48. Woodrow, H., Horne, M. K., Fernando, C. V. & Kotschet, K. E. A blinded, controlled trial of objective measurement in Parkinson's disease. *npj Parkinson's Disease* **6**, 35 (2020).
49. Powers, R. *et al.* Smartwatch inertial sensors continuously monitor real-world motor fluctuations in Parkinson's disease. *Science Translational Medicine* **13**, eabd7865 (2021).
50. Riggare, S., Scott Duncan, T., Hvitfeldt, H. & Hägglund, M. "You have to know why you're doing this": a mixed methods study of the benefits and burdens of self-tracking in Parkinson's disease. *BMC Medical Informatics and Decision Making* **19**, 175 (2019).
51. de Vries, N. M. *et al.* Exploring the Parkinson patients' perspective on home-based video recording for movement analysis: a qualitative study. *BMC Neurology* **19**, 71 (2019).
52. Heijmans, M. *et al.* Monitoring Parkinson's disease symptoms during daily life: a feasibility study. *npj Parkinson's Disease* **5**, 21 (2019).
53. Bloem, B. R. *et al.* The Personalized Parkinson Project – data quality enhancing strategies [abstract]. *Mov Disord.* vol. 35 (suppl https://www.mdsabstracts.org/abstract/the-personalized-parkinson-project-data-quality-enhancing-strategies/). (2020).
54. Wannheden, C. & Revenäs, Å. How People with Parkinson's Disease and Health Care Professionals Wish to Partner in Care Using eHealth: Co-Design Study. *Journal of Medical Internet Research* **22**, e19195 (2020).

55. Espay, A. J. *et al.* A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Movement Disorders* **34**, 657–663 (2019).

56. Xu, J. *et al.* Management of Parkinson's disease patients after DBS by remote programming: preliminary application of single center during quarantine of 2019-nCoV. *Journal of Neurology* (2020).

57. Zhang, C. *et al.* Utility of Deep Brain Stimulation Telemedicine for Patients With Movement Disorders During the COVID-19 Outbreak in China. *Neuromodulation: Technology at the Neural Interface* **24**, 337–342 (2021).

58. Ellis, T. D. *et al.* Comparative Effectiveness of mHealth-Supported Exercise Compared With Exercise Alone for People With Parkinson Disease: Randomized Controlled Pilot Study. *Physical Therapy* **99**, 203–216 (2019).

59. Flynn, A., Preston, E., Dennis, S., Canning, C. G. & Allen, N. E. Home-based exercise monitored with telehealth is feasible and acceptable compared to centre-based exercise in Parkinson's disease: A randomised pilot study. *Clinical Rehabilitation* **35**, 728-739 (2020).

60. Landers, M. R. & Ellis, T. D. A Mobile App Specifically Designed to Facilitate Exercise in Parkinson Disease: Single-Cohort Pilot Study on Feasibility, Safety, and Signal of Efficacy. *JMIR mHealth and uHealth* **8**, e18985 (2020).

61. Lai, B. *et al.* Exploring the uptake and implementation of tele-monitored home-exercise programmes in adults with Parkinson's disease: A mixed-methods pilot study. *Journal of Telemedicine and Telecare* **26**, 53–63 (2020).

62. van der Kolk, N. M. *et al.* Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *The Lancet Neurology* **18**, 998–1008 (2019).

63. Saiyed, M., Hill, A. J., Russell, T. G., Theodoros, D. G. & Scuffham, P. Cost analysis of home telerehabilitation for speech treatment in people with Parkinson's disease. *Journal of Telemedicine and Telecare* **28**, 524-529 (2020).

64. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03963388, PERsonalized SPEeCh Therapy for actIVE Conversation (PERSPECTIVE); 2019 May 23 [cited 2021 Mar 7]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03963388?term=personalized+speech+therapy&cond=Parkinson+Disease&cntry=NL&draw=2&rank=1

65. Isernia, S. *et al.* Efficiency and Patient-Reported Outcome Measures From Clinic to Home: The Human Empowerment Aging and Disability Program for Digital-Health Rehabilitation. *Frontiers in Neurology* **10**, (2019).

66. Gandy, M. *et al.* A feasibility trial of an internet-delivered psychological intervention to manage mental health and functional outcomes in neurological disorders. *Journal of Psychosomatic Research* **136**, 110173 (2020).

67. Dobkin, R. D. *et al.* Telephone-based cognitive behavioral therapy for depression in Parkinson disease. *Neurology* **94**, e1764-1773 (2020).

3

In-person when necessary and available, remotely when possible: How telemedicine can support palliative care for persons with Parkinson's disease

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Abstract

Background

Essential components of optimal palliative care for people with Parkinson's disease (PD) include adequate access and timely initiation of palliative care conversations. We investigated how telemedicine could support palliative care for people with PD.

Method

We interviewed 58 stakeholders in palliative care for PD from seven European countries, including 15 people with PD, six care partners and a diverse group of 37 healthcare professionals. The semi-structured interview guide was co-created with a patient advisor panel and covered three topics: remote communication, remote monitoring and online information provision and education. We analysed the data using thematic analysis.

Results

We identified four themes that describe how telemedicine could support palliative care for PD. First, *talking about palliative care remotely* enhances access to palliative care for people with PD and their care partners from within the comfort of their own homes. However, remote communication also creates a conversational barrier, as the loss of physical proximity hampered the ability to sense and feel the other. Second, *gaining a complete picture of the person with PD* is best achieved through physical examinations. Remote monitoring tools may provide additional at-home information about the person with PD, but the perceived utility of monitoring such information to inform palliative care is heterogeneous. Third, telemedicine supports the *transfer of knowledge about palliative care*. Online platforms facilitate communication and alignment between healthcare professionals whilst reducing travel time. People with PD and care partners desired online information sources with trustworthy, understandable and up-to-date information. Fourth, specific *prerequisites for successful implementation of telemedicine tools* apply. User-related barriers include low digital literacy, advanced age and PD-symptoms like cognitive decline, whilst a proactive personality and independence facilitate telemedicine use. At the organizational level, participants expressed concerns regarding privacy, ethical and financial issues.

Conclusions

Participants generally preferred to discuss palliative care topics physically, but remote consultations can sustain someone's access to care when a physical visit is no longer possible or feasible. Telemedicine was welcomed to transfer palliative care knowledge between healthcare professionals and towards people with PD and care partners.

Background

Parkinson's disease (PD) is the fastest growing neurodegenerative disease globally, with a predicted prevalence of over 12 million people in 2040.[1,2] PD is characterized by a large variety of motor and non-motor symptoms such as bradykinesia, freezing of gait, dysarthria and cognitive decline.[3] PD symptoms typically worsen gradually over the disease course. Especially in the advanced stages of the disease, symptom burden can be high, underrecognized and consequently undertreated, with a substantial impact on quality of life.[4–6] Palliative care is available to address this burden, as a healthcare approach that "prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual".[7] Palliative care interventions for people with PD have shown positive effects on quality of life and disease burden.[8–10]

Despite the pronounced benefits, challenges remain in the delivery of palliative care for persons with PD. These challenges include limited access to palliative care for people with PD [11] and a lack of time among healthcare professionals to have elaborate conversations about the typically complex (care) needs.[12,13] Furthermore, as the disease progresses, cognition declines and communication becomes impaired, jeopardizing discussions about care preferences. Early identification and documentation of palliative care needs and wishes is therefore crucial, yet this is challenging in practice as PD lacks clear defining moments for initiating palliative care.[14] Moreover, the emotional associations attached to palliative care as 'end of life care' make healthcare professionals hesitant in addressing palliative care topics, as they do not want to take away hope.[13–15] Finally, there is insufficient coordination of care,[16,17] including limited communication among healthcare professionals and insufficient education with respect to palliative care.[14,18]

Some of these challenges could potentially be addressed by telemedicine. Telemedicine is not a uniformly used term but, according to the WHO, telemedicine entails the provision of healthcare services at a distance by utilizing digital technology.[19] These services encompass remote consultations between patients and healthcare professionals, remote monitoring of a patient's health, interdisciplinary meetings between healthcare professionals as well as the transmission of medical data to healthcare providers.[19–22] Clear advantages of telemedicine include the reduction of travel burden and enhanced access to care, which is especially relevant for home- and bedbound people with PD, and for those living in populated regions or underserved areas of the world where physical access to care is challenging, if not simply unavailable.[11,23–25] Other benefits include the collection of information

about the person with PD in everyday life through remote monitoring technology [26] and the use of tele-education to facilitate long-distance learning among healthcare professionals.[27] In other fields, telemedicine is already being utilized to support palliative care. For example, a remote patient monitoring module was used in oncology to report pain severity at home and trigger healthcare actions based on predefined thresholds of pain.[28–31] In a broader palliative care context, videoconferencing allowed for multidisciplinary palliative care team meetings [30–32] and educational modules enhanced the self-management skills of patients and care partners.[28,30,31]

These findings support the idea that telemedicine might also help to overcome some of the challenges in the delivery of palliative care to people with PD. However, PD differs markedly from the tested chronic conditions, for example in the type of symptoms and speed of disease progression, necessitating further research before findings can be translated. Our aim is therefore to examine how and under what conditions telemedicine could support the delivery of palliative care for people with PD from the perspective of people with PD, care partners and healthcare professionals.

Method

Study design

This study was part of the PD_PAL project, a European randomized controlled trial that validates a new model of palliative care for PD.[33] We conducted semi-structured interviews with people with PD, care partners and a heterogeneous group of healthcare professionals to explore their experiences and opinions regarding the application of telemedicine in palliative care. We adhered to the COREQ guidelines for reporting qualitative research.[34] This study was approved by the local ethics committee (METC Oost-Nederland; file 2022-15724).

Sample and recruitment

In total, we have interviewed 58 persons: 14 with PD, 1 with multiple system atrophy-p (from here on all labelled as PD for conciseness), 6 care partners (including family caregivers and relatives), and 37 healthcare professionals (**table 1**). For inclusion, people with PD and care partners had to have experience with palliative care, for example by discussing advance care planning with a healthcare professional or attending courses about palliative care. The participating people with PD and care partners did not have to be related. Healthcare professionals had to have experience with providing palliative care to people with PD for at least 1 year.

Table 1. Demographic characteristics of interview participants.

	N	Gender women		Age		Years PD or PD care		Years palliative care experience	
		N	%	M	SD	M	SD	M	SD
People with PD*	15	9	60%	65.3	7.6	8.9	3.6	NA	NA
Care partners	6	3	50%	66.2	7.0	7.0	3.6	NA	NA
Movement disorder specialists	4	1	25%	54.5	11.6	27.5	9.9	9.5	4.2
Occupational therapists	6	5	83%	47.3	8.7	16.5	9.2	14.8	7.8
PD nurse (specialists)	7	7	100%	45.1	10.2	18.0	11.6	14.0	12.4
Physiotherapists	5	3	60%	48.4	13.6	15.0	4.1	13.8	4.9
Psychologists	3	3	100%	50.0	5.6	19.0	2.6	19.0	2.6
Specialist in elderly care	6	3	50%	46.5	14.1	13.2	6.7	12.5	5.9
Speech therapists	5	5	100%	43.0	11.6	17.0	14.3	15.3	15.9
Healthcare ethicist **	1								

PD = Parkinson's disease; NA = not applicable; M = mean; SD = standard deviation

* Includes 1 person with multiple system atrophy which is displayed together with data of people with PD for privacy reasons.

** We included one healthcare ethicist based on their extensive experience in combining telemedicine and palliative care. Demographic data is not provided to protect the privacy of the participant.

Initially, we purposively sampled from the professional network of our Parkinson's center of excellence to actively reach people with extensive experience in palliative care and PD (n = 27). To enlarge the generalizability of our findings, we also used convenience sampling (n = 27) to reach people outside of our network. These recruitment activities included a flyer at a national PD congress, an online video, an invite in a newsletter, contacting PD-specialized healthcare professionals through a national database called ParkinsonNet [35] and inviting a panel of ~60 people with PD who had previously expressed interest in research. Throughout study recruitment, we also allowed for snowball sampling (n = 4) when participants suggested an interesting follow-up conversation partner. In total, we recruited 4 movement disorder specialists, 2 nurses and 1 person with PD from six countries excluding the Netherlands: France (n=1), Germany (n=1), Greece (n=1), Italy (n=1), Sweden (n=2) and the United Kingdom (n=1).

For each participant, the recruitment procedure was similar. We reached out to potential participants through email, or they contacted us. We informed the participant with written information about the study background as well as the procedures and content of the interview. Participants could ask questions by email or telephone and could take as much time as needed to consider their participation. Each participant provided written informed consent.

Data collection

The construction of the interview guide is based on literature available on the subject, that means, we combined current challenges in the delivery of PD palliative care [12–14,16,36–38] with elements of current telemedicine systems already tested for palliative care in other chronic conditions.[29–31,39] By combining these sources, we highlighted potential areas of use of telemedicine for palliative care for PD. RB and BWD made an initial draft of the interview guide, which was discussed with MJM, CM, HLK and a panel of 2 patient advisors including one person with PD and one care partner (**supplementary table S1**). The three main topics of the interview guide were remote communication, remote monitoring and online information provision and education (**table 2;** full interview guide in **supplementary table S2**).

Table 2. The interview guide topics.

Topic	Sub-topics	PwPD	HCP
1. Background	Experiences with palliative care		X
	Familiarity with TM: Experiences, technology usage, digital skills, COVID-19	X	X
2. Remote communication	Preferred way of communication: Benefits and downsides of physical and remote contact	X	X
	Discussing advance care planning and palliative care: Preference for physical or remote, pre-conditions	X	X
	Impact TM on relationship with HCP/ PwP	X	X
	Multidisciplinary communication: Alignment and possible improvements	X	X
3. Remote monitoring	Previous experiences with monitoring: What, how, why	X	X
	Usefulness of monitoring for palliative care: What, motivation, concerns, relevancy	X	X
	For nursing homes: Impact on relevancy of monitoring		X
4. Information and education	Information provision for people with PD and care partners: Current practice and opportunities for TM	X	X
	Professional education: Need and opportunities for TM		X

PwPD = people with PD and care partners; HCP = healthcare professional(s); TM = telemedicine

RB and PB conducted the interviews between September 2022 and January 2023. The interviews took place physically at the place of preference of the participant (n = 9; 15%), through videoconferencing (n = 45; 78%) or by telephone (n = 4; 7%). There was no prior relationship between the interviewer and the participants. At the beginning of the interview, the interviewer explained their background and the goal of the study. By using semi-structured interviews, we could flexibly discuss the topics in our guide and go in-depth on topics where participants made interesting remarks or displayed elaborate opinions. Each interview was audio recorded and

transcribed verbatim. We drafted field notes directly after completing the interview to capture relevant impressions and ideas. After interviewing 2-3 participants from each group, we evaluated the collected information, updated the interview guide where necessary and decided per group whether data saturation was reached. After completing approximately 25 interviews, we discussed interim findings with the patient advisors who suggested to also include psychologists. Data saturation had been reached after approximately 50 interviews. This number was considerably high because of the diversity in stakeholder backgrounds, but was required to reach data saturation for the individual groups.

Data analysis

RB, PB and CM conducted a thematic analysis according to the six phases of Braun and Clarke.[40] Thematic analysis is a flexible and structured process suitable to distil recurrent patterns of shared meaning across a dataset. We approached the analysis from a reflexive, inductive standpoint in which themes were based on what we encountered in the dataset. After transcribing (verbatim) and becoming familiar with the interviews (step 1), RB and PB independently coded the same three interviews inductively (step 2) by using the software Atlas.ti version 23.[41] We discussed and resolved any discrepancies in code names or coded segments in various meetings. We again coded three interviews separately and discussed discrepancies, followed by coding the remaining interviews individually. Together with CM, we collated all related codes into themes (step 3) and checked whether each theme contained internally consistent codes that answered a unique part of the research question (step 4). If necessary, we revisited codes and coded segments according to new insights. We revised each theme, drafting a thematic map including names and definitions (step 5) and finally drafted the story of our data (step 6). We invited all participants via e-mail to provide feedback on the summary we had drafted from the interview data. In general, participants recognized and agreed with our summary, so no changes were made to the text.

Results

Demographic data of the 58 participants are presented in **table 1**. The interviews lasted on average 51 minutes (SD = 10.9, range = 27-77). From the interview data, we identified four themes that describe how telemedicine could support palliative care for people with PD, their care partners and healthcare professionals: 1) talking about palliative care remotely; 2) gaining a complete picture of the person with PD; 3) transferring knowledge about palliative care; and 4) prerequisites for successful implementation of telemedicine tools. Quotes are presented in the text to illustrate the themes and subthemes (**figure 1**).

Talking about palliative care remotely

Participants raised two factors related to remotely talking about palliative care: enhancing accessibility to care and the impact of physical distance on conversations.

First, accessibility to palliative care can improve by using remote communication technology such as videoconferencing or telephone. Both healthcare professionals and people with PD stated that such communication technology allows for quick and frequent contact in between physical meetings. Through short messages or a video call, specific questions or concerns could be resolved remotely or a physical appointment could be scheduled as follow-up.

> *Occupational therapist 2: "Sometimes it is nice to just feel or hear in between how someone is doing and if you hear some kind of alarm signals or get a certain gut feeling from the conversation, you can schedule a physical contact".*

Especially healthcare professionals working in nursing homes appreciated the ability to remotely include family members or care partners in the palliative care conversations. These family members or care partners would otherwise be unable to attend or visit because they cannot leave, e.g., their work to travel to the nursing home.

> *Specialist elderly care 1: "[We use telemedicine] for involving family for whom it is difficult to be available at certain times of the day".*

> *Person with PD 8: "This afternoon I have a telephone appointment, an evaluation meeting […] Then [the neurologist] is going to call me and my husband joins via WhatsApp, because he's not home right now. But*

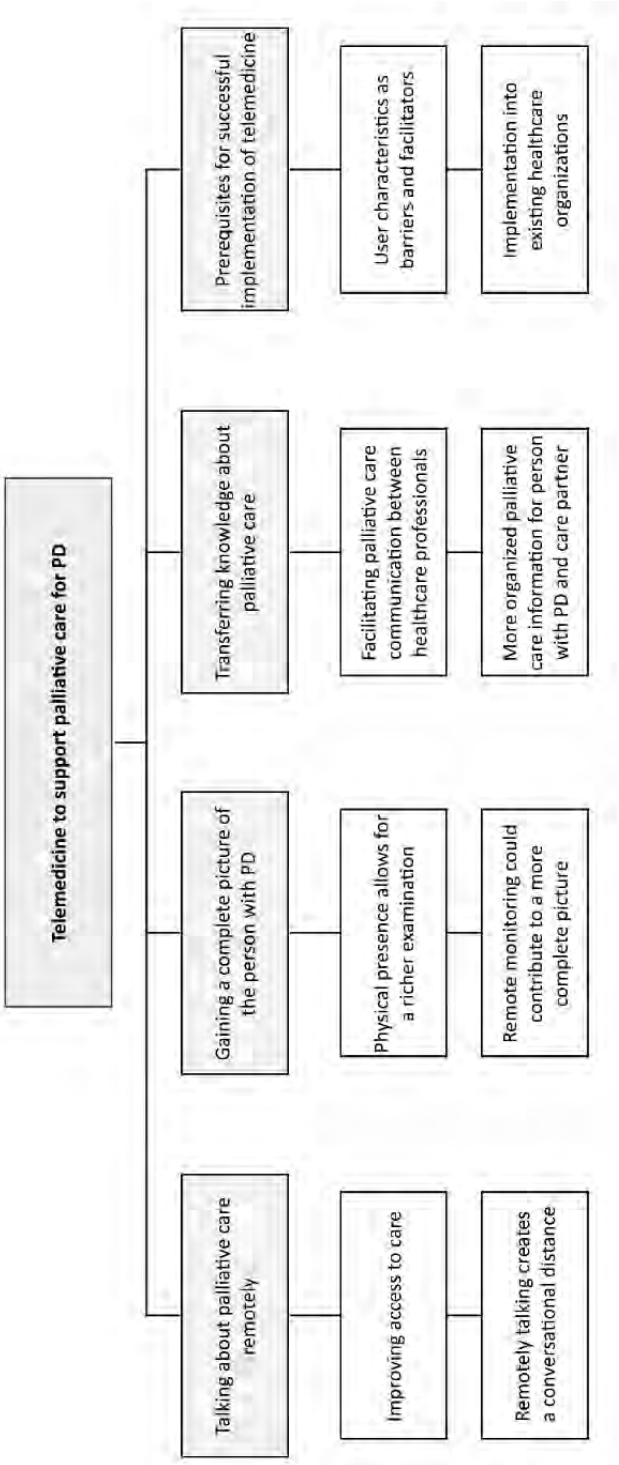

Figure 1. Schematic overview of themes and subthemes.

> *then that's another advantage, because he can't always come with me to the consultation for example".*
>
> *Care partner 2: "I think it [a video call] is a good way to keep contact and to make her busy. We try to visit her every week or every two weeks but she should not be alone. If the video is really running fine, I see it as a daily user".*

Similarly, remote communication technology can increase access to specialist care for people with PD if they become home- or even bedbound and in cases where people live far away from the hospital. Especially movement disorder specialists and nurses with experience in treating home-bound people with PD stressed the need for remote communication possibilities.

> *Movement disorder specialist 3: "It is a huge need, especially for countries where transportation is not easy. […] In my country we have mountains, narrow roads, long winters. Even for patients who are not moving, who are, you know, they can walk but they cannot really drive, so they depend on a relative to go to the remote village, pick them up, drive them all the way to my hospital, see them for a few minutes and then all the way back. Even if you are not bedridden, this is a huge burden. So still, we need telemedicine solutions."*

Second, most participants feared that remotely talking about palliative care could create a conversational distance. Noteworthy, none of the people with PD in our sample had discussed palliative care topics remotely despite the opportunity to do so. All people with PD were still able to travel to the hospital and preferred to talk in-person whenever possible. This preference originated from a feeling that remote communication reduced the ability to sense, feel and understand the other person, hampering the creation of a therapeutic relationship which was deemed important for good palliative care. Regardless of the technology used to communicate, both people with PD and healthcare professionals felt much non-verbal communication was missing such as a subtle facial expression, a tightened fist, a tapping foot or a quick gaze to the care partner. The loss of physical proximity during past telemedicine experiences had come with a loss of emotional proximity, with people not feeling heard and experiencing telemedicine as goal-oriented and quick contact. On the contrary, physical contact was described as more personal and allowed for more incisive and dynamic conversations.

Person with PD 2: "If I wanted to ask, "I want euthanasia", I don't think that's a subject to be dealt with over the phone."

Specialist elderly care 1: "In a video call, you can read the emotions a bit less and keep an eye on the non-verbal part, including how a possible care partner reacts to it, which you can do in a live conversation. So, if it's very complex or you have really difficult issues to discuss with each other, then I think somewhere live would still be my preference".

Nurse 1: "I still think that live contact is better and that you can talk to each other better and more dynamically, because now you really have to wait for a moment until someone has finished talking".

Despite the disadvantages of video or telephone contact, some people with PD mentioned that the physical distance can also bring conversational comfort. Being in the comfort and safety of your own home rather than in a hospital can make it easier to discuss difficult and emotional topics. Furthermore, two nurses in our sample had provided palliative care to people with PD completely or mostly remote. Their experiences contrast the opinions expressed by many participants, as these nurses could successfully deliver palliative care through video calls. Preferably, a therapeutic relationship had been established before the first remote contact, but creating this relationship was also possible online.

Person with PD 11: "When you are calling or video calling with someone, you can sit comfortably in your own environment".

Person with PD 3: "Yes, you can sit at home in your familiar surroundings. That's just the nice thing".

Nurse 7: "I think the patient could maybe find it easier to talk about the subjects that are embarrassing or a little bit taboo, if you take it by video, because it could bring more distance".

Nurse 6: "It [digital palliative care conversation] was feasible. And I say this word because I guess that, for me, it is the most important. Because actually, my biggest worry before starting in telemedicine was, would we be able to discuss about death, dying, advance care planning and also make the care plan and this kind of things in telemedicine? And the answer was yes".

Taken together, all participants agreed that telemedicine improves accessibility of palliative care, but most participants do not deem telemedicine a preferable way to talk about palliative care. Whenever possible, physical contact is preferred, which is perceived as more personal and suitable to talk about in-depth and sensitive topics due to the ability to literally sit next to someone, put an arm around the other and look each other in the eyes. However, remote communication can be used when physical contact is no longer possible or feasible.

Gaining a complete picture of the person with PD

Telemedicine has an impact on the healthcare professionals' ability to gain a complete picture of the person with PD, i.e., the ability to retrieve all information relevant and needed for optimal palliative care. We distinguished two subthemes: physical presence allows for a richer examination and the role of remote monitoring in capturing a complete picture of the person with PD.

First, healthcare professionals remarked that being physically present allowed for a richer examination of the person with PD, both in terms of functional and contextual assessment. Functional assessments are possible through remote communication technology, but healthcare professionals disliked that observations were confined to the camera's view and the microphone's quality. Both people with PD and healthcare professionals feared that this confined digital view makes them miss or overlook relevant symptoms or needs. Regarding contextual information, healthcare professionals praised the rich information gained from the small-talk when meeting physically or when visiting a person with PD at home. For example, a physiotherapist observed how someone walks at home, an occupational therapist sees whether someone is still able to make coffee or a psychologist senses a couple's dynamics when they enter the room. Remote communication was not deemed an equivalent alternative by many healthcare professionals who were accustomed to home visits. However, remote communication does provide a glance into the homes of people with PD for hospital-based healthcare professionals such as the movement disorder specialist and many nurses.

> *Nurse 7: "It was the symptoms to see if what I call shaking is that the same as they call the shaking. Because the patients often have difficulties describing the symptoms. And is it because of too much medicine or too little medicine? [...] If they get concentrated on something, then maybe even if they're stiff, then their feet began to dance and that you can't see on the telephone. So, it was the small things that I missed".*

Occupational therapist 4: "You see so much more. If I only have a screen to look at, I cannot see what you are doing with your hands […]. The overall picture is just so limited with telemedicine".

Psychologist 3: "I like that [a home visit] as well, because then I see how people live and then I can get a feel for the atmosphere".

Furthermore, physiotherapists, occupational therapists and speech therapists stated that they need or prefer physical presence to deliver their treatment. For example, physiotherapists train movements and posture to maintain physical functioning, occupational therapists give advice about safely maintaining activities of daily living such as eating and drinking, and speech therapists need to listen to the person's breathing and be able to change their posture. Many of the activities of these therapists benefit from physical presence as they use the person with PD's context and home environment to optimize treatment.

Physiotherapist 2: "The disadvantage again is if you're not right next to it you can't well, you can't feel what's happening or you can't just momentarily shift that rug or change some things in the context to see if someone can do it then. If I'm talking about a bed transfer for example or turning in bed, often you want to observe that on their own bed. If I stand next to it I can say okay if you hold my hand now, will it work? With a bed brace will it work? Of course, I can't do that when I'm looking at the transfer via video call. Then I can only purely observe".

Speech therapist 4: "What I often see very well in people with Parkinson's is that if an exercise becomes difficult that then, for example, the tremors become worse and you can see that better if you just have physical contact. You can monitor all the physical signals much better. You can also give much better instructions about what they can do in terms of posture".

Second, telemedicine in the form of remote monitoring tools could potentially contribute to obtaining a more complete picture of the person with PD, if deployed appropriately. When we asked healthcare professionals which topics they would like to monitor specifically for palliative care, they formulated answers in line with what is relevant for "regular" care as well. Healthcare professionals focused on the domains typically treated within their profession regarding more advanced PD: response fluctuations and polypharmacy by neurologists, nurses and specialists in elderly care; fall incidents by physiotherapists; swallowing impairments by speech

therapists; and problems with getting out of bed by occupational therapists. People with PD and their care partners named person-specific topics to monitor, such as sleep, balance and weight. Both healthcare professionals and people with PD stressed the need for monitoring tools to track both motor and non-motor symptoms to capture a broader diversity of symptom burden. Most tools currently used in practice were paper-based. Some movement disorder specialists had experience with wearable sensor-based remote monitoring, but these systems have very specific applications, e.g., optimizing medication intake when symptoms fluctuate heavily.

> *Movement disorder specialist 3: "So, we get some numbers […] and at the same time you can see at what hours of the day this is happening. […] So, you get an idea about the real everyday situation of this patient, and you get to know the real situation. For example, you see that in the afternoon there is no effect of the medication".*

Our participants expected that remote monitoring could help to collect high frequency and at-home data, which captures a picture of the person with PD that is closer to their daily life situation than in-clinic visits. However, the perceived utility of monitoring for palliative care varied between people with PD. Some considered monitoring as a means to stay in control of their PD and found the data motivating, whilst others experienced monitoring as a burden which constantly reminded them of their PD. Some healthcare professionals suggested that monitoring could be used to identify palliative care needs, e.g., the amount of time in bed, but others stated that they had no use for monitoring data as they collect all the information they need from a home or hospital-visit. Especially healthcare professionals working in nursing homes, such as the specialist in elderly care, had limited need for a digital monitoring device because they could visit the person with PD living in the care facility. Finally, many participants stressed that the wishes of the person with PD should always be leading when deciding whether to use a remote monitoring tool or not.

> *Person with PD 10: "So, when I write that [symptom] down every once in a while, I also know: there's progress, or stagnation, or whatever. I think it makes sense to keep track of it".*

> *Specialist elderly care 6: "We measure and observe a lot, but more together with the person with PD and other healthcare professionals than with a watch that measures tremor or so".*

Nurse 5: "Literally a digital button: 'I need help' and then a signal appears somewhere. […] Then people do not have to describe their problem or complete lists or numbers or whatever, but can send a signal for help. That's most important I think".

Transferring knowledge about palliative care

Telemedicine can play a role in the transmission of knowledge about palliative care. Two flows of information can be distinguished: between healthcare professionals and targeting the person with PD and the care partner.

First, healthcare professionals use various telemedicine tools to facilitate their palliative care-related communication. For example, healthcare professionals share electronic patient records through hospital systems and e-mail, use secure messengers for quick asynchronous communication and hold multidisciplinary team meetings through videoconferencing. Across all healthcare professionals, this application of telemedicine is deemed very appropriate and effective, as the necessary information can be exchanged, whilst also saving travel time. This way, telemedicine in the form of information and communication technology can facilitate the alignment between healthcare professionals. However, barriers were also mentioned, such as the multitude of available but isolated systems and the risk of receiving irrelevant information when connected to these systems. Besides inter-professional consultation, telemedicine was also considered suitable for professional education, for example as e-learning. Self-paced e-learnings and online symposia, congresses or training sessions have the advantage of reaching large groups of healthcare professionals that can flexibly attend. However, the suitability of telemedicine for remote education depends on the topic as theoretical knowledge can be shared but practical know-how typically requires physical presence.

Psychologist 2: "We also have some patient meetings and I must say that it is very convenient that these are online, because it saves a lot of travel time, because this region is quite large".

Nurse 1: "I am using a platform, but that doesn't include all patients, and that is inconvenient because I have to log in separately for that. […] [remote HCP communication] would be very nice, but I think it would have to be a nationwide, equal platform, and not many separate systems, because there are so many on the market, I think that would just cause confusion, and for everyone to have a new code and password, that's not convenient either".

> *Speech therapist 2: "It depends what kind of education it is or what you have to do. If the treatment itself is also very hands-on and for that you have to touch the patient, feel and so on, yes then it's convenient that you give such an education also live. If it's a lot of theoretical knowledge then that's fine online".*

Second, both people with PD and healthcare professionals desired more structured online information about palliative care available for people with PD and their care partners. Participants often stated that they are unaware of where to find information on the internet, which is up to date, trustworthy and understandable. The large number of available information sources, including both physical sources, e.g., flyers and books, and digital sources, e.g., websites and videos, was mentioned as confusing. As a solution, both healthcare professionals and people with PD suggested a coordinator within the (palliative) care team, to be appointed as a single point of contact. This person can guide the person with PD and the care partner to the right information, tailored to their preferences. Each person with PD and care partner will have different preferences regarding how, i.e., offline or online, and when information is provided. Therefore, online information was regarded as an additional option or tool to serve the needs of the people with PD and their care partners.

> *Person with PD 2: "When you start searching you quickly get lost from pillar to post, so if it was a little bit more organized that would be nice".*

> *Person with PD 1: "And indeed: information provision. Which there is just more and more of. If I start Googling, I will get thousands of hits. But which are correct?"*

> *Person with PD 5: "Yes, you can read through it [digital information] more quietly. And you can take it, you can take out your own notes, you can take out pieces, you can save those yourself in your, in a folder or whatever. Well, maybe it'll come out later, if it's applicable one time".*

> *Person with PD 12: "If that's really like: listen, we want to talk about informal care or a later stage [PD]. Yes, then you do get that startled reaction of: okay, do we need to, has something been found, is something wrong? You would rather have that physically then".*

Speech therapist 5: "[…] make sure that there is one place where people can go to for information, […] if they want to know anything they can go there and can also find regional items".

Prerequisites for successful implementation of telemedicine tools

For telemedicine to be used appropriately in the healthcare system, certain prerequisites must be met. These can be subdivided into two categories: user characteristics and organizational aspects.

First, participants named important characteristics of a person that are facilitators or barriers for successful use of telemedicine tools. Frequently mentioned barriers to the use of telemedicine include low digital literacy and advanced age. Also, specific PD-symptoms might hamper the use of telemedicine. For example, a person with PD might be unable to operate or understand remote monitoring tools when their fine motor skills or cognition is impaired. Another example is when reduced facial expression and speech impairments limit the use of video consultations. In contrast, some characteristics were mentioned as facilitators for the uptake of telemedicine, such as a proactive personality, high levels of independence and the presence of a care partner. Many participants expressed the concern that the barriers would outweigh the facilitators for people with PD in a more advanced stage, when palliative care is more typically recommended. Elaborate technical support was expected to overcome some of the barriers, but respondents also mentioned that for some people with PD telemedicine will just not be feasible.

Person with PD 11: "Also, not everyone is as digitally savvy, especially with people my age, but younger people are".

Specialist elderly care 4: "The people with Parkinson's that I see, so in the palliative phase, also have hallucinations. Can you distinguish whether that's your auditory hallucination talking to you? Or that it's your son sitting in the screen talking to you?"

Nurse 6: "Most patients were very young, 60 or 70. They were having a meeting with me and with the partner normally. So, both of them quite young and so they could manage with this technology thing. […] Sometimes, I have some couple, patient and care partner, and the son came and activated the personal computer, the meeting in Zoom and then he went away. So, the problem is that you need to have the technology, and you need somebody who can activate it for you if you

cannot do that. And that's the thing. I mean, not necessarily, the patient was dealing directly with technology, but he or she was supported by someone familiar to them".

Second, healthcare professionals and people with PD raised issues around the implementation of telemedicine tools into existing healthcare organizations, including privacy, ethical and financial issues. Privacy concerns were mentioned such as being continuously observed through remote monitoring tools, e.g., through watches or cameras, even when you are in a highly private setting. Also, participants feared data leaks, for example when they transferred a consultation report from one communication system to another. A prominent ethical concern that was raised was the use of telemedicine to increase efficiency to tackle capacity problems. On the one hand, telemedicine could help to reduce travel time and increase the number of people with PD a healthcare professional can visit. On the other hand, our healthcare professionals stated that they enjoyed working physically with people with PD and could provide the highest quality of care that way. Finding a right balance between efficiency, quality of care and work satisfaction is important for a sustainable long-term implementation of telemedicine. Finally, healthcare organizations often receive no structural financial compensation for the time and devices necessary for delivering telemedicine.

Person with PD 3: "Again, a video consultation, I am always afraid it [ACP-conversations] gets scattered or end up somewhere else or... You never know. And in a video call, I would never talk about it [ACP-related topics]. […] I did not think a video call was safe at all or... You hear a lot of weird stuff these days about hacking".

Speech therapist 5: "If I only had to give online speech therapy, it would certainly be to the detriment of my job satisfaction".

Movement disorder specialist 1: "[…] we really have a need for more capacity. And I think using phone and video is a way of increasing your capacity numbers of patients and number of visits. So, I think in that way, it's very good that we have that option. […] a visit to the outpatient unit is 30 minutes and a telephone call can also take longer than one thing, but mostly it's 10 to 15 minutes, you can cover the most important things on a phone or video".

Nurse 2: "I did say to our supervisor that we actually make an extra half hour every day anyway because of Siilo [healthcare chat system]. Every workday.

[…] And they also want us to communicate more with the primary care physician, with the office assistant, with home care, with physio".

Discussion

We investigated how and under what conditions telemedicine could support the delivery of palliative care for people with PD. The thematic analysis of the interview data showed that both healthcare professionals and people with PD prefer to discuss palliative care topics physically rather than remotely by phone or video call, as physical contact is regarded as more personal. However, communication through phone or video can bridge large geographical distances and can be more comfortable for the person with PD as they can feel more at ease in their own environment and do not have to travel. Therefore, a hybrid form was recommended by many participants: in-person when necessary and available, digital when possible. Furthermore, to gain a complete picture of the person with PD, healthcare professionals preferred physical examinations. Remote monitoring tools may complement the clinical picture of the person with PD in the future, but current opinions and experiences varied strongly between participants when considering the application of remote monitoring in palliative care. One of the most promising applications of telemedicine lays in intercollegiate communication between healthcare professionals. Healthcare professionals welcomed communication technology to improve collaboration and to share knowledge more easily, for example via asynchronous chat messengers, multidisciplinary video-based meetings and e-learnings. Participants from all groups desired better organized, trustworthy and up-to-date online information about palliative care directed to the person with PD and care partner. Finally, both user characteristics, e.g., digital illiteracy, and healthcare organization aspects, e.g., isolated communication systems, pose barriers to the sustainable deployment of telemedicine in palliative care. Below, we will discuss these findings in further detail.

Healthcare professionals providing palliative care aim to support people with PD by discussing emotionally loaden topics, such as what quality of life means for them, in what ways their disability can be relieved, and which future care directives they wish to record.[15] Logically, talking about such meaningful and sensitive topics can be difficult and confrontational for everyone involved. To accompany people with PD in this process, healthcare professionals need to rely heavily on *presence*.[42] Presence refers to a moment of standing still, reflecting on your own conceptions and opening up to the other, and using your full attention to become responsive to the other, to listen carefully

and to attune to the other person's experience of time.[42] By doing so, the healthcare professional creates a moment in which they can receive something from the person with PD, such as a story or a feeling. Our findings suggest that healthcare professionals and people with PD generally regard telemedicine as unsuitable to create this moment of presence. Communication through technology and the accompanying loss of physical presence were described as less personal and the technology hampered the ability to sense and feel the other, which is in line with other studies.[24,25,43,44] However, creating a moment of presence is also possible when people meet digitally. One nurse noted no marked differences between the palliative care conversations she had held physically or digitally, as she used the same skills to listen, accompany and counsel in both settings. Other healthcare professionals stated no preferred medium for palliative care conversations, as long as the medium was in line with the preferences of the person with PD. What seems to be important is the creation of a strong relationship between the person with PD and the healthcare professional in which all attention during a conversation is directed at the person instead of the technology.

The utility of remote monitoring tools for palliative care is heterogeneous. Many of our participants preferred to have conversations about palliative care topics rather than measuring them remotely through digital technology. At the same time, our participants named a plethora of to be monitored topics that would aid them in delivering better palliative care. These topics covered a broad range of motor and non-motor symptoms that were also identified in other studies not tailored to palliative care,[45,46] as well as broader topics such as quality of life, pain, and well-being. Despite this interest in a broad range of topics, the usage of the monitoring information elicited mixed reactions. Some participants praised the ability to optimize medication even in late-stage PD or to gain fine-grained information on time in bed, whilst others only saw additional load for an already overburdened population. These different reactions can partially be explained by the limited experiences with using remote monitoring tools in palliative care for people with PD and elderly in general.[28,47] Going forward, the field of PD might learn from the application of monitoring tools in other medical conditions, for example as trigger for healthcare actions.[28–31] Importantly, monitoring tools should be co-developed together with people with PD, their care partners and healthcare professionals to enhance their relevance and adoption.[48,49]

Telemedicine has the potential to enhance palliative care collaboration and education among healthcare professionals.[50] Remote communication systems such as secured chat messengers create the possibility for asynchronous communication, allowing for information exchange and alignment at times that are convenient for each healthcare professional individually.[22] Furthermore, by facilitating multidisciplinary

meetings through videoconferencing, telemedicine could support better integration of palliative care services[51], which is associated with an increased quality of life and reduced symptomatic burden.[8,10,52,53] Videoconferencing might be especially helpful when care needs become complex: more healthcare professionals from different institutions can get involved each with their own schedule and location.[14,16] Finally, telemedicine provides educational opportunities, such as e-learnings, to rapidly and efficiently spread knowledge about palliative care.[14] One study already showed an increase in self-rated palliative care knowledge when PD healthcare professionals followed an e-learning combined with an online network meeting with palliative care specialists.[54] Such easily accessible training programs form an excellent first step in enhancing large-scale palliative care knowledge.

Our findings focus on palliative care for PD, but show considerable overlap with 'regular' PD care as well. For example, remote video consultations were readily implemented, but after the COVID-pandemic many reverted back to physical visits when possible.[55] Remote monitoring tools are being developed across almost the entire PD disease span, yet the implementation of tools in clinical practice is still work in progress.[56] Also, beyond the field of palliative care, healthcare professionals welcome remote communication technology to enhance interprofessional collaboration.[57] General barriers to the implementation of telemedicine also apply to its implementation in palliative care,[58] such as on-going discussions regarding financial coverage of remote consultations [59,60] and inequalities in digital literacy.[61] Addressing such issues is essential for a feasible and sustainable implementation of telemedicine systems in future palliative care practice.

Strengths and limitations

A strength of our study is the extensive group of stakeholders that we interviewed. This diverse sample allowed us to examine our research question from an international multi-stakeholder perspective, covering as much as possible the variety of experiences and opinions regarding the topic. Furthermore, we leveraged the open and comprehensive nature of the interviews. The semi-structured interview enabled us to discuss a variety of relevant topics identified through the literature and to delve deeper into those topics that evoked elaborate or detailed opinions and experiences by the participants. However, our study was not without limitations.

First, in-practice experiences are rare for delivering PD palliative care through telemedicine. The knowledge about palliative care and PD is growing as is the use and implementation of telemedicine, especially in light of the COVID-19

pandemic.[62] Yet, both topics seem to be on a mostly individual developmental track. For example, many healthcare professionals, people with PD and care partners in our sample had experience with telemedicine in the form of remote consultations, but these consultations were often used for regular follow-up appointments. We tried to disentangle such general telemedicine experiences from those specific to palliative care as much as possible during both the interview and analysis.

Second, our sample might be slightly biased, for example towards people with PD, care partners and healthcare professionals who are comfortable with talking about palliative care in an interview or who are interested in the intersection of PD care and telemedicine. We were also unable to recruit people in the very advanced stages of PD as they were unable to communicate independently. At the least, our elaborate recruitment strategies seem to have been effective in reaching a diverse group of people in terms of years of experience with palliative care (**table 1**).

Finally, the concept of telemedicine itself also poses limitations on our work. Despite the definitions offered by, e.g., the WHO [19], telemedicine remains a broad term encompassing a multitude of applications. Our participants understood the concept differently, for example when discussing whether e-mail is a form of telemedicine or not. We provided each participant with the same written and verbal information regarding our definition of telemedicine, but always sought alignment with what the respective participant understood by it.

Future directions

In the future, the recognition of palliative care as an important pillar of optimal healthcare for people with PD will grow. Although limited for now, telemedicine can definitely have a role in supporting palliative care once the provision of palliative care has been established more profoundly. Several research avenues can be explored to amplify this process. For example, an ethical dilemma is posed by the fast-growing population of people with PD in an already overburdened healthcare system. Remote consultations could reduce travel time and increase efficiency, but they might negatively impact the quality of the care received as the potential to truly be with the person with PD is reduced.[42] Another topic requiring more research is the position and value of remote monitoring information within the healthcare system, e.g., how can we integrate objective sensor data with someone's subjective lived experience. Finally, providing online information that is trustworthy and accessible by all people with PD and care partners remains necessary. Together with people with PD, their care partners and healthcare professionals, platforms should be co-created and developed to spread reliable information to anyone regardless of their digital literacy.

References

1. Bach, J.-P., Ziegler, U., Deuschl, G., Dodel, R. & Doblhammer-Reiter, G. Projected numbers of people with movement disorders in the years 2030 and 2050: Prognosis on Prevalence of Movement Disorders. *Mov. Disord.* **26**, 2286–2290 (2011).
2. Dorsey, E. R., Sherer, T., Okun, M. S. & Bloem, B. R. The Emerging Evidence of the Parkinson Pandemic. *JPD* **8**, S3–S8 (2018).
3. Sveinbjornsdottir, S. The clinical symptoms of Parkinson's disease. *J Neurochem* **139 Suppl 1**, 318–324 (2016).
4. Coelho, M. *et al.* Late-stage Parkinson's disease: the Barcelona and Lisbon cohort. *J Neurol* **257**, 1524–1532 (2010).
5. Schrag, A. *et al.* The late stage of Parkinson's - results of a large multinational study on motor and non-motor complications. *Parkinsonism Relat Disord* **75**, 91–96 (2020).
6. Kluger, B. M. *et al.* Defining Palliative Care Needs in Parkinson's Disease. *Mov Disord Clin Pract* **6**, 125–131 (2019).
7. World Health Organization. *Palliative care.* Available from: https://www.who.int/news-room/fact-sheets/detail/palliative-care (2020).
8. Kluger, B. M. *et al.* Comparison of Integrated Outpatient Palliative Care With Standard Care in Patients With Parkinson Disease and Related Disorders: A Randomized Clinical Trial. *JAMA Neurol* **77**, 551–560 (2020).
9. Veronese, S. *et al.* Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: NE-PAL, a pilot randomised controlled study. *BMJ Support Palliat Care* **7**, 164–172 (2017).
10. Bock, M. *et al.* What's in the Sauce? The Specific Benefits of Palliative Care for Parkinson's Disease. *J Pain Symptom Manage* **63**, 1031–1040 (2022).
11. Katz, M. Telehealth increases access to palliative care for people with Parkinson's disease and related disorders. *Ann Palliat Med* **9**, S75–S79 (2020).
12. Lennaerts-Kats, H. *et al.* "No One Can Tell Me How Parkinson's Disease Will Unfold": A Mixed Methods Case Study on Palliative Care for People with Parkinson's Disease and Their Family Caregivers. *JPD* **12**, 207–219 (2022).
13. Lennaerts, H. *et al.* Palliative care for persons with Parkinson's disease: a qualitative study on the experiences of health care professionals. *BMC Palliat Care* **18**, 53 (2019).
14. Fox, S. *et al.* Interviews with Irish healthcare workers from different disciplines about palliative care for people with Parkinson's disease: a definite role but uncertainty around terminology and timing. *BMC Palliat Care* **15**, 15 (2016).
15. Boersma, I., Miyasaki, J., Kutner, J. & Kluger, B. Palliative care and neurology: time for a paradigm shift. *Neurology* **83**, 561–567 (2014).
16. Prizer, L. P. *et al.* A Mixed-Methods Approach to Understanding the Palliative Needs of Parkinson's Patients. *J Appl Gerontol* **39**, 834–845 (2020).
17. Lanoix, M. Palliative care and Parkinson's disease: managing the chronic-palliative interface. *Chronic Illn* **5**, 46–55 (2009).
18. Waldron, M., Kernohan, W. G., Hasson, F., Foster, S. & Cochrane, B. What Do Social Workers Think about the Palliative Care Needs of People with Parkinson's Disease? *British Journal of Social Work* **43**, 81–98 (2013).

19. World Health Organization. *Classification of Digital Health Interventions*. Available from: https://www.who.int/publications/i/item/WHO-RHR-18.06 (2018).
20. Finucane, A. M. *et al.* Digital health interventions in palliative care: a systematic meta-review. *npj Digit. Med.* **4**, 1–10 (2021).
21. Grimminger, S. *et al.* Palliative care as a digital working world (PALLADiUM) - A mixed-method research protocol. *BMC Palliat Care* **22**, 1–10 (2023).
22. May, S. *et al.* Digital technologies in routine palliative care delivery: an exploratory qualitative study with health care professionals in Germany. *BMC Health Serv Res* **22**, 1–12 (2022).
23. Wilkinson, J. R. *et al.* High patient satisfaction with telehealth in Parkinson disease: A randomized controlled study. *Neurol Clin Pract* **6**, 241–251 (2016).
24. Spear, K. L., Auinger, P., Simone, R., Dorsey, E. R. & Francis, J. Patient Views on Telemedicine for Parkinson Disease. *JPD* **9**, 401–404 (2019).
25. Shalash, A., Fathy, M., Dawood, N. L. & Hamid, E. Adopting Virtual Visits for Parkinson's Disease Patients During the COVID-19 Pandemic in a Developing Country. *Front. Neurol.* **11**, 582613 (2020).
26. Del Din, S., Kirk, C., Yarnall, A. J., Rochester, L. & Hausdorff, J. M. Body-Worn Sensors for Remote Monitoring of Parkinson's Disease Motor Symptoms: Vision, State of the Art, and Challenges Ahead. *JPD* **11**, S35–S47 (2021).
27. Cubo, E. & Delgado-López, P. D. Telemedicine in the Management of Parkinson's Disease: Achievements, Challenges, and Future Perspectives. *Brain Sci* **12**, 1735 (2022).
28. Bienfait, F., Petit, M., Pardenaud, R., Guineberteau, C. & Pignon, A. Applying M-Health to Palliative Care: A Systematic Review on the Use of M-Health in Monitoring Patients With Chronic Diseases and its Transposition in Palliative Care. *Am J Hosp Palliat Care* **37**, 549–564 (2020).
29. Pavic, M. *et al.* Feasibility and Usability Aspects of Continuous Remote Monitoring of Health Status in Palliative Cancer Patients Using Wearables. *Oncology* **98**, 386–395 (2020).
30. Tieman, J. J., Swetenham, K., Morgan, D. D., To, T. H. & Currow, D. C. Using telehealth to support end of life care in the community: a feasibility study. *BMC Palliat Care* **15**, 94 (2016).
31. Bonsignore, L. *et al.* Evaluating the Feasibility and Acceptability of a Telehealth Program in a Rural Palliative Care Population: TapCloud for Palliative Care. *Journal of Pain and Symptom Management* **56**, 7–14 (2018).
32. Perri, G.-A., Abdel-Malek, N., Bandali, A., Grosbein, H. & Gardner, S. Early integration of palliative care in a long-term care home: A telemedicine feasibility pilot study. *Palliat Support Care* **18**, 460–467 (2020).
33. Meinders, M. J. *et al.* Advance Care Planning and Care Coordination for People With Parkinson's Disease and Their Family Caregivers-Study Protocol for a Multicentre, Randomized Controlled Trial. *Front Neurol* **12**, 673893 (2021).
34. Tong, A., Sainsbury, P. & Craig, J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* **19**, 349–357 (2007).
35. Bloem, B. R. & Munneke, M. Revolutionising management of chronic disease: the ParkinsonNet approach. *BMJ* **348**, g1838–g1838 (2014).
36. Lennaerts-Kats, H. *et al.* "How Long Can I Carry On?" The Need for Palliative Care in Parkinson's Disease: A Qualitative Study from the Perspective of Bereaved Family Caregivers. *JPD* **10**, 1631–1642 (2020).
37. Fox, S. *et al.* Survey of Health Care Workers Suggests Unmet Palliative Care Needs in Parkinson's Disease. *Mov Disord Clin Pract* **2**, 142–148 (2015).

38. Fox, S. *et al.* Palliative care for Parkinson's disease: Patient and carer's perspectives explored through qualitative interview. *Palliat Med* **31**, 634–641 (2017).

39. Stern, A., Valaitis, R., Weir, R. & Jadad, A. R. Use of home telehealth in palliative cancer care: a case study. *J Telemed Telecare* **18**, 297–300 (2012).

40. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qualitative Research in Psychology* **3**, 77–101 (2006).

41. Scientific Software Development GmbH. Atlas.ti 8. Available from https://atlasti.com (2022).

42. Guité-Verret, A., Vachon, M. & Girard, D. Intentional presence and the accompaniment of dying patients. *Med Health Care Philos* **26**, 477-486 (2023).

43. Mulroy, E. *et al.* Telemedicine in Movement Disorders: Leçons du COVID-19. *Movement Disorders* **35**, 1893–1896 (2020).

44. Pigott, J. S. *et al.* Remote Consultations for People With Parkinson Disease and Cognitive Impairment: Interview Study With Patients, Caregivers, and Health Care Professionals. *JMIR Neurotech* **1**, e39974 (2022).

45. Evers, L. J. W., Peeters, J. M., Bloem, B. R. & Meinders, M. J. Need for personalized monitoring of Parkinson's disease: the perspectives of patients and specialized healthcare providers. *Front Neurol* **14**, 1150634 (2023).

46. Riggare, S., Scott Duncan, T., Hvitfeldt, H. & Hägglund, M. "You have to know why you're doing this": a mixed methods study of the benefits and burdens of self-tracking in Parkinson's disease. *BMC Med Inform Decis Mak* **19**, 175 (2019).

47. Sandic Spaho, R., Uhrenfeldt, L., Fotis, T. & Kymre, I. G. Wearable devices in palliative care for people 65 years and older: A scoping review. *Digit Health* **9**, 20552076231181212 (2023).

48. Wannheden, C. & Revenäs, Å. How People with Parkinson's Disease and Health Care Professionals Wish to Partner in Care Using eHealth: Co-Design Study. *J Med Internet Res* **22**, e19195 (2020).

49. Kenny, L. *et al.* The Views and Needs of People With Parkinson Disease Regarding Wearable Devices for Disease Monitoring: Mixed Methods Exploration. *JMIR Form Res* **6**, e27418 (2022).

50. Funderskov, K. F. *et al.* Telemedicine in specialised palliative care: Healthcare professionals' and their perspectives on video consultations—A qualitative study. *Journal of Clinical Nursing* **28**, 3966–3976 (2019).

51. Bock, M. A. *et al.* Does a novel community-based outpatient palliative care intervention for Parkinson's disease and related disorders improve care? Qualitative results from patients and care partners. *Palliat Med* **38**, 240–250 (2024).

52. Fleisher, J. E. *et al.* IN-HOME-PD: The effects of longitudinal telehealth-enhanced interdisciplinary home visits on care and quality of life for homebound individuals with Parkinson's disease. *Parkinsonism & Related Disorders* **102**, 68–76 (2022).

53. Kluger, B. M. *et al.* Patient and Family Outcomes of Community Neurologist Palliative Education and Telehealth Support in Parkinson Disease. *JAMA Neurol* **81**, 39 (2024).

54. Lennaerts-Kats, H. *et al.* The Effect of a Multidisciplinary Blended Learning Program on Palliative Care Knowledge for Health Care Professionals Involved in the Care for People with Parkinson's Disease. *JPD* **12**, 2575–2584 (2022).

55. Goetz, C. G. & Stebbins, G. T. Is Telemedicine the New Normal or Is the Office Visit Still the Movement Disorder Option of Choice? *Movement Disorders* **36**, 1481–1482 (2021).

56. Espay, A. J. *et al.* A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Movement Disorders* **34**, 657–663 (2019).

57. Bloem, B. R. *et al.* Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology* **19**, 623–634 (2020).

58. Laar, A., Silva de Lima, A. L., Maas, B. R., Bloem, B. R. & De Vries, N. M. Successful implementation of technology in the management of Parkinson's disease: Barriers and facilitators. *Clinical Parkinsonism & Related Disorders* **8**, 100188 (2023).

59. Mehrotra, A. & Uscher-Pines, L. Informing the Debate about Telemedicine Reimbursement - What Do We Need to Know? *N Engl J Med* **387**, 1821–1823 (2022).

60. Hughes, H. K., Hasselfeld, B. W. & Greene, J. A. Health Care Access on the Line - Audio-Only Visits and Digitally Inclusive Care. *N Engl J Med* **387**, 1823–1826 (2022).

61. Nimmons, D. *et al.* Exploring the experiences of people and family carers from under-represented groups in self-managing Parkinson's disease and their use of digital health to do this. *Digit Health* **8**, 205520762211022 (2022).

62. Hassan, A. *et al.* Global Survey on Telemedicine Utilization for Movement Disorders During the COVID -19 Pandemic. *Movement Disorders* **35**, 1701–1711 (2020).

4

Usability and utility of a remote monitoring system to support physiotherapy for people with Parkinson's disease

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Abstract

Background

Physiotherapy for persons with Parkinson's disease (PwPD) could benefit from objective and continuous tracking of physical activity and falls in daily life. We designed a remote monitoring system for this purpose and describe the experiences of PwPD and physiotherapists who used the system in daily clinical practice.

Methods

Twenty-one PwPD (15 men) wore a sensor necklace to passively record physical activity and falls for six weeks. They also used a smartphone app to self-report daily activities, (near-)falls and medication intake. They discussed those data with their PD-specialized physiotherapist (n=9) during three regular treatment sessions. User experiences and aspects to be improved were gathered through interviews with PwPD and physiotherapists, resulting in system updates. The system was evaluated in a second pilot with 25 new PwPD (17 men) and eight physiotherapists.

Results

We applied thematic analysis to the interview data resulting in two main themes: usability and utility. First, the *usability of the system* was rated positively, with the necklace being easy to use. However, some PwPD with limited digital literacy or cognitive impairments found the app unclear. Second, the perceived *utility of the system* varied among PwPD. While many PwPD were motivated to increase their activity level, others were not additionally motivated because they perceived their activity level as high. Physiotherapists appreciated the objective recording of physical activity at home and used the monitoring of falls to enlarge awareness of the importance of falls for PwPD. Based on the interview data of all participants, we drafted three user profiles for PwPD regarding the benefits of remote monitoring for physiotherapy: for profile 1, a monitoring system could act as a flagging dashboard to signal the need for renewed treatment; for profile 2, a monitoring system could be a motivational tool to maintain physical activity; for profile 3, a monitoring system could passively track physical activity and falls at home. Finally, for a subgroup of PwPD the burdens of monitoring will outweigh the benefits.

Conclusions

Overall, both PwPD and physiotherapists underline the potential of a remote monitoring system to support physiotherapy by targeting physical activity and (near-)falls. Our findings emphasize the importance of personalization in remote monitoring technology, as illustrated by our user profiles.

Background

Parkinson's disease (PD) is the fastest growing neurological movement disorder affecting approximately 7 million people worldwide.[1,2] The disease can cause a wide range of motor and non-motor symptoms, such as slowness of movement, tremor, falls, rigidity, cognitive dysfunction, and anxiety. Medical treatment can ameliorate various symptoms, but the complex nature of the disease necessitates multidisciplinary care management.[3] One important professional discipline is physiotherapy. Within physiotherapy, persons with PD (PwPD) learn how to safely maintain activities of daily life, remain their physical capacity, and train their balance and gait.[4,5]

Important management targets for the physiotherapist are physical activity and fall incidents.[4] Physical activity is important to preserve physical capacity and functioning, which are both necessary to continue activities of daily life.[6,7] Performing high-intensity physical activities may even slow down disease progression by stimulating neuroplasticity.[8,9] However, many PwPD remain or become physically inactive due to problems with gait, balance, and physical functioning.[10,11] Fall incidents are also important because they can negatively impact a person's quality of life[12]; for example by instilling a fear of renewed falls, or by causing a (hip) fracture.[13–15] A vicious cycle between physical activity and fall incidents can occur when a fear of falling leads to reduced physical activity,[16] and reduced physical activity leads to increased fall risk because of general weakness.[12] Conversely, promoting physical activity through a therapeutic exercise regime may paradoxically increase falls, which by definition occur more often in those who are physically more active.

Accurate assessment of physical activity and falls during common daily activities would be a tremendous help for the physiotherapist to create individually tailored treatment plans. For example, a fall caused by festination requires a different treatment plan than a fall caused by muscle weakness. Usually, physical activity and falls are assessed with short questionnaires, in-clinic motor tasks, or self-reports.[4,12] However, in-clinic physical assessments often give a false impression as PwPD typically behave differently in the clinic than in their own homes.[17,18] Self-reports or questionnaires can also be burdensome and are subject to recall bias, and even more so among those with coexistent memory or other cognitive problems.[19,20]

By contrast, wearable sensor data can provide accurate, continuous, and objective information to support physiotherapy. Wearable sensors often exist of accelerometers

and gyroscopes which are unobtrusively packed in, e.g., smartwatches and smartphones.[21] Their size and shape make them a feasible option to be worn in daily life.[22] Even for prolonged periods, ranging from 6 weeks up to two years, excellent compliance can be achieved with monitoring PD using a smartwatch or sensor.[23–25] Additionally, wearable sensors can be used to quantify both physical activity and falls in daily life.[26–28] Despite their feasibility and accuracy, only a few studies have tested the application of wearable sensors in physiotherapy practice. Preliminary findings show that it is feasible to capture sensor data during in-clinic training sessions and that the data can support balance training through sensor based biofeedback.[29,30] Furthermore, physical activity training could be remotely supervised by streaming vital sign data to a tele-coach.[9,31] However, to advance implementation in clinical practice, more studies are needed in which both physical activity and falls data are combined into a single system that is rigorously tested in everyday life.

In this study, we designed a remote monitoring system for physical activity and falls. The system consisted of a necklace tracking movement, an app for PwPD to review recorded activities and manually add undetected ones, and a physiotherapist app to review any incoming data. We evaluated the usability and utility of the system to support physiotherapy for PwPD. We employed an iterative design process in which we closely collaborated with both physiotherapists and PwPD and tested the system twice in-practice for six weeks.

Methods

Study design and participants

In an iterative process, we developed and evaluated a remote monitoring system consisting of a wearable sensor and mobile app, further described under "Materials". The study consisted of two pilots which were one year apart (2017 and 2018) and which spanned six weeks each. In both pilots, PwPD used the remote monitoring system and discussed the collected data during three regular treatment sessions with their physiotherapist. Before pilot 2, the system was updated according to user feedback from pilot 1.

Pilot 1 included nine physiotherapists and pilot 2 included eight physiotherapists, one of whom also participated in pilot 1. We recruited the physiotherapists via ParkinsonNEXT, an online platform that facilitates research participation for healthcare professionals and PwPD in the Netherlands. Physiotherapists were eligible if they were members of ParkinsonNet, a network of healthcare professionals specialized in PD.[32]

Subsequently, the included physiotherapists recruited PwPD from their own practice. The inclusion criteria for PwPD in pilot 1 and 2 were largely similar. For both pilots, participants needed to be diagnosed with PD by a neurologist or movement disorder specialist, be at least 30 years of age, receive physiotherapy for PD for at least four weekly sessions within six weeks after study enrolment. In pilot 1, we aimed to include 20 PwPD who were required to own and (cognitively) be able to use a smartphone with Android operating system ≥ 5.0. In pilot 2, we aimed to include 25 PwPD of whom 20 were required to own or use a smartphone and five were not. These five PwPD could test the wearable sensor without the smartphone app. Amongst these 25 PwPD, we aimed to include at least 10 PwPD who had fall or balance problems, as judged by the physiotherapist.

The study was conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki and was approved by the local ethics committee (CMO regio Arnhem-Nijmegen; file 2017-3382). All participants gave written informed consent prior to enrolment. We adhered to the Consolidated Criteria for Reporting Qualitative Research checklist for reporting the qualitative part of our study.

Materials

The remote monitoring system, i.e., the Vital@Home system, consisted of a wearable sensor in the form of a necklace (the "GoSafe"), a Wi-Fi hub, a custom developed Android smartphone app for PwPD, and a custom developed Android tablet app for physiotherapists. We created a first prototype of this system based on recommendations for physiotherapy in PD,[4] prior experiences with wearables and physiotherapy within the research team, as well as technical feasibility. For the latter, four PwPD used this first prototype at home for two weeks to pilot test the interaction with the patient app. Consequently, we made minor adjustments in the user interface to improve the usability. Then, the system was evaluated in the two pilots reported here. Below, we describe the system as it was used in pilot 1. **Table 1** describes the changes made to the system after pilot 1 and the desired changes to the system mentioned in pilot 2.

The GoSafe necklace

The GoSafe necklace (**figure 1**; Philips Lifeline, Framingham, MA, USA) is a wearable sensor that is commercially available in the United States as part of a medical alert service. The necklace contains multiple sensor types, including an accelerometer, barometer, and GPS sensor. We derived the person's physical activity and fall incidents from the sensor data using proprietary algorithms developed by Philips

Research.[33,34] The algorithm is based on continuously collected accelerometer data and walking bouts of at least 10 minutes. Fall incidents were detected based on continuously collected accelerometer and barometer data. Data collected with the GoSafe were streamed via the Wi-Fi hub to a secured Amazon server located in Germany, managed by Philips. The GoSafe necklace has received FDA approval. A European Declaration of conformity was provided for use in this study.

Figure 1. The Philips Lifeline GoSafe necklace.

Vital@Home patient and physiotherapist apps

The Vital@Home apps were developed as part of a European Institute of Innovation & Technology (EIT) funded collaboration between TU Berlin, Curamatik, Radboudumc, Philips Research, and University College London. The display language of both apps was Dutch for the current study, although an English version was also available.

The app for PwPD ran on an Android smartphone and contained three sections: physical activities, falls, and medication intake (**figure 2**). For physical activities, the app provided an overview of all gait bouts detected by the GoSafe necklace. In addition, users were encouraged to manually enter sports activities that were not automatically detected, such as cycling or swimming. For all manually entered activities, users were asked to report the type, duration, and level of exertion using the BORG Rating of Perceived Exertion scale.[35] The app gave feedback on how close users were to reaching their daily and weekly activity goals. These activity goals were determined by the PwPD and physiotherapist together based on clinical judgment and personal preferences. The app automatically prompted the participant with a questionnaire at the end of the day (18:00 hrs) asking for verification of any detected fall and followed up with questions about the context of the fall incident. These questions were based on the falls diary included in the European Physiotherapy Guideline for Parkinson's Disease [4] and included questions about the self-perceived cause of the fall incident, environment, and motor state (off/on/on with dyskinesias). Also, users could manually start this questionnaire at any time of the day to register near-falls or falls. Users could also manually register their medication intake during the day. All the gathered information was accessible to the PwPD in the app.

The app for physiotherapists ran on an Android tablet and could display the information from their client during a treatment session. The physiotherapist app contained an overview of all recorded physical activities and the progression towards the weekly goals. It also showed the number of (near-)falls and the answers to the fall-context questionnaire. The app displayed patterns over time, but could also show individual registrations of physical activities and falls. The physiotherapist could only access the sensor data during the treatment session by using the physiotherapist app to scan a QR code displayed on the app of the PwPD. For pilot 2, some participants did not use the app so their physiotherapist could always see the data.

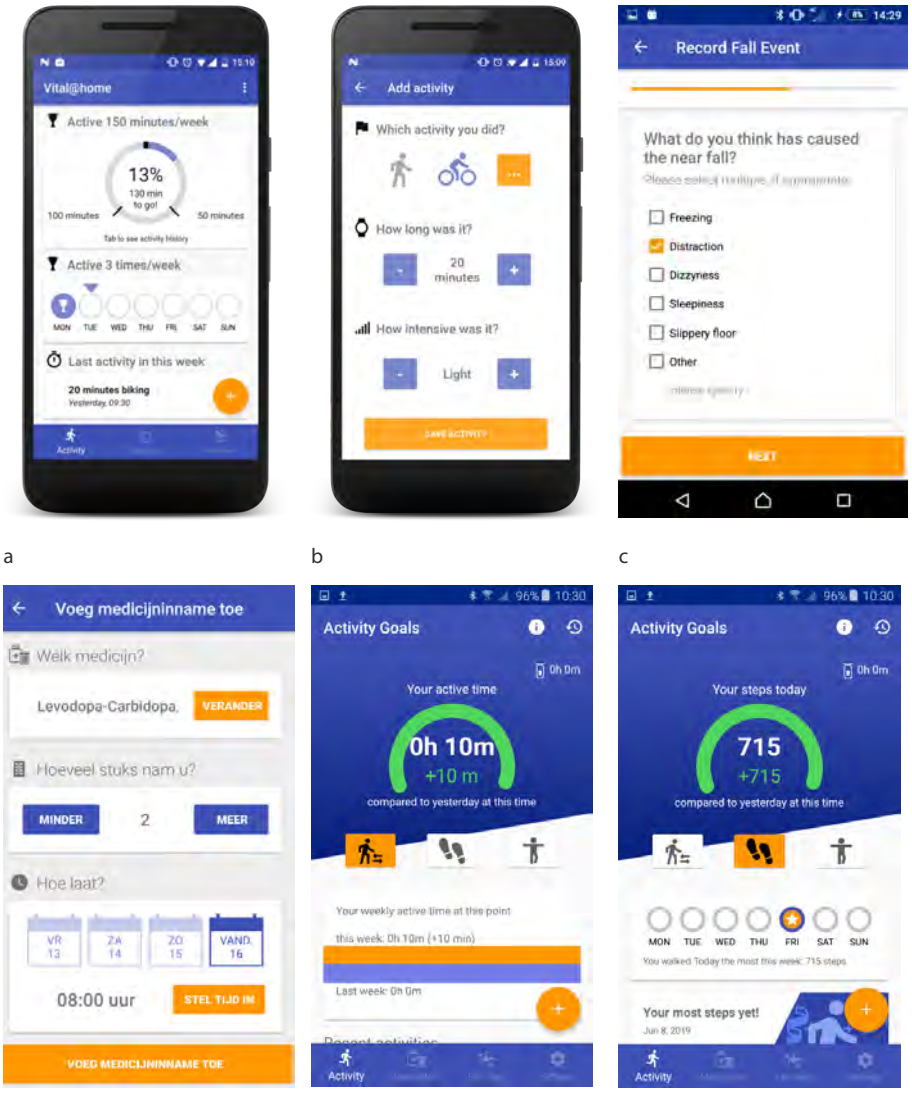

Figure 2. The Vital@Home application for persons with PD in pilot 1 (a-d) and pilot 2 (e-f), including the homepage of the app displaying progress towards physical activity goals (a), the manual entry of activities (b), a part of the fall questionnaire (c), the medication registration (d), and the reworked activity (e) and step count (f) homepage for pilot 2. Translation of 2d. Top: Add medications; Questions in the middle: Which medication? How many did you take? At what time?; Bottom: Confirm medication intake.

Table 1. The features of the Vital@Home system across both pilots as well as desired future features.

	Pilot 1	Added in pilot 2	Future wishes
Physical activity	• Walking detected • Self-report others • Progress towards physical activity goals displayed	• Feedback on wearing compliance • Number of steps displayed	• Detect more diverse activities (biking, household, swimming), less self-report • Detect activities shorter than 10 min • Assign intensity level to all activities • Personalized activity goals • Real-time data transmission to the app
Falls	• Daily questionnaire at 18:00 • Manual report during the day through app	• Falls detected by necklace • Daily questionnaire only when fall detected • Feedback on step time and step time regularity to assess fall risk • Freezing of gait diary	• Automatic alarm when wearer does not respond • Balance measurement • Elaborate fall risk assessment based on algorithms • Automatic FOG detection • Daily life gait and transfer analysis extended (e.g., stride length, walking speed)
Medication	• Daily manual medication registration	• Option to enter daily medication scheme and set reminders • Option to report individual medication intakes by responding to medication reminders	• Personally adjustable medication dose • All manual registrations can be corrected
Additional features		• Personal exercise program	• More in-person guidance and support on operating the system • Option to comment on data, e.g., *moved less because of bad weather*
Technical components	• Necklace • Wi-Fi hub • V@H patient app • V@H physio app	• Necklace • Wi-Fi hub • V@H patient app (optional) • V@H physio app	• Necklace or smartwatch (choice) • No Wi-Fi hub • V@H app (optional)

Procedures

The procedures for each pilot were largely similar. In both pilots, physiotherapists were recruited and trained on study procedures, study assessments, and usage of the Vital@Home system. Then, each physiotherapist recruited two or three PwPD within their own practice. These PwPD were scheduled to have at least four weekly physiotherapy sessions after study enrolment. Participants were prospectively followed for at least four weeks with a maximum of six weeks. During the first study visit, physiotherapists conducted a clinical assessment (see "Outcomes and analyses") and instructed PwPD on the usage of the Vital@Home system. After the first study visit, the PwPD wore the necklace at home during the day and charged it during the night. Preferably, a minimum of eight hours of sensor data were collected per day to provide enough information. The PwPD and physiotherapist discussed the collected information during three consecutive treatment visits. A member of the research team was available for technical support throughout the study duration.

After the fourth visit, a researcher interviewed each physiotherapist face-to-face and each PwPD via telephone for 20-40 minutes to capture their experiences using the Vital@Home system. LE (male) and AS (female, both PhD students) conducted all interviews after receiving qualitative interviewing training. There was no relationship between the interviewer and the participants prior to the interview, except for any contact necessary for enrolment and participation in the study. The interviews were semi-structured meaning that the interviewer used a guide to conduct the interview but was free to diverge from the guide and go more in-depth when the interviewee expressed an interesting or elaborate opinion on a topic. The guide covered five topics: general experiences of using the system including future wishes, usability of specific features, utility of specific features, technical functioning, and reliability of the registrations. The interviews were audio recorded and transcribed verbatim. PwPD also completed an online version of the System Usability Scale.[36]

Based on the results of pilot 1, improvements and new features were implemented in the Vital@Home apps (**Table 1**). The updated version of the app was tested in pilot 2 with another group of physiotherapists and PwPD. One physiotherapist and two PwPD participated in both pilots. All participants in pilot 2 adhered to the same procedure as in pilot 1 to test the system in practice. The only three differences were: the updated system version, PwPD wearing the necklace also at night, and the GoSafe-only option for participants without a smartphone. In pilot 2, participants charged the necklace whenever needed instead of specifically during the night. **Figure 3** gives an overview of the study procedures and collected data.

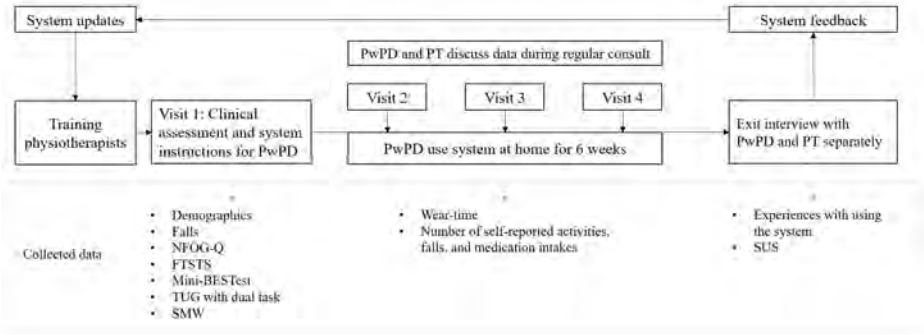

Figure 3. Overview of study procedures and measured outcomes. The procedures were completed twice. PT: physiotherapist. PwPD: person with Parkinson's disease. NFOG-Q: New Freezing of Gait Questionnaire, self-reported amount of FOG moments in the past month. FTSTS: Five Times Sit To Stand, measures balance during transfers. Mini-BESTest: Mini Balance Evaluation Systems Test, measures static and dynamic balance. TUG: Timed Up & Go, measures functional mobility. SMW: Six Meter Walk, measures comfortable walking speed, for pragmatic reasons shortened version of 10 Meter Walk. SUS: System Usability Scale, measures perceived usability of the system.

Outcomes and analyses

In both pilots, we collected demographic and clinical assessment data of PwPD to characterize our sample. The assessments were performed by physiotherapists during the first study visit and included a falls history, the Mini-BESTest including the Timed up and Go with and without dual task,[37] the presence of freezing according to the New Freezing Of Gait Questionnaire,[38] the Five-Times-Sit-To-Stand test to assess balance and fall risk,[39] and the Six Meter Walk test to measure comfortable walking speed, which, for pragmatic reasons, is a shortened version of the 10 Meter Walk test.[4]

As the primary outcome measure, we report the qualitative experiences of PwPD and physiotherapists who used the system. We applied a thematic analysis to the anonymized transcripts of the interviews with PwPD and physiotherapists.[40] First, two researchers read all transcripts and independently coded meaningful sections of the first 20 interviews. Any discrepancies between the coded segments were discussed and resolved. Subsequently, each researcher independently coded half of the remaining interviews which were checked by the other. We coded deductively based on five themes derived from the interview guide: usability, utility, technical functioning, reliability of the registrations, and suggestions for improvement. However, we also allowed for new themes to be inductively identified in the data. We generated non-overlapping themes and subthemes based on our deductive and inductive coding process aiming for internally consistent themes that each

captured a unique aspect of the dataset. We constantly compared new codes and themes against codes and themes we already had and periodically went back to our already created codes and themes. We discussed the phrasing and content of themes as well as the thematic structure within the research group to ensure the high quality of the work. We kept track of the analytical process and researcher decisions with memos. The research team agreed upon the final version of the thematic structure. ATLAS.ti version 8 was used for the qualitative analysis.[41]

As secondary outcome measures, we collected data on compliance in two forms: the number of days with at least eight hours of sensor data collected across the minimal study duration of 28 days, and the number of self-reports entered in the app. We also computed the score on the system usability scale (SUS, range: 0-100).[36] We report descriptive statistics of sample characteristics, compliance, and SUS as calculated with R Statistical Software v4.1.3.[42,43]

Finally, we drafted user profiles based on the interviews to understand when, why, and for whom the monitoring system can add value. User profiles represent typical user' characteristics such as skills, motivations, behaviours, needs, and goals of the users.[44] They capture common patterns or similarities in these characteristics to create a better understanding of system users. During the interviews, physiotherapists were asked for which patient population they thought the system would add value. We corroborated their answers with the interview data from PwPD, which contained information on the user profile domains. The first author drafted a first outline of the user profiles by grouping participants based on the interview data regarding digital literacy, behaviours, needs of the person, and the perceived utility of the system. Thereby, the user profiles were grounded in recurrent statements across interviews with participants. The profiles were then discussed with other members of the research team (LE, NdV, MM, RvdM) until consensus was reached.

Results

We included nine physiotherapists and 21 PwPD in pilot 1 and eight physiotherapists and 25 PwPD in pilot 2. Eleven out of the 25 PwPD in pilot 2 used the GoSafe only, either because they did not possess a smartphone (n = 6) or their smartphone version was not compatible with the app (n = 5). In pilot 1, three PwPD dropped out during the study because the system was too complicated for them. They were included in the interview. No PwPD dropped out during pilot 2. **Table 2** shows the demographic and clinical characteristics of all PwPD.

Table 2. Demographic and clinical characteristics of the persons with Parkinson's disease participating in the two consecutive pilot studies. Data are presented as mean ± SD or n (%), except for time since diagnosis (median and range). Calculations are based on valid data.

	Unit of measurement	**Pilot 1 n = 21**	**Missing (n)**	**Pilot 2 n = 25**	**Missing (n)**
Gender	*No. of men*	15 (71%)	0	17 (68%)	0
Age	*Years*	65.5 ± 8.0	0	68.7 ± 9.4	0
Hoehn and Yahr stage	*≤2*	5 (50%)	11	15 (83%)	7
	3	5 (50%)		2 (11%)	
	≥4	0 (0%)		1 (6%)	
Time since diagnosis	*Years*	3.5 (1-17)	11	*	25
Medication usage	*Levodopa*	20 (95%)	0	23 (92%)	0
	Dopamine agonist	8 (38%)		2 (8%)	
	Other	5 (24%)		2 (8%)	
Experienced ≥1 near fall(s) in past 12 months	*Yes*	1 (5%)	2	13 (59%)	3
Experienced ≥1 fall(s) in past 12 months	*Yes*	4 (20%)	1	16 (64%)	0
Experienced freezing of gait (NFOG-Q)	*Yes*	6 (29%)	0	6 (24%)	0
FTSTS	*Time (seconds)*	12.5 ± 4.6	0	13.7 ± 4.9	1
Mini-BESTest	*Average score*	24.1 ± 3.6	3	22.8 ± 4.2	3
	Score ≤22	5 (28%)		9 (41%)	
TUG with dual task	*Time (seconds)*	12.5 ± 5.7	0	13.2 ± 12.2	0
SMW	*Walking speed m/s*	1.30 ± 0.33	0	1.21 ± 0.24	0

NFOG-Q: New Freezing of Gait Questionnaire, self-reported amount of FOG moments in the past month. FTSTS: Five Times Sit To Stand, measures balance during transfers. Mini-BESTest: Mini Balance Evaluation Systems Test, measures static and dynamic balance; scores ≤22 indicate significant balance problems. TUG: Timed Up & Go, measures functional mobility. SMW: Six Meter Walk, measures comfortable walking speed. SD: Standard Deviation. * Not assessed during pilot 2

Compliance with wearing the sensor varied considerably in pilot 1, with 9 participants having 15 or fewer compliant days out of 28, whilst 10 participants had more than 21 compliant days (2 missing, **figure 4**). In pilot 2, compliance was higher with 22 out of 25 participants having 21 or more compliant days (1 missing, **figure 4**). In pilot 1, PwPD created 1893 medication reports and reported 30 (near-)falls in six weeks (at the time of writing, this data was unavailable for pilot 2). The SUS score among PwPD was higher in pilot 1 ($M = 63$, $SD = 16$) compared to pilot 2 ($M = 54$, $SD = 25$).

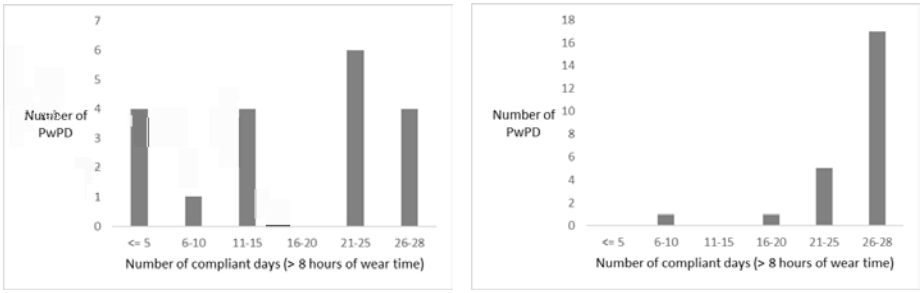

Figure 4. Frequency distribution of the number of compliant days for all persons with Parkinson's disease (PwPD) wearing the GoSafe necklace in pilot 1 (left) and pilot 2 (right).

User experiences with the system

Initially, we started the qualitative analysis with five themes. However, throughout the analytical process, we identified two themes that best characterize the users' experiences with the system: the usability of the system and the utility of monitoring information. Statements regarding technical functioning and reliability of the registrations gave context to the usability and utility, but were not clearly demarcated themes on their own. The future wishes are separately listed within the overview of system features (**table 1**). Some are also highlighted under subthemes when applicable. Quotes illustrating the subthemes are given in-text and in **table 3**. The results of pilot 1 and 2 are jointly discussed as feedback was highly comparable.

Usability of the system

The usability of the system, i.e., its ease of use, was overall rated positively. We identified three subthemes that characterize this theme. First, participants described how they *operated the system in daily life*. Most PwPD mentioned that wearing the necklace was not burdensome. Some found the cord annoying, especially during the night, but most PwPD were positive about its ease of use. While most PwPD were not bothered by the necklace being visible to others, some left the necklace at home when they left the house as to not raise any questions. In the future, the necklace's battery life of this prototype should be increased and fluctuate less, as these fluctuations

made participants uncertain about how long the battery would last that day. A clear indicator of the remaining battery life could take away much of this uncertainty.

> *Pilot 1 PwPD 1: You get up in the morning and after showering you put it around your neck and forget about it*

> *Pilot 1 PwPD 2: Look, but if you go among people then, well, I leave it [the necklace] at home pretty quick. Then I say it has worked enough for today. […] you also don't want to make yourself look more disabled than you already are.*

> *Pilot 1 PwPD 3: So if it was charged then it was a constant green light, but then you don't know if it's really already properly charged and with a smartphone you can just see how full it is.*

The Wi-Fi hub, necessary for data transfer, puts little strain on the PwPD and their caregivers as it was often permanently placed in the charger and required little further attention. Participants were instructed to carry the hub with them when leaving the house for 3+ hours, which was no problem for most of them.

The user interface of the app was regarded as very clear, intuitive, and user friendly by both PwPD and physiotherapists. Only a few PwPD had issues with understanding the different screens.

> *Pilot 1 physiotherapist (PT) 1: That's a clear screen. Yes, clear. At a glance you could see that.*

However, many PwPD from pilot 1 mentioned that registering their medication intake in the app was not user-friendly. For example, medications had to be entered manually each day and mistakes were not correctable. In pilot 2, the medication function was thoroughly revised so that a medication schedule was repeated throughout the weeks which could be confirmed with a single button, only requiring deviant medication intakes to be manually entered. Also, automatic reminders of medications were sent. As many PwPD have stable medication schemes, this was experienced as very helpful.

> *Pilot 2 PwPD 1: But the drugs on the other hand that was great. (What was good about that?) Well pre-programming of course with time. It's just confirming and that's it. Last year I think you had to fill everything in again.*

The second subtheme regarding the usability of the system was the importance of the *digital literacy* of the participants and the *support* offered by the environment. In pilot 1, all participants had to manage the necklace, hub, and the app, which was no problem for technically adept participants. However, some PwPD and physiotherapists struggled with the technology. For example, they did not understand when the devices were connected to each other and how they could see that. The technical support offered throughout the study was appreciated and used by participants. Assistance of the partner also helped to retain less digitally skilled PwPD in the study.

> *Pilot 1 PwPD 4: I was stuck with the fact that those things made a lot of mistakes in the beginning, it was all uncomfortable. And I didn't understand yet how it all fits together logically. That just takes a few days to get used to.*

> *Pilot 1 PwPD 5: It is more difficult for older people. They already have problems with a computer, so sometimes you don't understand it, or something. But yes, you can call you, you can call the physiotherapist. So you do have enough backing if you want to know something.*

Despite the offered support, the system proved too difficult for some PwPD due to suspected cognitive impairments and insufficient experience with digital technology. For example, an older caregiver mentioned that monitoring the connection of the Wi-Fi-hub as well as the battery of the necklace and smartphone was too much to manage at the same time.

> *Pilot 2 partner of PwPD 2: I once looked in the beginning [in the app], but you know? Our age is pretty high. We're 79 and 80, so we didn't grow up with all that stuff. [...] also with keeping an eye on the fact that it has to be charged. Then there are three different things - your phone and the device and the Wi-Fi - that you have to keep an eye on. [Partner] can't do that anyway, but anyway, you're often busy with all sorts of things and then you forget about it.*

Finally, participants mentioned *technical prerequisites* as being important for the usability of the system, such as data being accurate, automatically recorded, and correctable. The participants stated that the system accurately detected walking activities. However, the system required other activities such as housekeeping and cycling on a home trainer to be manually entered. The possibility to manually register non-detected activities was valued by some participants, but was typically experienced as burdensome as participants continuously had to remember the

duration and intensity of their activities. Furthermore, PwPD could make mistakes when manually entering activities and medication intakes. For example, sometimes the data transfer from the sensor to the app spanned more than a day, making PwPD believe that the activity had not been recorded. They would manually enter the activity which resulted in double registration of activities once the sensor data became visible. PwPD could not correct these mistakes which caused some frustration. In the future, PwPD desired the automatic detection of more diverse activities and real-time data transfer.

> *Pilot 1 PwPD 6: Initially in the first week I entered my own walks, because it didn't indicate that. But after a week, then all of a sudden it was all in there, with the result that it was all in there twice of course*

> *Pilot 1 PwPD 3 and partner: We still do as much or as little [...] because then that app says if I fill it in wrong then that round was closed again and then it said: completed. And then I think: yes, that is nonsense actually because that is not correct at all.*

Utility of monitoring information

The utility, i.e., added value, of the monitoring information can be described by three subthemes. First, the monitoring of *physical activity* elicited mixed reactions by PwPD and physiotherapists. Some PwPD stated that tracking physical activity was not adding value to them because they were already aware of how active they were. Also, several PwPD and physiotherapists stated that the data lacked detail to draw strong conclusions from. For example, some PwPD mentioned that walking up and down the stairs was quite challenging for them. They wondered why such short bouts of activities were not displayed in the app.

> *Pilot 1 PwPD 7: No, because in that situation [daily life] I think I know what I'm moving and what I'm doing, I still work fulltime, so I know exactly what I'm doing and what not.*

> *Pilot 2 PT 1: And certainly in this target group, I think, because I think that for some people, for example, walking for eight minutes can be quite a lot and if that doesn't actually count, then that's a shame. Then it actually works against them, so to speak.*

In contrast, numerous PwPD stated that the system motivated them to move more. Seeing their data made them aware of their activity levels and motivated them to

reach their weekly goals by becoming more active. Some participants even became so enthusiastic about tracking their physical activity that they, after the study had ended, bought commercially available smartwatches to continue self-monitoring. For some physiotherapists, the objective data formed a pleasant confirmation of the assumed physical activity level of the PwPD at home. In pilot 2, a video-based exercise section was added to the patient-app (**table 1**) so that PwPD could have video-examples of how to exercise at home. The exercises were purely informative and not specifically monitored as our study was not concerned with the remote delivery of physiotherapy sessions. The exercise-examples in the app were appreciated by some PwPD and a couple of physiotherapists found it useful to see which at home exercises were being completed. However, this feature held limited utility as many PwPD already knew how to complete the exercises or were using a different app provided by the physiotherapist.

> *Pilot 1 PwPD 8: Yes, it certainly works, it certainly works for me. Yes, really, because then you are forced to face the facts, you think: yes, I must exercise more. Because you sometimes postpone it because you often have difficulty with it, because walking is sometimes more difficult for me. Also because your balance is not so good anymore, and then you think: yes, it is best for me actually, that I do it, to move.*

> *Pilot 2 PwPD 3: Well, I bought myself a wristband now [...] Because if I haven't moved enough, it means I have to walk around the block in the evening, because I plan to take so many steps a day.*

> *Pilot 1 PT 2: It does add that you get confirmation if someone is indeed exercising, if someone is moving or not.*

Second, the monitoring of *falls* was mentioned as being important by both physiotherapists and PwPD. One advantage was that PwPD were made more aware of the importance of (near-)falls. Also, physiotherapists liked the insight into the context and timing of a fall, e.g., knowing how physically active people were or linking the fall to medication intake. However, the fall-related section of the system was not relevant for many PwPD, as they did not experience any (near-)falls during the six weeks use of the system.

> *Pilot 1 PT 3: But with that fall agenda, I found that, just to make people already aware of those near-fall incidents... because you do mention that, but ... much more often consciously, like, 'oh, if I fall backwards or if*

I want to grab a .. and find support against the wall.' So I thought it made sense anyway to make patients more aware.

Pilot 2 PT 2: Then it would be nice to have a combination of: gosh, what did they do that day? Look, if someone feels like they haven't been doing all that much, but we think, hey, they're overexerting themselves and that's why they're falling, yeah, I think you can get some nice feedback on that. And you just have, when people wear it for a longer time and people actually fall more often, yes, then you just get an overview of hey, then and there and then and there.

Third, both physiotherapists and PwPD mentioned the *role of the system in the consultation*. As a benefit, physiotherapists stated that the objective sensor-based information and the subjective self-reports provided them a view and insight into the at-home activities and daily life functioning of the PwPD. Discussing the information provided them more structure during the consultation to systematically address the topic of physical activity and falls. However, the added value of the system was limited for several physiotherapists and PwPD because the therapy goals were already clear and manageable, meaning there was limited room for improvement of therapy based on the additional information.

Pilot 1 PT 3: But usually you just ask about it [physical activity], but to really have it come back so systematically, and that it is also even more important what they do at home, to make them even more aware of it, I thought it was very nice to do it this way.

Pilot 1 PwPD 9: We didn't go all that deep into it, but then again, if there were no problems then you don't have anything to talk about, do you?

Importantly, many PwPD highly valued the relationship and interaction with the physiotherapist. Many PwPD therefore enjoyed discussing the data with their physiotherapist. Several PwPD felt extra motivated to move more to show the physiotherapist how active they had become.

Pilot 1 PwPD 8: Yes, that [discussing the data] is always positive, of course. But that happens anyway, because we had a conversation about it every time. Because it also stimulates to undertake more activities, doesn't it?

Pilot 2 PT 1: And every week I took the tablet and looked at it. They liked that, because they are participating, so then it's kind of... Yes, they liked that.

The physiotherapists noted that the system could become more relevant within the consultation (**table 1**). For example, they desired more advanced analyses of gait and balance parameters to adjust therapy. In pilot 2, we added a gait pattern analysis section to the app. This section provided physiotherapists with a -3 to +3 score reflecting the quality of gait of the PwPD. The interpretation of this score was yet unclear to physiotherapists, but the potential use of such analyses was apparent to them.

Pilot 2 PT 3: Yes, because the step length, step frequency are things that I would like to get though, if there is a change in that.

Table 3. Quotes reflecting the user experiences with the Vital@Home remote monitoring system. PT: physiotherapist. PwPD: person with Parkinson's disease.

	Usability
Operating the system in daily life	*Pilot 2 PwPD 3: But apart from that, the necklace, so to speak, around the neck did not bother me at all. I just kept it on day and night and it didn't bother me at all.*
	Pilot 1 PwPD 10: Yes, the size of the device and the cord were not pleasant.
	Pilot 1 PwPD 11 about Wi-Fi hub: That was annoying at times, because I forgot about it. And when you're at home it's all fine, but when you leave it's a bit more complicated. Then you have to think about it.
	Pilot 2 PwPD 1 about the app: Yes, that was clear. That is not a problem.
Digital literacy and support	*Pilot 1 PT 2: In the beginning I found it quite a hassle, especially for the patient. You have to explain, they don't quite understand, and I don't quite know myself either. So it took a while... but after two weeks you get used to it.*
	Pilot 1 PwPD 4: Yes, that perhaps it [digital support] is not so easy from a distance. [...] That perhaps you should discuss together in a kind of circle conversation, what the questions exactly mean and what you can do. It is so distant.
	Pilot 2 PT 3: I think I would go for that [GoSafe only] more because then patients just have to carry it and not add any additional actions and then when they come to me, we can look at their app together and then retrace or analyse or discuss things, rather than them having to do all that themselves.
	Pilot 1 partner of PwPD 3 managing the app for him: So we did sit on the sofa together in the evening and then we entered everything, because I wanted my husband to know what I was doing. And then I would say: shall I [enter] so many minutes step or so many minutes... so that it all comes from him, so to speak.
Technical prerequisites	*Pilot 1 PwPD 12: Yes, that [walking detection] is pretty good, because when we went for a walk, my wife came along every time, we would check beforehand, I'll call it we're leaving five to nine thirty, and I'll be home at a quarter past ten, that's how long we've walked. And there might be a minute or two or three in it all together, but otherwise he's good.*
	Pilot 1 PwPD 4: And... yes, the annoying thing is that then you type in the data and you see that you have made a mistake, but you cannot correct it.

Table 3. Continued

	Utility
Physical activity monitoring	Pilot 1 PwPD 13: For example, when I'm doing my household, I go upstairs, I go downstairs again, it doesn't register that. And if I for example vacuum my whole house, yes, I find that quite an effort, because then I have to rest now and then. But it doesn't register that at all. Pilot 1 PT 2: So, I notice that it works in this way for the patients to be more active, to realise more that exercise is important. And yes, also for themselves, because I didn't encourage them to move more, I didn't say anything about that, because I always say you're doing well, but they just started setting some kind of goals. Like oh, but then [I] want to... because they know that they can see it [sensor data] back with me. So, it does work that way. Pilot 1 PwPD 1: And then with three days I had closed the circle and I could finish the week with 200 minutes extra, so to speak. And that gave me a good feeling. So, I was constantly challenging myself.
Falls monitoring	Pilot 1 PT 4: And you can see, also with the falling, when it goes wrong and if that has to do with the medication or with other activities. Whether they have become very active and then fall. […] So, I really do see potential in that. Pilot 1 PwPD 9: Was that last question... Have you fallen today? I have not fallen during that whole period, I have never fallen.
Role of system in consultation	Pilot 1 PT 2: I actually already knew [...] how much someone moves and how often they exercise. You want to have insight into that. And yes, that was actually just a confirmation. But that's not to say that it doesn't work, it just hasn't added anything to my treatment. Pilot 2 PT 2: I don't know if that could be that you, speed indeed, but also a certain rhythm, or that people change speed, so whether people start festering or people start freezing, if indeed you could see that.

User profiles

We drafted three user profiles that describe how a remote monitoring system can add value to physiotherapy (**table 4**).

Profile 1 represents persons who are typically in an early phase of their PD, with good technical skills. They visit the physiotherapist a couple of times per year to proactively tackle small issues and stay physically active. For them, a monitoring system could act as a flagging dashboard. The objective sensor data could provide in-depth analyses of, e.g., gait parameters in daily life. If such parameters worsen, both the physiotherapist and PwPD could be notified and an appointment could be scheduled. That way, the PwPD does not need to be in constant treatment so that overtreatment could be prevented, whilst maintaining a reassuring view on the PwPD's status at home.

Table 4. User profiles of persons with PD receiving physiotherapy drafted from interviews.

Persons without physiotherapy related problems	**Profile 1**	
	Stage of PD	Early-Mid
	Digital technology skills	**+++**
	Cognition	**+++**
	Physical activity level	**+++**
	Fall incidents	Absent
	Physiotherapy goals	• Early identification and treatment of issues, e.g., inactivity or fear to move • Potential to slow disease progression
	Utility of the system	• Keep motivated to stay physically active • Prevent major issues by proactively screening for beginning problems (flags), e.g., through an in-depth analysis of gait parameters • Track disease progression to know when to initiate treatment, thereby preventing overtreatment
	Usability of the system	• Operates sensor and app to (self-) monitor at home independently • Analyses data alone and together with physiotherapist
Persons not interested in monitoring their disease		

Profile 2	Profile 3	
Mid	Mid-Late	
++	+	
+++	+	
++ / +	+	
Rarely, or near-fall experiences	More frequent	
• Desires to move more • Challenge to keep motivation high • Treat issues with balance to prevent falls	• Treat issues with balance to prevent falls • Keep functional mobility to perform day-to-day tasks	**Persons for which monitoring is too burdensome or technically too complicated**
• Increase and maintain higher levels of physical activity • Discuss data with physiotherapist to raise awareness of importance of physical activity and falls, and to support understanding of own PD • Track disease progression to set treatment goals, and easily share information amongst healthcare professionals	• Collect objective and accurate data about mobility and balance at home for physiotherapist • Context questionnaire can provide insight into falling circumstances	
• Operates sensor and app to monitor at home with support • Interested in seeing data but analysis depends on physiotherapist	• Wears sensor 4x/year for a week • App only when partner can manage • Physiotherapist views and analyses data, provides insight to PwPD during consultation	
Persons not interested in monitoring their disease		

Profile 2 represents PwPD who are typically in the mid-phase of their PD. They find it challenging to stay physically active and might experience near-fall incidents. For them, a monitoring system could add value as a motivational tool. For example, the PwPD and physiotherapist could set physical activity goals per week and use the sensor data to see if these goals were reached. Additionally, repeatedly collecting and discussing sensor data could increase awareness and understanding of important topics such as (near-)falls.

Profile 3 represents PwPD who are typically in a mid- to late-phase of their PD. Their physiotherapy goals focus on managing (further) fall incidents and maintaining mobility, to safely perform daily activities. For them, a monitoring system could serve as a supportive tool. These PwPD start to experience cognitive impairments, which makes it difficult to remember, e.g., when, where, and why a fall occurred. A sensor could collect such objective information about falls and physical activity in the home situation. This information could be provided to the physiotherapist to optimize treatment.

Throughout the interviews, it became clear that monitoring systems are not adding value for all PwPD. Some of the PwPD said they already know their PD well enough and do not need support in that. They were typically very early in their disease course and currently had limited physiotherapy-related issues. Other PwPD had no interest in monitoring their disease in general. They did not wish to be constantly reminded of the disease through monitoring, as they often already struggled with accepting the disease in the first place. Finally, some PwPD said that managing daily tasks was burdensome for them and they had no energy or time to deal with an additional system as well.

Discussion

We designed and evaluated a remote monitoring system to support physiotherapy for PwPD. Overall, both PwPD and physiotherapists were positive about the usability and utility of the monitoring system for physiotherapy practice. Evaluating the usability and utility of any remote monitoring system is essential before implementation in real-life clinical practice is pursued. Specifically for our system, physiotherapists see potential in objectively capturing physical activity and (near-) falls in daily life. The system motivated several PwPD to move more because of the continuous and objective tracking of their physical activity. PwPD and physiotherapists also enjoyed discussing the collected data. However, the system has clear improvement items before long-term implementation can be considered.

For example, PwPD and physiotherapists preferred automatic detection of a more diverse repertoire of activities, thereby minimizing the burden on the user.

Most PwPD were capable of independently using the necklace and app at home without major issues. This is in line with another study suggesting that a majority of PwPD can use technologies such as computers and smartphones in daily life.[45] At the same time, we noticed that some participants got frustrated with the system. The system was too difficult for them, for example because the system contained too many features, or because the PwPD had few technical skills or slight cognitive impairments. We ensured that these PwPD could also use and evaluate the system by offering a sensor-only option (i.e. merely passive recording) and we provided them with extensive remote technical support. Pursuing equal access to telehealth innovations requires constant attention as specific subgroups of PwPD might be underrepresented in our research.[46,47] One possibility to increase equal access to innovations is to personalize the required user interactions with the tools. A modular system, for example based around a smartphone, can be designed to which different sensors can connect. Each person can then connect the sensors best fitting their needs and technical skills. Future studies are required to identify potential disparities in access to telemedicine and create specific solutions to mitigate these.[48]

Several PwPD emphasized the importance of the relationship with their physiotherapist. They looked forward to discussing the data with the physiotherapist, to see how they were doing, and to show the effort they had put into being more active. In turn, the physiotherapist encouraged the PwPD to remain physically active and continue the use of the system. This finding is comparable to other literature that showed the importance of personal contact in adopting remote monitoring technology.[49] Typically, when the amount of physical, social interaction with the physiotherapist or other group members decreased, the satisfaction with the therapy also decreased for the participants.[31,50] Other large-scale studies on the long-term adoption of sensor-based telemedicine have shown that compliance drops over time.[24] This can be prevented or minimized when participants have a personal point of contact [25] and are motivated by relatives.[9] The successful implementation of a teletreatment therefore strongly depends on a thorough understanding of the social context in which it is embedded.

Our study confirms that monitoring physical activity and falls is generally regarded as important,[51,52] but also confirms earlier impressions that a person-specific balance exists between the benefits and burdens of monitoring.[53] All participants

in our study used the same system which elicited highly divergent opinions. Some participants were not bothered by the necklace at all and were enthusiastic about the new insights they gained from the system. Others disliked wearing the necklace and felt the data were not accurate enough to be useful or did not want to be continuously reminded of their PD. Although the benefits of monitoring might never outweigh the burdens for some PwPD, we strive to design inclusive monitoring systems useful for all PwPD. Our user profiles describe this benefits-burdens balance for several groups of PwPD, but should be regarded as a starting point from which to explore even more personalized monitoring needs and wishes. For example, the profiles could be combined with other known benefits and burdens of monitoring,[53,54] physiotherapy treatment mechanisms,[4] and personality traits such as coping [55,56] and information seeking styles. [57] Drafting user profiles of physiotherapists as well could help to create systems that also accommodate their needs and preferences.

A strength of this study is the unique insight gained from daily practice about how a sensor-based monitoring system can support physiotherapy. We had an extensive study period duration of six weeks, allowing for substantive wear and use periods leading to grounded conclusions by the participants. By deploying an iterative design process, we could intermediately incorporate the feedback from PwPD and physiotherapists to improve the system.

However, this study was not without limitations. First, the SUS was lower in pilot 2 despite seeming improvements of the system and an increased compliance. An explanation could be that the added features of the system also made the system more complex. As these features were not readily used, this could decrease the usability of the system. Another explanation could be that we recruited more affected persons with PD in pilot 2 who experienced more difficulties with operating the system. To be able to elaborately test the fall-section of the system, we specifically recruited more persons with PD who experienced (near) falls in pilot 2 (**table 2**). Most likely as a consequence of our recruitment strategy, the pilot 2 participants have worse scores on all clinical outcomes compared to pilot 1 participants, except for the Hoehn and Yahr stage which is difficult to accurately classify. Furthermore, the SUS could be lower because we encountered some technical problems in pilot 2 such as data not showing in the app. Based on the user feedback in pilot 1, we increased the available technical support for pilot 2. This support was appreciated and ensured that people were retained in the study. In total, only three participants dropped-out during both pilots because the app was too difficult for them or because they were frustrated by the lack of correctable data.

Second, the user profiles were only indirectly assessed within the interviews since the interviews were specifically aimed at evaluating the system. However, we grounded the user profiles as much as possible in the available data through a rigorous analysis, including discussions with the research team. Future research should focus on further developing these profiles, for example by refining their content and applicability through co-creation sessions with PwPD and physiotherapists. Furthermore, we drafted these profiles to understand how monitoring tools could add value for specific subgroups of PwPD by generalizing people's similarities. We are aware that each PwPD is unique and has their own context and wishes, so PwPD may or may not find resemblances in our profiles.

Third, our sampling method poses limitations on the generalizability of our findings regarding both physiotherapists and PwPD. The physiotherapists taking part in our study were all part of ParkinsonNet in the Netherlands, and as such were thoroughly trained in treating PwPD. [32] Being part of the Dutch ParkinsonNet also means that the participating physiotherapist will attract a much higher caseload, which will presumably also help as an encouragement to start using a new technological system for that specific population, unlike more generically trained therapists who only sporadically encounter PwPD in their practice. In other countries, the role of the physiotherapist in the treatment of PwPD might be different, instigating different usability and utility evaluations. However, the high quality of specialized Parkinson-specific physiotherapy does make the Netherlands a suitable test-climate for the development and evaluation of such tools. Regarding the PwPD, a selection bias might have occurred because they were selected from the database of the physiotherapist. Physiotherapists might have invited participants who, for example, have an above average affinity with technology. We partly mitigated this problem in pilot 2 by allowing participants to only use the sensor if using the app was too complicated. Still, our sample most likely contains PwPD who are interested in monitoring technology or healthcare innovations in general. Testing the system in these PwPD leads to relevant conclusions as they are also most likely to adopt monitoring systems. However, this also means that our findings might not generalize to a broader PD population for whom monitoring tools will also become accessible in the future.

Our study has shown that physiotherapists and PwPD are interested in sensor-based data, but our system requires further development and testing before it is ready for actual implementation in clinical practice. The development of the system should focus on improving its technical maturity as well as expanding its functionalities, which should be driven by specific use cases for remote monitoring

and individual characteristics of the users. We organized our findings related to this in different user profiles, which can guide the future development. Specifically for PwPD, future tools should become more adjustable to each individual person. For example, PwPD should be able to choose whether they see the same detailed data as the physiotherapist or only receive high-level summaries. Also, automatically detecting more diverse physical activities is important to reduce the burden of the tool. Yet, adding more subjective measures such as feelings and motivations should be possible as they give context to the objective data (**table 1**). Specifically for physiotherapists, the treatment of falls could be supported by providing them with more sensor-based indicators of fall risk, e.g., a more in-depth analysis of the free-living gait pattern and transfers. Finally, rigorous testing is needed to establish the added value of this sensor-based information for clinical practice.[58] After developing such matured systems, future research should examine the long-term effect of monitoring systems on therapy decision making, their impact on quality of life, and their cost-effectiveness, all within well-defined target populations.

References

1. Dorsey, E. R., Sherer, T., Okun, M. S. & Bloem, B. R. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis* **8**, S3–S8 (2018).
2. Feigin, V. L. *et al.* Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **18**, 459–480 (2019).
3. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* **397**, 2284–2303 (2021).
4. Keus, S. *et al.* European Physiotherapy Guideline for Parkinson's Disease. *KNGF/ParkinsonNet, the Netherlands* (2014).
5. Radder, D. L. M. *et al.* Physiotherapy in Parkinson's disease: A meta-analysis of present treatment modalities. *Neurorehabil Neural Repair* **34**, 871–880 (2020).
6. Borrione, P. Effects of physical activity in Parkinson's disease: A new tool for rehabilitation. *World J Methodol* **4**, 133 (2014).
7. Lauzé, M., Daneault, J.-F. & Duval, C. The effects of physical activity in Parkinson's disease: A review. *J Parkinsons Dis* **6**, 685–698 (2016).
8. Johansson, M. E. *et al.* Aerobic exercise alters brain function and structure in Parkinson's disease: A randomized controlled trial. *Ann Neurol* **91**, 203–216 (2022).
9. van der Kolk, N. M. *et al.* Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: A double-blind, randomised controlled trial. *Lancet Neurol* **18**, 998–1008 (2019).
10. Schootemeijer, S. *et al.* Barriers and motivators to engage in exercise for persons with Parkinson's disease. *J Parkinsons Dis* **10**, 1293–1299 (2020).
11. Dontje, M. L. *et al.* Quantifying daily physical activity and determinants in sedentary patients with Parkinson's disease. *Parkinsonism Relat Disord* **19**, 878–882 (2013).
12. Fasano, A., Canning, C. G., Hausdorff, J. M., Lord, S. & Rochester, L. Falls in Parkinson's disease: A complex and evolving picture. *Movement Disorders* **32**, 1524–1536 (2017).
13. Okunoye, O., Kojima, G., Marston, L., Walters, K. & Schrag, A. Factors associated with hospitalisation among people with Parkinson's disease – A systematic review and meta-analysis. *Parkinsonism Relat Disord* **71**, 66–72 (2020).
14. Santos García, D. *et al.* Falls predict acute hospitalization in Parkinson's disease. *J Parkinsons Dis* 1–20 (2021).
15. Chen, Y.-Y., Cheng, P.-Y., Wu, S.-L. & Lai, C.-H. Parkinson's disease and risk of hip fracture: An 8-year follow-up study in Taiwan. *Parkinsonism Relat Disord* **18**, 506–509 (2012).
16. Kader, M., Iwarsson, S., Odin, P. & Nilsson, M. H. Fall-related activity avoidance in relation to a history of falls or near falls, fear of falling and disease severity in people with Parkinson's disease. *BMC Neurol* **16**, 1–8 (2016).
17. Warmerdam, E. *et al.* Long-term unsupervised mobility assessment in movement disorders. *Lancet Neurol* **19**, 462–470 (2020).
18. Gaßner, H. *et al.* Clinical relevance of standardized mobile gait tests. Reliability analysis between gait recordings at hospital and home in Parkinson's disease: A pilot study. *J Parkinsons Dis* **10**, 1763–1773 (2020).
19. Camicioli, R. & Majumdar, S. R. Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-Year Prospective Cohort Study. *Gait Posture* **32**, 87–91 (2010).

20. Latt, M. D., Lord, S. R., Morris, J. G. L. & Fung, V. S. C. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Movement Disorders* **24**, 1280–1289 (2009).
21. del Din, S., Kirk, C., Yarnall, A. J., Rochester, L. & Hausdorff, J. M. Body-worn sensors for remote monitoring of Parkinson's disease motor symptoms: Vision, state of the art, and challenges ahead. *J Parkinsons Dis* **11**, S35–S47 (2021).
22. Block, V. A. J. *et al.* Remote physical activity monitoring in neurological disease: A systematic review. *PLoS One* **11**, e0154335 (2016).
23. Ellis, T. D. *et al.* Comparative effectiveness of mHealth-supported exercise compared with exercise alone for people with Parkinson disease: Randomized controlled pilot study. *Phys Ther* **99**, 203–216 (2019).
24. Silva de Lima, A. L. *et al.* Feasibility of large-scale deployment of multiple wearable sensors in Parkinson's disease. *PLoS One* **12**, e0189161 (2017).
25. Bloem, B. *et al.* The Personalized Parkinson Project – data quality enhancing strategies. Abstract in *Movement Disorders* **35**, 873 (2020). Available from: https://www.mdsabstracts.org/abstract/the-personalized-parkinson-project-data-quality-enhancing-strategies/. Accessed July 1, 2023.
26. Weiss, A., Herman, T., Giladi, N. & Hausdorff, J. M. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. *PLoS One* **9**, e96675 (2014).
27. Silva de Lima, A. L. *et al.* Home-based monitoring of falls using wearable sensors in Parkinson's disease. *Movement Disorders* **35**, 109–115 (2020).
28. del Din, S., Godfrey, A., Mazzà, C., Lord, S. & Rochester, L. Free-living monitoring of Parkinson's disease: Lessons from the field. *Movement Disorders* **31**, 1293–1313 (2016).
29. Carpinella, I. *et al.* Wearable sensor-based biofeedback training for balance and gait in Parkinson disease: A pilot randomized controlled trial. *Arch Phys Med Rehabil* **98**, 622-630.e3 (2017).
30. Conradsson, D., Nero, H., Löfgren, N., Hagströmer, M. & Franzén, E. Monitoring training activity during gait-related balance exercise in individuals with Parkinson's disease: A proof-of-concept-study. *BMC Neurol* **17**, 1–8 (2017).
31. Lai, B. *et al.* Exploring the uptake and implementation of tele-monitored home-exercise programmes in adults with Parkinson's disease: A mixed-methods pilot study. *J Telemed Telecare* **26**, 53–63 (2020).
32. Bloem, B. R. *et al.* ParkinsonNet: A low-cost health care innovation with a systems approach from the Netherlands. *Health Aff* **36**, 1987–1996 (2017).
33. Smits, T. & Ryter, A. Personal emergency response system with optimized automatic fall detection shows greater effectiveness than PERS alone. Available from: https://cdn2.hubspot.net/hubfs/5835435/Sr.%20Living%20Philips_Lifeline_June2019%20Theme/Digital%20Resources/WhitePaper%20-%20PERS%20AA.pdf (2015).
34. Saporito, S. *et al.* Remote timed up and go evaluation from activities of daily living reveals changing mobility after surgery. *Physiol Meas* **40**, 035004 (2019).
35. Penko, A. L., Barkley, J. E., Koop, M. M. & Alberts, J. L. Borg scale is valid for ratings of perceived exertion for individuals with Parkinson's disease. *Int J Exerc Sci* **10**, 76–86 (2017).
36. Bangor, A., Kortum, P. T. & Miller, J. T. An empirical evaluation of the System Usability Scale. *Int J Hum Comput Interact* **24**, 574–594 (2008).
37. Franchignoni, F., Horak, F., Godi, M., Nardone, A. & Giordano, A. Using psychometric techniques to improve the Balance Evaluation Systems Test: The mini-BESTest. *J Rehabil Med* **42**, 323–331 (2010).
38. Nieuwboer, A. *et al.* Reliability of the new freezing of gait questionnaire: Agreement between patients with Parkinson's disease and their carers. *Gait Posture* **30**, 459–463 (2009).

39. Whitney, S. L. *et al.* Clinical measurement of sit-to-stand performance in people with balance disorders: Validity of data for the Five-Times-Sit-to-Stand Test. *Phys Ther* **85**, 1034–1045 (2005).
40. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qual Res Psychol* **3**, 77–101 (2006).
41. Scientific Software Development GmbH. Atlas.ti 8. Available from https://atlasti.com (2022).
42. R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.
43. Wickham, H. The split-apply-combine strategy for data analysis. *J Stat Softw* **40**, 1-29 (2011).
44. LeRouge, C., Ma, J., Sneha, S. & Tolle, K. User profiles and personas in the design and development of consumer health technologies. *Int J Med Inform* **82**, e251–e268 (2013).
45. Marxreiter, F. *et al.* The use of digital technology and media in German Parkinson's disease patients. *J Parkinsons Dis* **10**, 717–727 (2020).
46. Domingos, J. M. *et al.* Cognitive impairment in fall-related studies in Parkinson's disease. *J Parkinsons Dis* **5**, 453–469 (2015).
47. Maas, B. R. *et al.* Time trends in demographic characteristics of participants and outcome measures in Parkinson's disease research: A 19-year single-center experience. *Clin Park Relat Disord* **8**, 100185 (2023).
48. Nouri, S., Khoong, E. C., Lyles, C. R. & Karliner, L. Addressing equity in telemedicine for chronic disease management during the Covid-19 pandemic. *NEJM Catalyst* **1**, 1–13 (2020).
49. Flynn, A., Dennis, S., Preston, E., Canning, C. G. & Allen, N. E. Exercising with Parkinson's: The good, the bad and the need for support to keep exercising. A qualitative study. *Clin Rehabil* **36**, 1332–1341 (2022).
50. Flynn, A., Preston, E., Dennis, S., Canning, C. G. & Allen, N. E. Home-based exercise monitored with telehealth is feasible and acceptable compared to centre-based exercise in Parkinson's disease: A randomised pilot study. *Clin Rehabil* **35**, 728–739 (2021).
51. Serrano, J. A. *et al.* Participatory design in Parkinson's research with focus on the symptomatic domains to be measured. *J Parkinsons Dis* **5**, 187–196 (2015).
52. Mathur, S. *et al.* Challenges of improving patient-centred care in Parkinson's disease. *J Parkinsons Dis* **7**, 163–174 (2017).
53. Riggare, S., Scott Duncan, T., Hvitfeldt, H. & Hägglund, M. "You have to know why you're doing this": A mixed methods study of the benefits and burdens of self-tracking in Parkinson's disease. *BMC Med Inform Decis Mak* **19**, 1–16 (2019).
54. Kenny, L. *et al.* The views and needs of people with Parkinson disease regarding wearable devices for disease monitoring: Mixed methods exploration. *JMIR Form Res* **6**, e27418 (2022).
55. Liebermann, J. D., Witte, O. W. & Prell, T. Association between different coping styles and health-related quality of life in people with Parkinson's disease: A cross-sectional study. *BMJ Open* **10**, e036870 (2020).
56. Nilsson, M. H., Oswald, F., Palmqvist, S. & Slaug, B. Coping styles among people with Parkinson's disease: A three-year follow-up study. *Behavioral Sciences* **10**, 190 (2020).
57. Lubi, K., Vihalemm, T. & Taba, P. Illness-related information seeking: The case of Parkinson's disease patients. in *2nd International Conference on Social Science and Health* (ed. Lee, G.) 98–111 (Information Engineering Research Institute, 2014).
58. Maetzler, W., Klucken, J. & Horne, M. A clinical view on the development of technology-based tools in managing Parkinson's disease. *Movement Disorders* **31**, 1263–1271 (2016).

5

A route towards prevention: A mixed methods study of modifiable causal factors, causal pathways and population attributable fractions for complications in Parkinson's disease

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Abstract

Background

Medical complications are the leading cause for hospitalization and death for people with Parkinson's disease (PD). To support secondary prevention, we identified modifiable causal factors for six of the most impactful complications for people with PD: fall related fractures, pneumonias, urinary tract infections, psychotic symptoms, mood disorders and dementia.

Methods

We conducted a four-step mixed methods study. First, we systematically searched the literature for reviews, meta-analyses and original/empirical research articles on causal factors for each complication. Second, we checked the face validity of the causal factors by inviting healthcare professionals to select and prioritize the causal factors based on their clinical experience in an online national survey. Third, using this refined overview, we mapped the modifiable causal factors for each complication along a causal pathway based on expert opinion. Finally, we estimated the population attributable fractions of each modifiable causal factor in the causal pathway as an illustration of our methodology to identify targets for prevention.

Results

The literature search yielded 88 articles, describing 103 unique causal factors across all six complications. In total, 99 healthcare professionals from 10 medical disciplines completed the survey. They reviewed the causal factors and suggested to add 11. Together with 10 experts in PD from eight medical disciplines, we mapped the causal factors into causal pathways for each complication. Finally, for each causal factor included in the pathways, we used the PRIME-NL cohort study data (n = 920) to estimate population attributable fractions. To demonstrate our approach, we highlight these calculations for falls (60.2%, 95% confidence interval [33.4% - 80.4%]) and urinary tract infections (21.5%, 95% confidence interval [2.0% - 47.4%]).

Conclusions

This study illustrates a mixed-methods approach which could help to map modifiable causal factors of common complications in PD, opening new avenues for the prevention of these complications.

Background

Parkinson's disease (PD) is the fastest growing neurodegenerative movement disorder globally and has a large impact on people's quality of life.[1,2] The progression of the disease cannot yet be prevented or halted. However, we might be able to prevent complications that people with PD experience. A complication is an undesirable but preventable event or condition that arises as a result of someone's condition. Important complications for PD are fall-related fractures, aspiration pneumonias, urinary tract infections, psychotic symptoms such as hallucinations and delirium, mood disorders such as depression and anxiety, and dementia.[3] These complications are major contributors to hospitalisation and mortality rates, cause severe disease burden, increase healthcare costs and are associated with poor recovery rates.[4–7] Therefore, preventing these complications is pivotal.

Effective secondary prevention of these complications requires a proactive healthcare system and knowledge about relevant causal factors. In the context of this study, secondary prevention entails the early detection of warning signals and treatment thereof before a complication manifests.[8] Secondary prevention efforts encompass a broad variety of activities, such as optimal medical treatment, lifestyle modification, social and psychological support and, importantly, regular monitoring.[7] Regular monitoring ensures that problems are detected early and are treated at their inception, rather than waiting for problems to exacerbate. That way, instead of remaining reactive, healthcare can become proactive, aiming to timely tackle problems before they lead to medical complications.[3,7] Preferably, regular monitoring captures changes in relevant causal factors, i.e., a variable that increases the likelihood of a person with PD developing a complication. Causal factors can be personal characteristics, conditions or behaviours and can broadly be categorized as modifiable, e.g., physical inactivity and alcohol consumption, and non-modifiable causal factors, e.g., age and sex (for example, see [9,10]).

The relevance of a causal factor for population-based secondary prevention can be determined by causal pathways and population attributable fractions. A causal pathway is a schematic diagram detailing how each causal factor leads to the next causal factor, up until the complication.[11] The pathway provides insight into the working mechanism behind the complication and tells us why a causal factor is important, i.e., what role it plays. The population attributable fraction is an epidemiological measure that describes the theoretical reduction in the occurrence of a complication if a causal factor could be eliminated from the population (e.g. [12]). For example, when the population attributable fraction of smoking is 10% for

pneumonia, we can reduce the number of pneumonias by 10% if everyone in the population would quit smoking. Taken together, a causal factor will be a relevant target for prevention whenever it holds an important position in the causal pathway and yields a considerable population attributable fraction.

Much research has been conducted in the field of PD regarding the aforementioned complications, but only few studies have provided a comprehensive overview of causal factors (e.g. [10,13,14]) or described a causal pathway.[15] To advance secondary prevention efforts across the medical fields, we demonstrate a route to identify relevant targets for prevention. This route consists of four steps leveraging various methods: 1) search the literature systematically to identify causal factors, 2) ensure face validity and prioritize the causal factors based on clinical experience, 3) map the identified causal factors into causal pathways with experts, and 4) estimate the population attributable fractions based on the causal pathways. In this proof-of-principle study, we applied these four steps to PD-related complications including fall-related fractures, pneumonias, urinary tract infections, psychotic symptoms, mood disorders and dementia.

Methods

Study design

The aim of our four-step mixed methods approach was to identify relevant targets for complication prevention in PD (**figure 1**). The complications we focused on are known for their large impact on quality of life and hospitalization and mortality rates and included falls and related fractures, urinary tract infections, pneumonias, psychotic symptoms, mood disorders (depression and anxiety) and dementia.[3–6] We acknowledge that psychotic symptoms, mood disorders and dementia could be regarded as inherent parts of PD, but we decided to include them given their large impact on an individual's quality of life and potential treatability.

We used a mixed methods design because qualitative methods allowed us to understand why a causal factor was relevant whilst quantitative methods allowed us to estimate the proportion of preventable complications. First, we identified causal factors for each complication through a systematic literature search. Second, we surveyed PD healthcare professionals to ensure face validity and prioritize the causal factors identified in the literature based on their clinical experience. Third, using this refined overview, we mapped the modifiable causal factors for each complication along a causal pathway based on expert opinion. Finally, we

estimated population attributable fractions per causal pathway for each modifiable causal factor available in the PRIME-NL cohort study data. We describe each step in more detail below.

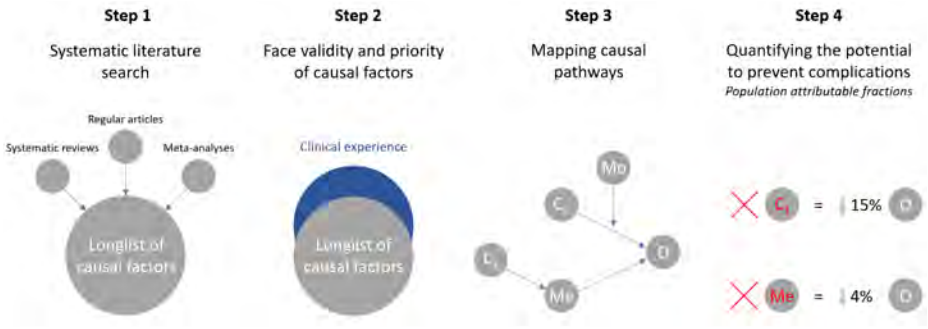

Figure 1. Overview of the four-step method. Step 3: C1 and C2 represent causal factors, Me a mediator, Mo an effect modifier and O the outcome, i.e., the complication. Step 4: The population attributable fraction shows the percentage of complications that could be prevented if a causal factor (e.g., C1), mediator (Me) or effect modifier (Mo) could be removed from the population.

This study was conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki, and was approved by the ethics committee (METC Oost-Nederland; file 2019-5618 and 2022-13744). Before enrolment, participants gave informed consent either digitally (step 2), verbally (step 3) or in writing (step 4).

Step 1: Systematic literature search to identify causal factors

The goal of the systematic literature search was to create an overview of known causal factors for each complication.

Search strategy and selection criteria

We searched the PubMed and Cochrane Review databases for systematic reviews and meta-analyses in English, published up until March 2022. The specific search terms are detailed in **supplementary file S1**. In general, we combined 'Parkinson' with a term for each of the complications, e.g., 'pneumonia'. Articles were eligible if they examined persons with PD and described the association between at least one causal factor and at least one of the complications. The first author screened titles, then read abstracts and subsequently read full texts. Despite the broad search terms, only a few relevant systematic reviews and meta-analyses were found, mainly for falls. Therefore, we broadened our search strategy. First, we searched for original PD research articles, i.e., not limited to systematic reviews and meta-analyses, and

added terms such as 'risk' to confine the search. This search yielded relevant articles for psychotic symptoms, mood disorders and dementia. However, for pneumonia and urinary tract infection we found very limited results. Therefore, we again broadened the search for pneumonia and urinary tract infection to also encompass systematic reviews and meta-analyses from the general elderly population.

Data extraction

From each included article, we extracted the causal factors that were associated with the complication. We excluded protective factors as well as the majority of medications because of confounding by indication, i.e., a false association between a medication and the outcome caused by the indication which prompts the medication use and causes the outcome. Every statistically associated causal factor was included into the overview, regardless of the number of articles supporting the causal factor and the strength of the association. Ultimately, we compiled the causal factors across articles to generate a list of unique causal factors for each complication.

Step 2: Online survey for healthcare professionals to ensure face validity and prioritize causal factors

The goal of the online survey was to ensure face validity and prioritize the causal factors identified in step 1 based on the clinical experience of healthcare professionals.

Participants

We targeted healthcare professionals in the Netherlands specialized in PD care. No restrictions were applied concerning discipline or years of experience. The only requirement was self-rated clinical experience with the treatment or prevention of one or more complication in people with PD.

Materials and procedures

We converted the causal factor list for each complication to an online survey hosted between September and November 2022 by ParkinsonNEXT. ParkinsonNEXT is an online platform that facilitates research participation for PD healthcare professionals in the Netherlands. The survey was promoted through social media and the ParkinsonNEXT participant database. Participants first had to enter demographic data and indicate their clinical experience with the complications. For the complications they had selected, the healthcare professionals were asked to review the causal factor lists by selecting the causal factors they recognized from their clinical experience and rank order them by importance. Finally, the healthcare professionals could suggest additional causal factors that were missing according to them in an open text field.

Analyses

For each causal factor, we calculated both the frequency of selection and average rank order. We continued the analyses based on the frequency only, as the frequency and rank order were highly correlated ($r > .75$). The open answers provided by healthcare professionals were summarized and subsequently reviewed by two authors (RB and SKLD): a suggested causal factor was incorporated when relevant and distinct from already included causal factors.

Step 3: Mapping causal pathways based on expert opinion

The goal of the interviews with experts in PD was to map causal pathways leveraging their clinical PD experience. These causal pathways explain how a causal factor leads to a complication, thereby helping us understand why a causal factor is relevant.

Participants

We invited experts in the field of PD and in one of the complications. These experts were purposively sampled based on their specific knowledge, for example a PD-specialized clinical psychologist to discuss mood disorders (see **table 1** for an overview of experts). We recruited the experts from the professional network of our center of expertise for Parkinson and Movement Disorders.

Table 1. Experts consulted to map the causal pathways. UTI = urinary tract infection.

	Falls	Pneumonia	UTI	Psychotic symptoms	Mood disorders	Dementia
PD specialized neurologist	X	X	X	X	X	X
Resident in neurology	X					
PD rehabilitation specialist	X					
PD physiotherapist	X	X				
PD speech therapist (n = 2)		X				
Urologist			X			
PD nurse				X		
Psychiatric nurse				X		
Clinical neuropsychologist					X	X

Materials and procedures

After explaining the goal of the study, we invited the experts for a one-on-one 30-minute interview. The interviews took place between March and September 2023 and were not recorded. At the start of the interview, RB presented the expert the complete causal factor list including the frequencies created in step 2. We

subsequently asked the expert to arrange these causal factors in a causal chain towards the complication, i.e., explain which causal factor comes first and leads to another. As much as possible, we focused on specific and modifiable causal factors in the causal pathway as non-modifiable causal factors offer little opportunity for prevention. The expert was free to design the pathway according to their knowledge but was asked to explain the position of each causal factor. RB summarized these explanations to capture the story of each causal pathway.

Within the causal pathways, we use the terms *causal factor*, *mediator* and *effect modifier* to represent the role each factor can take in the pathway. A causal factor forms the beginning of the pathway and only has outgoing arrows. A mediator forms an intermediary step from causal factor to the outcome and therefore has both in- and outgoing arrows. An effect modifier influences the association between two elements in the pathway and is therefore directed towards another arrow in our causal pathway (**figure 1**). In the remainder of the text, we write 'causal factor' to refer to all three roles for conciseness, except when the term mediator or effect modifier is needed for understanding.

Analyses

Once all experts had been interviewed, the drafted causal pathway and accompanying story were shared with the experts within each complication. The experts provided written or verbal feedback on the pathway and the story and changes were made by RB where necessary. The causal pathways were refined in several iterations until all involved experts agreed upon the final form. In this final form, we have simplified the available knowledge for all causal pathways to maintain clarity and understanding. We therefore left out arrows for residual variance and limited the number of included effect modifiers as much as possible. We excluded relevant genetic and environmental factors because they currently cannot be modified readily in a clinical setting. Therefore, non-modifiable causal factors have been excluded from the causal pathways, including age, sex and disease duration. Instead, we have adjusted our estimates for these three causal factors in step 4. For psychotic symptoms, we made an exception and included disease severity and traumatic life events as non-modifiable factors due to the complex aetiology of this complication (**supplementary file S7**).

Step 4: Population attributable fractions to assess potential for prevention

The goal of the population attributable fraction estimations was to explore the theoretical potential for prevention of each complication.

Participants

We used the baseline questionnaire data from the PRIME-NL cohort study,[16] because this questionnaire covers many causal factors and complications. PRIME-NL aims to evaluate a new model of care for people with PD by implementing a multitude of innovations in a specific region in the Netherlands. For inclusion, the people with PD had to live in the Netherlands and receive treatment in a regional hospital. The PRIME-NL questionnaire sample has shown to be representative of the broader PD population in the Netherlands.[17]

Materials and procedures

The materials and procedures used to collect the PRIME-NL questionnaire data are detailed elsewhere.[16] In short, each interested person with PD was called to discuss the study procedures. After providing informed consent, the person with PD answered various questionnaires either on paper, digitally or by phone. The questionnaires cover a broad range of topics including extensive demographic questions, motor and non-motor symptom assessments and experienced complications. The baseline data were collected between January and December 2020.

Analyses

For all of our analyses, we used the cross-sectional PRIME-NL questionnaire data of the people with PD without distinguishing between the intervention and control group participants. We re-coded all data into binary variables as defined in **supplementary file S5**. We applied case-wise deletion when data were missing, as the proportion of missing data was low (0-6%).

In the context of our study, the population attributable fraction shows the percentage of complications that would not occur if the causal factor was to be eliminated from the population. The population attributable fraction combines the prevalence of a causal factor with the relative risk, i.e., the strength of the association between the causal factor and complication. We have detailed our analytical approach in **supplementary file S6**. In short, we used an adaptation of Levin's formula to account for non-independence between causal factors by weighing the population attributable fractions by the communalities of each causal factor: [12,18–20]

$$Adjusted\ PAF_e = \ w_e * \left(\frac{P_e(RR_e - 1)}{1 + P_e(RR_e - 1)}\right)$$

where adjusted PAF_e is the adjusted population attributable fraction for each exposure, i.e., causal factor, w_e is the weighing factor defined as 1 – the communality of the causal factor, i.e., the remaining unique variance, P_e is the prevalence of the

causal factor and RR_e the relative risk of the complication occurring because of the causal factor. The total adjusted population attributable fraction is defined as:

$$Adjusted\ PAF = 1 - \prod(1 - adjusted\ PAF_e).$$

In our reporting, we grouped population attributable fractions into motor symptoms, non-motor symptoms and others. We lacked power to test mediation and effect modification. Therefore, we estimated population attributable fractions for mediators similarly to regular causal factors following the steps above. For effect modifiers, we repeated the estimation of the overall population attributable fraction with only the largest subgroup of participants for the effect modifier. For example, as a proof of principle for the moderating effect of fear of falling on falls, we selected the participants who did not experience fear of falling and estimated the overall population attributable fraction for these participants. All analyses were conducted in R version 4.1.3.[21] The R script is available upon request.

Results

Step 1: Systematic literature search

After screening 2174 articles, we included 88 articles from the systematic literature search (flowchart in **supplementary file S2**). These 88 articles described 103 unique causal factors: 37 for falls, 32 for pneumonia, 26 for urinary tract infection, 22 for psychotic symptoms, 31 for depression, 19 for anxiety and 25 for dementia. For each complication, the list of unique causal factors and the supporting literature is given in **supplementary file S3**.

Step 2: Online survey for healthcare professionals

In total, 99 healthcare professionals answered the online survey (84 women; mean age = 47.9, standard deviation = 10.7; average years of experience = 15.4, standard deviation = 9.3; median number of people with PD treated per year = 25; median years of clinical experience = 15). This included physiotherapists (n = 49), PD nurses (n = 19), occupational therapists (n = 13), speech therapists (n = 10), dieticians (n = 2), psychologists (n = 2) and one pharmacist, one specialist in elderly care, one neurologist and one dentist. Most healthcare professionals indicated to have experience with falls and fractures (n = 82), followed by dementia (n = 66), pneumonia (n = 50), urinary tract infections (n = 50), depression (n = 50), anxiety (n = 37) and psychotic symptoms (n = 26). In **supplementary file S4**, we show how often each causal factor was selected by the healthcare professionals and detail which causal factors were added (n = 11) based on the suggestions from healthcare professionals.

Step 3: Mapping causal pathways

To draft the causal pathways, we interviewed 10 experts in the field of PD (**table 1**). We have detailed the decisions we made with the experts concerning each causal factor in **supplementary file S4**. The decision to in- or exclude a causal factor was generally in correspondence with the frequencies based on the online survey. After reviewing the results from step 1-3 for dementia, we decided that conceptualizing PD dementia as a preventable complication is insufficiently justified at this moment because of a lack of known modifiable causal factors. The causal pathways for falls (**figure 2**) and urinary tract infections (**figure 3**) are presented below to illustrate the result of our approach; an elaborate explanation and presentation of all causal pathways except for dementia is provided in **supplementary file S7**.

Step 4: Population attributable fractions

The PRIME-NL dataset contained 920 people with PD (**table 2**). The number of participants used for each calculation varied somewhat due to missing data, with the lowest number of participants for mood disorders (n = 864). Again, we report the population attributable fractions for the causal factors available in the PRIME-NL dataset for falls (**table 3**) and urinary tract infections (**table 4**) below to illustrate our results; all detailed estimations for each complication except dementia are given in **supplementary file S7**. In short, the total adjusted population attributable fraction was 60.2% for falls (95% confidence interval (CI) [33.4% - 80.4%]), 34.2% for pneumonias (95% CI [-37.3% - 75.8%]), 21.5% for urinary tract infections (95% CI [2.0% - 47.4%]), 43.1% for psychotic symptoms (95% CI [17.8% - 65.4%]), 61.9% for depressive symptoms (95% CI [35.1% - 80.3%]) and 46.6% for symptoms of anxiety (95% CI [22.0% - 67.4%]).

Effect modification for falls and fractures

For both fear of falling and physical activity, we examined effect modification as outlined in the methods. The initially estimated total population attributable fraction remained similar when we examined only the participants with a moderate amount of physical activity (60.7%, 95% CI [33.2% - 80.9%]); yet the total population attributable fraction was lower when we examined only the participants without a fear of falling (50.6%, 95% CI [24.0% - 71.2%]).

Effect modification for urinary tract infection

We also examined effect modification for cardinal motor symptoms and cognitive impairment. The initially calculated total population attributable fraction changed slightly when we included only the participants without severe cardinal motor

symptoms (15.1%, 95% CI [-4.0% - 47.8%]) and the participants without cognitive impairments (16.7%, 95% CI [-6.1% - 57.3%]).

Table 2: Demographic data of PRIME-NL participants used for calculating population attributable fractions.

Variable		Number (%) or mean (SD)
Total n		920
Age		69.6 (8.1)
Gender: Women		359 (39%)
Disease duration in years		5.8 (4.9)
Diagnosis Parkinson's disease		920 (100%)
Hoehn and Yahr		
	Stage 1	274 (30%)
	Stage 2	312 (34%)
	Stage 3	140 (15%)
	Stage 4	143 (16%)
	Stage 5	32 (3%)
Education*		
	Primary	234 (25%)
	Secondary	238 (26%)
	Tertiary	444 (48%)
Living situation		
	Alone	131 (14%)
	With partner or family	773 (84%)
	In facilitated care	16 (2%)
Retired		765 (83%)
Complications		
Any complication <12 months		597 (65%)
Falls <12 months		382 (42%)
Pneumonia <12 months		32 (3%)
Urinary tract infection <12 months		81 (9%)
Psychotic symptoms <12 months		119 (13%)
Depression <12 months		130 (14%)
Anxiety <12 months		334 (36%)
Dementia		3 (<1%)

SD = Standard deviation *Classification of the Dutch educational system. Primary educated = no education, primary school, pre-vocational education (VMBO); secondary educated = senior general secondary education (HAVO), pre-university education (VWO), post-secondary vocational education

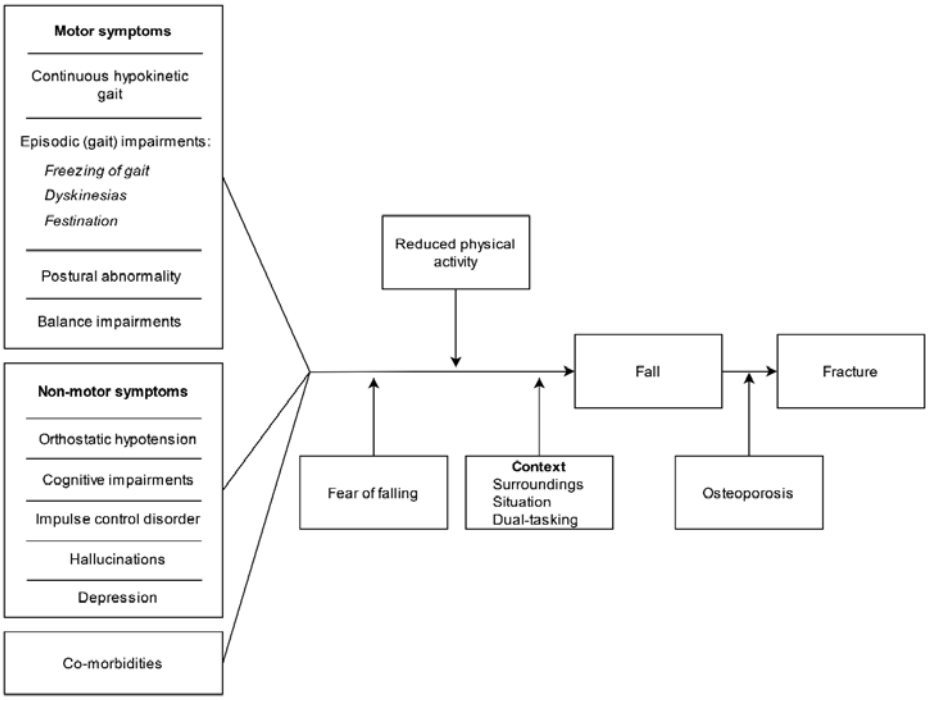

Figure 2. The causal pathway for falls and fractures. We grouped causal factors as motor symptoms, non-motor symptoms and co-morbidities. The joint effect of these causal factors is modified by a fear of falling, physical activity and a person's context. If a fall occurs, osteoporosis negatively modifies the risk of a subsequent fracture occurring.

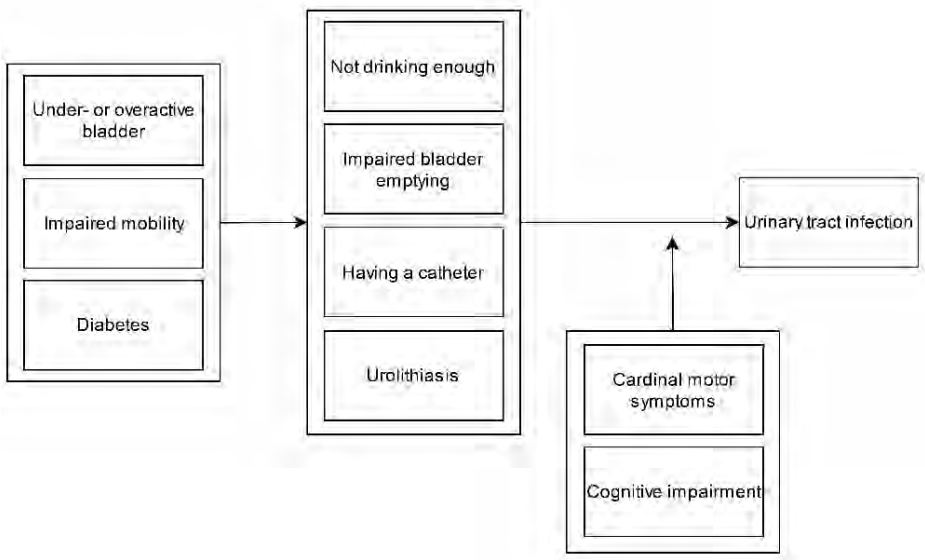

Figure 3. The causal pathway for a urinary tract infection. We identified several causal factors including an under- or overactive bladder and impaired mobility. The effect of these causal factors is mediated by factors such as not drinking enough, impaired bladder emptying and having a catheter. Finally, cardinal motor symptoms and cognitive impairment modify the effect between the mediators and a urinary tract infection, for example when a hand tremor hampers sterile insertion of the catheter.

Table 3. Population attributable fractions for falls and fractures.

Causal factor	Prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					**37.1%**
Balance impairments	25.2%	3.65 [2.59; 5.17]	50%	40% [28.5; 51.2]	14.8% [8.2; 19.8]
Hypokinetic rigid gait	68%	1.85 [1.35; 2.55]	38%	36.6% [19.1; 51.4]	13.6% [7.5; 18.2]
Freezing of gait	22.8%	2.34 [1.65; 3.33]	50%	23.4% [13; 34.7]	8.7% [4.8; 11.6]
Dyskinesias					NA
Festination					NA
Postural abnormalities					NA
Non-motor symptoms					**15.1%**
Depression	13.8%	2.34 [1.56; 3.54]	29%	15.6% [7.1; 25.9]	5.8% [3.2; 7.7]
Hallucinations	12.8%	2.38 [1.55; 3.69]	50%	15% [6.5; 25.5]	5.6% [3.1; 7.4]
Cognitive impairments	35.9%	1.27 [0.94; 1.71]	41%	8.8% [-2.2; 20.3]	3.3% [1.8; 4.4]
Orthostatic hypotension	0.6%	3.02 [0.39; 61.85]	49%	1.1% [-0.3; 25.7]	0.4% [0.2; 0.6]
Impulse control disorder					NA
Other					**8.0%**
Arthrosis	18.8%	1.67 [1.17; 2.38]	71%	11.1% [3; 20.7]	4.1% [2.3; 5.5]
Alcohol abuse	18.1%	1.4 [0.98; 2.01]	84%	6.8% [-0.4; 15.5]	2.5% [1.4; 3.4]
Heart disease	22.2%	1.17 [0.83; 1.66]	51%	3.7% [-3.9; 12.7]	1.4% [0.8; 1.9]
Osteoporosis					NA
Total					**60.2% [33.4; 80.4]**

CI = Confidence interval; PAF = Population attributable fraction; NA = Not available in the PRIME-NL dataset.

Table 4. Population attributable fractions for urinary tract infections.

Causal factor	Prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					**14.6%**
Overactive bladder	13.2%	2.36 [1.33; 4.11]	56%	15.2% [4.2; 29.1]	6.2% [0.6; 13.8]
Underactive bladder	10.8%	2.32 [1.09; 4.71]	51%	12.5% [0.9; 28.6]	5.1% [0.5; 11.3]
Impaired mobility	6%	2.48 [1.14; 5.16]	58%	8.1% [0.9; 20]	3.3% [0.3; 7.4]
Impaired bladder emptying					NA
Other					**6.7%**
Having a catheter	1.2%	13.83 [3.01; 56.63]	60%	13.3% [2.4; 40]	5.4% [0.5; 12]
Diabetes	5.1%	1.66 [0.53; 4.34]	37%	3.3% [-2.5; 14.6]	1.3% [0.1; 3]
Not drinking enough					NA
Urolithiasis					NA
Total					**21.5% [2.0; 47.4]**

*CI = Confidence interval; PAF = Population attributable fraction; NA = Not available in the PRIME-NL dataset.*Effect modification for falls and fractures

Discussion

In this paper, we present a novel approach to identify modifiable causal factors for the prevention of complications in PD. First, we systematically searched the literature for known causal factors. Second, we ascertained the face validity of these causal factors and prioritized them through an online survey with PD healthcare professionals. These healthcare professionals also used their unique in-practice experience to complement the list of literature-based causal factors. Third, we mapped causal pathways together with experts for each complication using the causal factor lists from step 2. Finally, we explored the estimation of the proportion of preventable complications through population attributable fractions calculated from the PRIME-NL dataset.

Using our mixed methods approach, we came across several challenges of which we highlight two in particular. First, the knowledge base in the literature is asymmetrical. The literature search yielded several relevant systematic reviews and meta-analyses for some complications in people with PD, in particular for falls.[13] Other complications, such as urinary tract infections, are less well-studied and we had to extend our search to other populations because of limited data on people with PD.[22] This asymmetry can be caused by a difference in prevalence, impact or treatability of each complication.[4,5] Yet, the addition of qualitative data based on the clinical experience of healthcare professionals in step 2 and 3 filled some of this knowledge gap. For example, many healthcare professionals expressed experience with urinary tract infections and pneumonias, despite being the complications with fewest literature findings. Although the survey sample itself could be skewed towards physiotherapists and nurses, our method illustrates the value of combining quantitative data from previous literature and qualitative data based on clinical experience.

Second, a complex interplay exists between many of the causal factors displayed in the causal pathways. Examples of this interplay, i.e., effect modification, include the reversed U-shape relation of fear of falling and physical activity with falls,[13,23] the combined effect of dysphagia and dystussia on pneumonia [24] and the compound effect of cognitive impairments, sleep deprivation and stress on psychotic symptoms.[25] Furthermore, complications can also cause each other, for example a urinary tract infection causing psychotic symptoms or a fall,[15] a fall leading to hospitalization and subsequent pneumonia, or psychotic symptoms being associated with dementia.[10] Although we displayed a simplified version of a complex reality in the causal pathways, we aimed to capture and clearly present

important and well-established relationships. To disentangle known relationships as much as possible, we tried to pull apart variables that yield predictive value yet provide little explanation of how they operate. Examples of such 'black-boxes' found in the literature include age, disease severity or the prior occurrence of the complication. Such variables can be used in screening and predictive tools to identify at-risk people with PD (e.g. [26,27] and **figure 4**), but their non-modifiable nature and the absence of a clear working mechanism, i.e., how they cause the outcome, decrease their usefulness for proactive prevention efforts.

Our mixed methods approach can support the development of models of proactive clinical care. Proactive care relies heavily on regular monitoring: assessing relevant variables to detect early warning signs and pre-emptively addressing those. Other studies already showed the positive effects of proactive care. For example, a proactive outreach program called vulnerable and often homebound people with PD during the COVID-19 pandemic to address medication prescriptions, home safety and wellbeing.[28] These phone calls were highly appreciated by the people with PD, especially those without a strong social network. Another study deployed a telemonitoring tool to routinely assess people with PD on both motor and non-motor symptoms.[29] Outpatient visits to the clinic were only scheduled when needed, e.g., scores worsened, reducing healthcare visits by 29% after one year. Similarly, our models can help clinicians, people with PD and policy makers to decide which variables should be monitored within such proactive healthcare initiatives. However, we note that the causal pathways display group-level patterns which require translation and adaptation to individual persons with PD and their context. Clinicians and people with PD can use our findings as a broadly informed starting point from where to tailor the pathway to an individual. To support this translation to clinical practice, we displayed three levels of modifiability in **figure 4**.

Besides the potential clinical implications, our approach also has implications for research on prevention. First, we recommend others to adapt and apply our four-step approach when investigating new routes towards prevention. The mixed methods approach helps to gain a thorough and comprehensive overview of all available knowledge. Second, our causal pathways and population attributable fractions highlight the complexity and interrelatedness of causal factors, with many causal factors having a communality above 50%. This high degree of overlap between causal factors will lead to overestimation of relative risks across studies when each study examines causal factors in isolation or in small groups. Rather than solving single causal factor questions in isolation, we recommend combining (prospective) cohort study data using meta-analyses to adjust estimates.

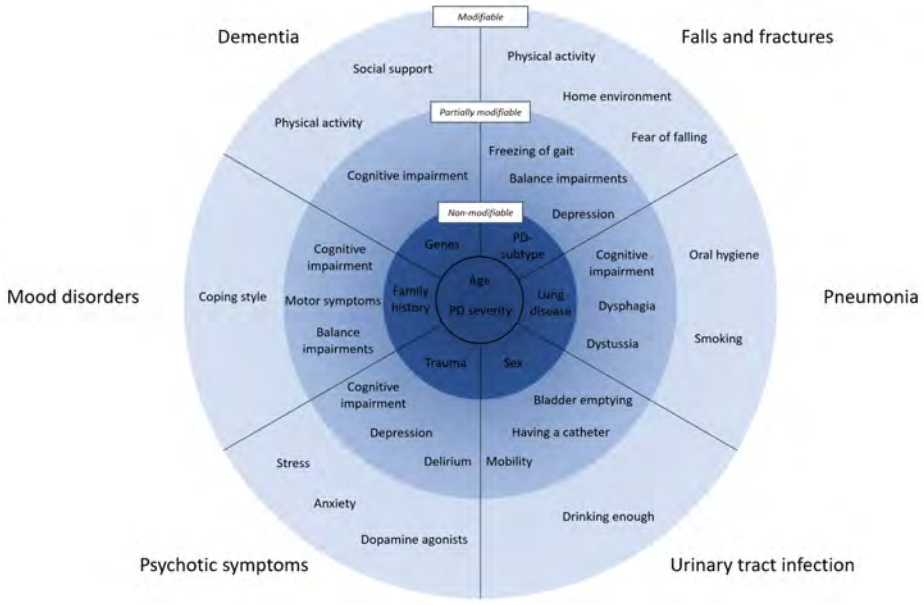

Figure 4. Levels of modifiability. Some causal factors are non-modifiable, but can act as risk-group identifiers, for example sex for urinary tract infection; other causal factors are partially modifiable meaning that the right treatment can reduce, but likely not eliminate the risk completely, for example reducing balance impairments with physiotherapy; and some causal factors are, in theory, completely modifiable and form clear prevention targets, for example fear of falling.

This mixed methods study was not without limitations. First, we must note that population attributable fractions are a theoretical construct. Not all causal factors can be completely eliminated from the population (**figure 4**). Furthermore, when we take preventive measures such as adjusting medication, providing specialised therapy or optimising a person's home environment, these interventions will inevitably have a ripple effect on the other factors.[15,30] This ripple effect hampers our ability to predict the impact of eliminating one specific causal factor.

Second, we used the PRIME-NL dataset to obtain proof-of-principle estimates of the population attributable fractions in step 4. We chose this dataset because it has a relatively broad coverage of causal factors and a representative sample of people with PD.[17] However, the PRIME-NL study was not specifically designed for the purpose of our current project, so there are several inherent limitations to the available data. Our estimates of population attributable fractions should therefore be interpreted with caution. In particular, the dataset yields retrospective and cross-sectional data. Participants' responses might therefore suffer from recall

bias and we were unable to correct estimates for prior exposures to causal factors. Furthermore, the dataset consists of self-report questionnaire data which limits the accuracy of the data. For example, people might be unaware of subtle symptoms such as beginning dysphagia or bladder dysfunction, leading to underestimation of the prevalence thereof.[15,31] Another issue could be that the questionnaire offered no room to provide relevant details, such as the distinction between falls with and without syncope, which come with different causal factors.[13] In light of these limitations, our population attributable fractions can best be interpreted relative rather than absolute: motor symptoms contribute more to fall incidents as compared to non-motor symptoms and having a catheter contributes more to urinary tract infections than having diabetes.

Future research efforts are needed to advance and refine our methodology and the findings, preparing them for implementation in clinical practice. First, the individual causal pathways require further refinement as our base of knowledge grows.[32] For example, embedding a dynamic life-course approach [33] and non-modifiable factors into the pathways enlarges the explained person-level variance. Also, some broad causal factors such as coping style or cognitive impairment could be further specified, for example by incorporating psychological variables like self-perception, loss of control, hopes and beliefs. Second, data from prospective cohort samples can be used to replicate our analyses and refine our estimates. Enhancing the statistical power would allow for tests of mediation and effect modification, as well as estimating how the distribution of population attributable fractions changes in different subgroups of people with PD. Third, future research should examine whether incorporating the most relevant causal factors into monitoring systems helps to improve outcomes for people with PD. For example, digital health records could contain tailored pre-consultation questionnaires [34] which provide early flagging of problems, making earlier similar systems more specific.[29] Finally, our study may inspire similar mixed-methods research to unravel the potential to prevent complications in other chronic diseases.

References

1. Feigin, V. L. *et al.* Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* **18**, 459–480 (2019).
2. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* **397**, 2284–2303 (2021).
3. Tenison, E. *et al.* Proactive and Integrated Management and Empowerment in Parkinson's Disease: Designing a New Model of Care. *Parkinson's Disease* **2020**, 1–11 (2020).
4. Okunoye, O., Kojima, G., Marston, L., Walters, K. & Schrag, A. Factors associated with hospitalisation among people with Parkinson's disease – A systematic review and meta-analysis. *Parkinsonism & Related Disorders* **71**, 66–72 (2020).
5. Low, V. *et al.* Measuring the burden and mortality of hospitalisation in Parkinson's disease: A cross-sectional analysis of the English Hospital Episodes Statistics database 2009–2013. *Parkinsonism & Related Disorders* **21**, 449–454 (2015).
6. Macleod, A. D., Taylor, K. S. M. & Counsell, C. E. Mortality in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord.* **29**, 1615–1622 (2014).
7. Bloem, B. R. *et al.* Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology* **19**, 623–634 (2020).
8. Ben-Shlomo, Y. *et al.* The epidemiology of Parkinson's Disease. *The Lancet* **403**, 283-292 (2024).
9. Sharma, J. C., Bachmann, C. G. & Linazasoro, G. Classifying risk factors for dyskinesia in Parkinson's disease. *Parkinsonism & Related Disorders* **16**, 490–497 (2010).
10. Marinus, J., Zhu, K., Marras, C., Aarsland, D. & Van Hilten, J. J. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet Neurology* **17**, 559–568 (2018).
11. Rothman, K. J. *Epidemiology: An Introduction*. (Oxford University Press, Oxford, 2012).
12. Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K. & Brayne, C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *The Lancet Neurology* **13**, 788–794 (2014).
13. Fasano, A., Canning, C. G., Hausdorff, J. M., Lord, S. & Rochester, L. Falls in Parkinson's disease: A complex and evolving picture: Falls and PD. *Mov Disord.* **32**, 1524–1536 (2017).
14. Murueta-Goyena, A., Muiño, O. & Gómez-Esteban, J. C. Prognostic factors for falls in Parkinson's disease: a systematic review. *Acta Neurol Belg* **124**, 395-406 (2023).
15. Hogg, E. *et al.* Urinary Tract Infection in Parkinson's Disease. *JPD* **12**, 743–757 (2022).
16. Ypinga, J. H. L. *et al.* Rationale and design to evaluate the PRIME Parkinson care model: a prospective observational evaluation of proactive, integrated and patient-centred Parkinson care in The Netherlands (PRIME-NL). *BMC Neurol* **21**, 286 (2021).
17. Gelissen, L. *et al.* Assessing the validity of a Parkinson's care evaluation: the PRIME-NL study. *Eur J Epidemiol* (in press).
18. Levin, M. L. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* **9**, 531–541 (1953).
19. Mukadam, N., Sommerlad, A., Huntley, J. & Livingston, G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *The Lancet Global Health* **7**, e596–e603 (2019).
20. Nianogo, R. A. *et al.* Risk Factors Associated With Alzheimer Disease and Related Dementias by Sex and Race and Ethnicity in the US. *JAMA Neurol* **79**, 584 (2022).

21. R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.
22. Van Der Maarel-Wierink, C. D., Vanobbergen, J. N. O., Bronkhorst, E. M., Schols, J. M. G. A. & De Baat, C. Risk Factors for Aspiration Pneumonia in Frail Older People: A Systematic Literature Review. *Journal of the American Medical Directors Association* **12**, 344–354 (2011).
23. Allen, N. E., Schwarzel, A. K. & Canning, C. G. Recurrent Falls in Parkinson's Disease: A Systematic Review. *Parkinson's Disease* **2013**, 1–16 (2013).
24. Hegland, K. W., Okun, M. S. & Troche, M. S. Sequential Voluntary Cough and Aspiration or Aspiration Risk in Parkinson's Disease. *Lung* **192**, 601–608 (2014).
25. Chang, A. & Fox, S. H. Psychosis in Parkinson's Disease: Epidemiology, Pathophysiology, and Management. *Drugs* **76**, 1093–1118 (2016).
26. Almeida, L. R. S., Valenca, G. T., Negreiros, N. N., Pinto, E. B. & Oliveira-Filho, J. Predictors of Recurrent Falls in People with Parkinson's Disease and Proposal for a Predictive Tool. *JPD* **7**, 313–324 (2017).
27. Carlisle, T. C., Medina, L. D. & Holden, S. K. Original research: initial development of a pragmatic tool to estimate cognitive decline risk focusing on potentially modifiable factors in Parkinson's disease. *Front. Neurosci.* **17**, 1278817 (2023).
28. Sennott, B. *et al.* Novel Outreach Program and Practical Strategies for Patients with Parkinsonism in the COVID-19 Pandemic1. *JPD* **10**, 1383–1388 (2020).
29. Wijers, A., Hochstenbach, L. & Tissingh, G. Telemonitoring via Questionnaires Reduces Outpatient Healthcare Consumption in Parkinson's Disease. *Movement Disord Clin Pract* **8**, 1075–1082 (2021).
30. Van Der Marck, M. A. *et al.* Consensus-based clinical practice recommendations for the examination and management of falls in patients with Parkinson's disease. *Parkinsonism & Related Disorders* **20**, 360–369 (2014).
31. Takizawa, C., Gemmell, E., Kenworthy, J. & Speyer, R. A Systematic Review of the Prevalence of Oropharyngeal Dysphagia in Stroke, Parkinson's Disease, Alzheimer's Disease, Head Injury, and Pneumonia. *Dysphagia* **31**, 434–441 (2016).
32. Camicioli, R. *et al.* Prevention of Falls in Parkinson's Disease: Guidelines and Gaps. *Movement Disord Clin Pract* **10**, 1459–1469 (2023).
33. Ben-Shlomo, Y. & Kuh, D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology* **31**, 285-293 (2002).
34. Peerbolte, T. F., Van Diggelen, R. J. A., Meinders, M. J., Bloem, B. R. & Van Den Berg, S. W. If you only have 7 minutes, make them count! *Pract Neurol* **23**, 539–541 (2023).

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Assessing the validity of a Parkinson's care evaluation: The PRIME-NL study

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Abstract

Background

The PRIME-NL study prospectively evaluates a new integrated and personalized care model for people with parkinsonism, including Parkinson's disease, in a selected region (PRIME) in the Netherlands. We address the generalizability and sources of selection and confounding bias of the PRIME-NL study by examining baseline and 1-year compliance data.

Methods

First, we assessed regional baseline differences between the PRIME and the usual care (UC) region using healthcare claims data of almost all people with Parkinson's disease in the Netherlands (the source population). Second, we compared our questionnaire sample to the source population to determine generalizability. Third, we investigated sources of bias by comparing the PRIME and UC questionnaire sample on baseline characteristics and 1-year compliance.

Results

Baseline characteristics were similar in the PRIME (n = 1430) and UC (n = 26250) source populations. The combined questionnaire sample (n = 920) was somewhat younger and had a slightly longer disease duration than the combined source population. Compared to the questionnaire sample in the PRIME region, the UC questionnaire sample was slightly younger, had better cognition, had a longer disease duration, had a higher educational attainment and consumed more alcohol. 1-year compliance of the questionnaire sample was higher in the UC region (96%) than in the PRIME region (92%).

Conclusion

The generalizability of the PRIME-NL study seems to be good, yet we found evidence of some selection bias. This selection bias necessitates the use of advanced statistical methods for the final evaluation of PRIME-NL, such as inverse probability weighting or propensity score matching. The PRIME-NL study provides a unique window into the validity of a large-scale care evaluation for people with a chronic disease, in this case parkinsonism.

Background

Parkinson's disease is a neurodegenerative progressive and chronic syndrome affecting roughly 7 million people globally.[1] The clinical presentation and progression is highly heterogeneous, whilst current models of care insufficiently address the person-specific needs of people with PD and related neurodegenerative diseases characterized by parkinsonism.[2] Models of care for chronic, neurological disorders could specifically enhance their multidisciplinary collaboration, timely detection and proactive management of problems, and further facilitate the empowerment and involvement of people with parkinsonism and carers in their own healthcare process.[3] To address these challenges, an international panel of multidisciplinary healthcare professionals designed a new integrated and personalized care model for people with parkinsonism called 'PRIME Parkinson': Proactive and Integrated Management and Empowerment in Parkinson's disease.[4] The model seeks to achieve a quadruple aim of healthcare [5,6]: enhancing patient and carers experience of care, improving population health, maintaining neutral healthcare costs and improving professional fulfilment of healthcare providers involved in the care of people with parkinsonism.

In the Netherlands, the PRIME Parkinson care model has gradually been introduced as a replacement of usual care from 2021 onwards in one tertiary healthcare centre and four regional hospitals (PRIME region).[7] We focused on hospital-based care as the majority of people with PD in the Netherlands (>95%) receive it. Except for the PRIME region, the rest of the Netherlands continued providing usual care (UC region). To determine the impact of the PRIME Parkinson care model with regard to the quadruple aim, a prospective multifaceted evaluation was initiated called the PRIME-NL study. Note that a complementary study is underway in the south-west of England, termed the PRIME-UK study.[8]

The PRIME-NL study collects both healthcare claims data and annual questionnaires in the PRIME and UC region for five years. We use the healthcare claims data to assess the population health domain of the quadruple aim by measuring, amongst other variables, the occurrence of parkinsonism-related complications amongst all people with Parkinson's disease (PD) in the Netherlands. The annual questionnaires include a questionnaire sample of people with parkinsonism, care partners and healthcare professionals from both the PRIME and UC region. The questionnaires cover a broad range of topics addressing the four domains of the quadruple aim, such as experience of care, quality of life, empowerment and healthcare professional fulfilment. Data collection for PRIME-NL started in January 2020, one

year before the implementation of the PRIME Parkinson care model, which serves as the baseline measurement. In this paper, we only analyse the data from persons with parkinsonism because we also had access to their healthcare claims data, unlike the situation for carers and healthcare professionals.

Because of the real-life nature of the evaluation, several methodological challenges may hamper a valid evaluation of the PRIME Parkinson care model. Three questions stand out in particular and will be addressed in this paper. The first question is whether the source population of people with PD differs between the PRIME and UC region. The second question is whether the combined questionnaire sample of participants from both regions is representative of all people with PD in the Netherlands, i.e. whether the questionnaire sample findings can be generalized to the source population. The third question is whether potential selection and confounding bias is the same or different between the PRIME and UC questionnaire sample, i.e., we examine those as important aspects of the internal validity. **Figure 1** demonstrates the conceptual framework of possible pathways through which selection and confounding bias may affect the evaluation of PRIME-NL.

Methods

Overview

The source population is defined as all people with PD in the Netherlands, divided in either the PRIME or the usual care region receiving hospital-based neurological care.[7] From both source populations, we recruited a questionnaire sample containing an unmatched and self-enrolled group of people with PD (convenience sampling). To examine the research questions, we 1) investigated the regional differences in baseline characteristics between the source population in the PRIME and UC region in the healthcare claims data, 2) determined the generalizability of the questionnaire sample by comparing their characteristics to the source population, and 3) tested for the presence of selection and confounding bias by comparing the PRIME and UC questionnaire sample at baseline and 1-year follow-up (**figure 2**). The PRIME-NL study was exempted from further ethical approval after the study had been reviewed by the ethical committee of the Radboudumc (file 2019-5618).

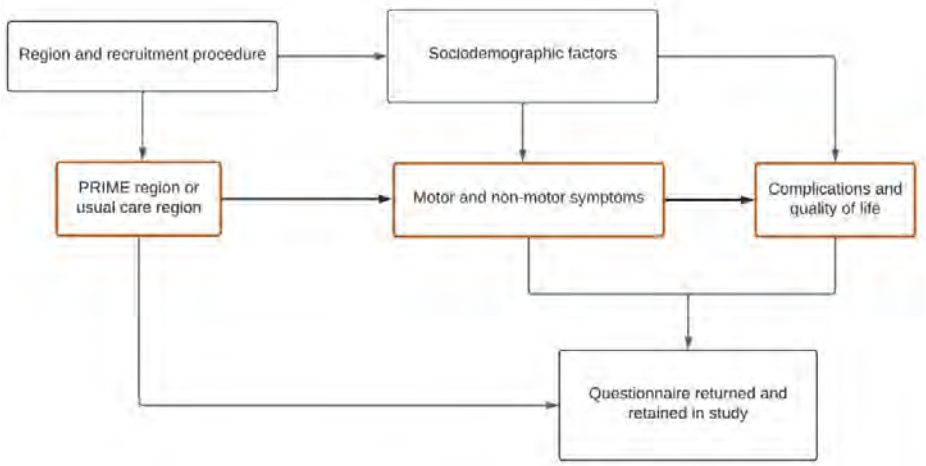

Figure 1. Directed Acyclic Graph (DAG) of possible potential sources of bias that may influence the eventual evaluation of the PRIME-NL study.

In orange, a highly simplified version of the effect of PRIME care is displayed (middle pathway): improved care can ameliorate motor and non-motor symptoms which in turn reduce the amount of complications and improve the quality of life. However, for an adequate evaluation of the PRIME Parkinson care model, several methodological challenges and potential sources of bias need to be identified. First, PRIME Parkinson care has been implemented in a specific, non-randomized region of the Netherlands which might be different from the rest of the Netherlands (UC region) at baseline. The regions can differ in sociodemographic factors that impact the presence of symptoms, complications, and quality of life (top pathway). Sociodemographic factors can thereby introduce confounding bias, e.g. the PRIME participants are older, and older age is associated with more symptoms and more complications, making PRIME look worse on the final evaluation when not correcting for age. Second, we might have differentially recruited people from the source populations into the questionnaire sample, e.g. through the letter by the neurologists in the PRIME region. This letter might have reached specific subgroups of participants in the PRIME region, e.g. people with more symptoms, introducing selection bias. Third, collider bias might create an artificial association between the region and outcomes when differential loss to follow-up occurs. For example, if we assume that we have recruited more affected people in the PRIME region and participants with more symptoms are less likely to return their questionnaire, the PRIME region will appear worse compared to UC in which fewer highly affected participants are retained (bottom pathway). We have not illustrated information bias in this DAG since participants were unaware of the study group at baseline. However, at follow-up, because the study is unblinded, they will be aware and this could introduce differential measurement error.

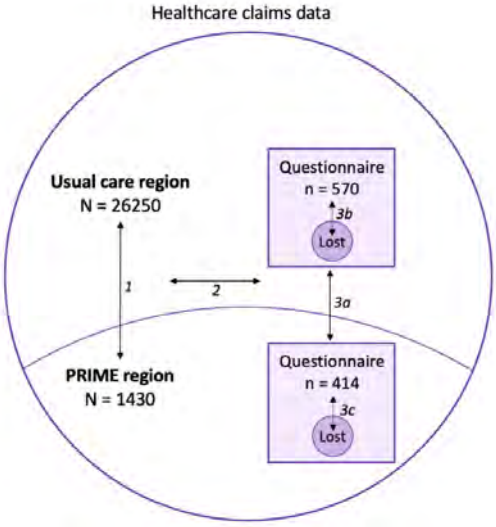

Figure 2. Overview of the comparisons made. First, we assessed regional baseline differences between the PRIME and the usual care (UC) region using healthcare claims data of almost all people with Parkinson's disease in the Netherlands (the source population) (1). Second, we compared the combined questionnaire sample of participants from both regions to the source population to determine if the questionnaire sample findings will be generalizable to all people with PD in the Netherlands (2). Third, to assess selection and confounding bias between the two regions, we compared the PRIME and UC questionnaire sample on baseline characteristics (3a) and investigated whether there is differential 1-year compliance (3b and 3c).

Healthcare claims data on source population

People with PD were identified in the national healthcare claims data of Vektis, which contains the data of more than 99% of all people with PD in the Netherlands. For this specific analysis, we included only people with PD, based on diagnostic hospital code DBC501, because the diagnostic hospital code for atypical parkinsonism is also used for other types of movement disorders. The inclusion criteria were: 1) received the 501 code in 2018, 2019 or 2020, 2) alive in 2020, and 3) primarily received outpatient care at a regional hospital instead of a university medical centre, because PRIME Parkinson care is restricted to regional hospitals as they better reflect usual care for the majority of people with parkinsonism. The hospital of care was classified as regional if people with PD received more than 75% of their care in a regional hospital in the years 2018, 2019 and 2020. In our analysis of baseline data, we examined regional differences in age, sex, disease duration, socio-economic status, Charlson comorbidity index, hospital admissions for orthopaedic fractures and pneumonia's, as well as prescribed medication for anxiety, depression, and cognitive impairments. As part of Dutch health insurance policy, all persons in the Vektis database agreed on using their data anonymously for scientific study purposes.

Furthermore, we leveraged data from the Central Bureau of Statistics (CBS) of the Netherlands to determine regional differences regarding variables not included in the healthcare claims database.[9] This includes migratory background, overweight based on body mass index (BMI), COVID-19 occurrence, smoking behaviour, alcohol consumption, education, and living situation. Although these data are extracted from the general population instead of the PD specific population, they are the only and best proxy for determining regional differences at baseline for the PD population for the variables missing in the healthcare claims data. If a relationship between these variables and PD exists [10], we assumed that such a relationship will be similar between both regions. We extracted data on a provincial level because no municipality-level data were available (see **supplementary file S1** for details). Therefore, in this analysis only, we used the provinces Gelderland, Noord-Brabant and Limburg as a proxy for the PRIME region, because they cover the population of the PRIME hospitals.[7] We are mindful that these provinces also include considerable subregions that are not part of the PRIME region, so we interpret this analysis with caution.

Questionnaire sample

Participants

People with a clinical diagnosis of parkinsonism, which was confirmed by a letter of the general practitioner or neurologist, were eligible to participate in the questionnaire study, irrespective of whether the specific diagnosis was PD or atypical parkinsonism. People with medication-induced parkinsonism and those who received their treatment in university medical centres were excluded. Potential participants must have visited the neurology outpatient clinic of a regional hospital at least once during the last year for inclusion in questionnaire-based assessments.[7]

Materials

The questionnaire consisted of various tailor-made sub-questionnaires aimed at retrieving socio-demographic characteristics as well as several existing (clinical) questionnaires to measure, e.g., depression or anxiety. For this paper, the following variables were examined: region, recruitment procedure, sex, age, disease duration, COVID-19 burden, education, work situation, living situation, smoking behaviour, alcohol consumption, BMI, comorbidities, anxiety, depression, cognition, complications, motor symptoms, disease stage based on the Hoehn and Yahr score, and quality of life. All items in the questionnaire were mandatory to complete for participants. An overview of included variables and associated questionnaires is provided in **supplementary table S1**.

Procedures

Prior to study inclusion, potential participants were called by one of the well-trained research assistants of the assessment team to inform them about study procedures and screen on inclusion criteria. When eligible for the study, participants were sent an informed consent form. Participants had up to 10 days to think about participating in the study. They were called again to discuss any questions and, if they were still interested, to sign the informed consent on paper or digitally and to assess cognitive performance using the telephone Montreal Cognitive Assessment (t-MoCA). Afterwards, participants could either self-complete questionnaires electronically or on paper or answer the questions during a phone call with one of the research assistants. Only the paper version of the questionnaire allowed participants to not complete questions. If this was the case, the assessment team called, e-mailed or sent a letter to the participant to complete the questionnaire(s). When the questionnaire was administered via a phone call, the research assistant would encourage the participant to answer all questions. We implemented identical recruitment strategies in both regions, except for an additional information letter sent by the treating neurologists to the persons with parkinsonism in the PRIME region because recruitment was lagging behind (**table 1**).

Statistical analyses

Source population differences

The healthcare claims and CBS data were used to examine the regional demographic differences at baseline (2020) between persons with PD in the PRIME and UC region (**table 2A**). We used t-tests for age, disease duration, socioeconomic status and comorbidities. For each outcome, we inspected histograms and standard deviations per group to assess the assumptions of normality and homoscedasticity. If these assumptions were violated, we performed the Mann-Whitney U-test instead of the t-test. We performed Chi-square tests for sex, anti-anxiety medication, anti-depressive or cognitive medication, orthopedic fractures and pneumonia's to compare both regions. For the CBS data comparisons (**table 2B**), we performed no statistical tests as these data reflect population-measures. We adhered to a 5% difference as cut-off for meaningful differences.

Table 1. Recruitment procedures and strategies to restrain the loss to follow-up in the PRIME-NL study.

Recruitment procedures (adapted from [7])		
Phase 1	PRIME and UC region	Members of ParkinsonNEXT across the Netherlands were invited via a letter.[a]
		The Parkinson Association[b] sent newsletters to their members and shared posts on their website.
		A brochure with a reply card was shared with potential participants at different events for people with parkinsonism and their carers.
	Exclusively in PRIME region	Neurologists sent information letters to all people with parkinsonism they treated.
Phase 2	PRIME and UC region	People with parkinsonism could express interest in participating via a website, telephone, email or a reply card by post. Then, they received more information about the study by a call from a member of the research team.
Phase 3	PRIME and UC region	People with continued interest received an information letter and consent form by e-mail or post. They signed the informed consent before enrolment.
Efforts of the assessment team to encourage people with parkinsonism for participation		
1	The assessment team analysed through sampling in the questionnaire sample how participants want to be informed about the study, and how they wish to be involved in study.	
2	Participants are called personally, when possible by the same assessor, prior to each questionnaire to inform them of the upcoming questionnaire, re-iterate the study content and allow participants to ask questions.	
3	Every year, in December, a personal Christmas card is sent to every participant.	
4	A quarterly newsletter is sent out to participants with the latest study updates.	
5	Assessors could answer questions from participants via telephone and email.	

[a] A web-based platform for people with parkinsonism and their carers who have expressed an interest in participating in research

[b] A Dutch association for people with Parkinson's disease and parkinsonism

Generalizability

We tested whether the source population and questionnaire sample, both with combined regions, were different in age and disease duration with t-tests. For sex and the number of pneumonia's, we performed Chi-square tests to compare the source population and questionnaire sample (**table 2C**). To make a fair comparison to the source population, we excluded the people with atypical parkinsonism from the questionnaire sample for this analysis. Furthermore, we adjusted the combined questionnaire sample estimates through inverse probability weighting. This was necessary to account for the selective overrepresentation of PRIME participants in the questionnaire sample, as we recruited 27% of the PRIME source population versus 2% of the UC source population.

Selection and confounding bias

To examine the presence of selection bias and the potential for confounding bias in the questionnaire sample, we tested whether the PRIME region and the UC region (predictor) differed with respect to baseline characteristics (outcome) (**table 3**). Furthermore, to assess whether the recruitment procedure introduced selection bias, we compared people within the PRIME region who were recruited by their neurologist with people who were not recruited by their neurologist (predictor) on baseline characteristics (outcome) (**table 4**). For both analyses, we used linear regression for continuous outcomes and multinomial or binary logistic regression for nominal and ordinal outcomes, adjusting all analyses for age, sex and disease duration. Outliers were included. Continuous variables that did not meet the assumptions for linear regression were log transformed before conducting linear regression.

To examine if the loss to follow-up caused selection bias, differences between participants who remained in the study and who were lost were assessed with linear regression for continuous outcomes (age, motor symptoms, depression, anxiety, cognition, quality of life, disease duration) and with multinomial (education and disease stage) or binomial (sex) logistic regression, using compliance as predictor in all models (**table 5**). We performed these analyses for each region separately as we expect a test for interaction across all outcomes and regions to be underpowered given the low number of drop-outs. We log-transformed continuous outcomes that did not meet the assumptions for linear regression. We define a loss to follow-up as a participant who no longer provided questionnaire data for any reason. Therefore, the loss to follow-up numbers contain both deceased participants as well as actively dropped-out participants. All p-values were adjusted according to the Benjamini-Hochberg method.[11]

All data analyses were conducted in R Studio version 2022.02.1.[12] We pre-registered our analyses at the Open Science Framework. In our interpretation of all analyses, we consider both p-values, effect estimates and confidence intervals to judge whether differences between groups are meaningful.

Results

Source population differences and generalizability

Based on the inclusion criteria, data from 27680 people with PD were extracted from the healthcare claims data. The source populations of people with PD were similar in both regions in terms of age, sex, comorbidity scores, and number of fractures and pneumonias (**table 2A**). However, people with PD living in the PRIME region had a slightly shorter disease duration (0.2 years, 95% confidence interval (CI) 0.01 to 0.39, p <.0001), used fewer anti-depressive or cognitive medications (odds ratio (OR) 0.85, 95% CI 0.75 to 0.97, p = .016), used fewer anti-anxiety medications (OR 0.77, 95% CI 0.66 to 0.91, p = .002) and had a lower socioeconomic status (mean difference = -0.14, 95% CI -0.20 to -0.08, p <.0001) compared to people with PD in the UC region. The CBS data showed no meaningful differences between the PRIME and UC source populations (**table 2B**).

People with PD in the questionnaire sample were younger than the source population (-4.30 years, 95% CI -4.90 to -3.71, p <.0001), had a longer disease duration (1.35 year, 95% CI 1.12 to 1.59, p <.0001) and experienced more pneumonia's (OR 1.86, 95% CI 1.21 to 2.84, p = .004). The proportion of men and women was similar in the questionnaire sample and source population (**table 2C**).

Table 2. Comparison of baseline characteristics in A) the UC and PRIME source populations based on the healthcare claims data, B) the same comparison based on the CBS data and C) the source population as a whole and the PRIME-NL questionnaire sample.

A	UC region claims data (n = 26250)	PRIME region claims data (n = 1430)	Mean difference or odds ratio [95% CI] [b]	p
Age: mean (SD) [a]	72.7 (9.1)	73.0 (8.9)	0.3 [-0.18, 0.78]	.22
Sex (men): n (%)	15794 (60)	872 (61)	1.04 [0.93, 1.15]	.54
Disease duration in years: mean (SD) [c]	5.3 (3.5)	5.1 (3.5)	0.2 [0.01, 0.39]	<.0001
Participants with at least one anti-depressive or cognitive medication: n (%)	6621 (25)	320 (22)	0.85 [0.75, 0.97]	.016
Participants with at least one anti-anxiety medication: n (%)	3906 (15)	170 (12)	0.77 [0.66, 0.91]	.002
Charlson comorbidity index: mean (SD)	2.91 (1.00)	2.95 (0.99)	0.04 [-0.01, 0.09]	.14
Socioeconomic status (standardized): mean (SD)	-0.11 (1.1)	-0.25 (1.1)	-0.14 [-0.20, -0.08]	<.0001
Participants with at least one fracture: n (%)	940 (3.6)	56 (3.9)	1.10 [0.83, 1.45]	.51
Participants with at least one pneumonia: n (%)	359 (1.4)	18 (1.3)	0.92 [0.57, 1.48]	.73

B	UC region CBS data	PRIME region CBS data
Migratory background: n (%) [d]	146895 (5.5)	107912 (7.0)
Overweight: n (%)	1147860 (56.9)	683477 (58.2)
COVID-19 hospitalizations: n (%)	13805 (0.61)	10140 (0.80)
Smoking: n (%)	190114 (9.4)	107498 (9.2)
Excessive alcohol consumption: n (%)	154825 (7.7)	80192 (6.8)
Education: n (%) [e]		
Primary	2517444 (27.6)	1438755 (31.1)
Secondary	3657181 (40.0)	1870024 (40.5)
Tertiary	2960875 (32.4)	1311749 (28.4)
Living situation: n (%)		
Alone	849094 (44.1)	416979 (40.5)
With partner or child(ren)	1074807 (55.9)	612565 (59.5)

C	Source population claims data (n = 27680)	Questionnaire sample questionnaire data (n = 920) [f]	Mean difference or odds ratio [95% CI] [b]	p
Age: mean (SD)	72.7 (9.1)	68.4 (8.0)	-4.30 [-4.90, -3.71]	<.0001
Sex (men): n (%)	16666 (60)	536 (58)	0.92 [0.81, 1.05]	.23
Disease duration in years: mean (SD)	5.3 (3.5)	6.65 (5.3)	1.35 [1.12, 1.59]	<.0001
Participants with at least one pneumonia: n (%)	377 (1.4)	23 (2.5)	1.86 [1.21, 2.84]	.004

[a] SD = standard deviation.

[b] CI = confidence interval. T-tests were applied on age, the Charlson comorbidity index and socioeconomic status; a Mann-Whitney U-test was used for disease duration due to non-normal distributions in both groups for table 2A, for disease duration in table 2C we used a t-test because of the inverse probability weighting; Chi-square tests for independence were applied on sex, participants with at least one anti-depressive or cognitive medication, participants with at least one anti-anxiety medication, participants with at least one fracture and participants with at least one pneumonia.

[c] Disease duration was determined by the number of years from first 501 code.

[d] CBS data for this outcome is based on people aged > 60 years, other variables are based on people >65 years

[e] CBS data for this outcome is based on people aged > 18 years. Due to changes in the educational system, no data was available on a provincial level for only people >60 years.

[f] We included only people with PD and applied inverse probability weighting based on the sampling ratio to account for selective overrepresentation of the PRIME region participants.

Selection and confounding bias in the questionnaire sample

Differences in baseline characteristics

In total, 984 participants completed the baseline questionnaire, including 920 people with PD (93.5%) and 64 people with atypical parkinsonism (6.5%). In both the PRIME and the UC region, most participants answered the questionnaire online (54% and 78% respectively). However in the PRIME region more people filled in the paper questionnaire (45%) compared to the UC region (21%; **supplementary table S2**). **Table 3** presents an overview of all baseline characteristics and their distribution across both regions. Compared to the questionnaire participants in the UC region, the participants in the PRIME region were older and had more cognitive impairments. The participants in the UC region had a longer disease duration than the PRIME participants, were more likely to receive tertiary education and tended to drink alcohol more often. No statistically significant differences were found between the PRIME and UC participants on the other outcomes when correcting for differences in age, sex and disease duration. However, the region-specific estimates suggest that participants in the PRIME region may have had more anxiety, a slightly higher BMI and a lower quality of life than participants in the UC region.

Impact of recruitment strategy

In the PRIME region, 263 participants (66%) indicated that they were introduced to the PRIME-NL study by their neurologist. Although not statistically significant, the estimates suggest that the participants recruited through their neurologist may have been older, might have had a shorter disease duration and might have been less likely to receive tertiary education than the participants recruited via the other recruitment strategies. Both groups were similar in terms of sex, motor symptoms, depression, anxiety, cognition, quality of life and disease stage (**table 4**).

Table 3. Baseline characteristics of questionnaire participants.

Variables [a]	Overall (n = 984)	PRIME (n = 414)	Usual Care (n = 570)	(Log-) B-weights / odds ratio [95% CI] [b]	Adj. p
Age (years): mean (SD)	69.7 (8.1)	71.8 (7.8)	68.2 (7.9)	-3.54 [-4.53, -2.55]	<.0001
Sex (men): n (%)	601 (61)	271 (65)	330 (58)	0.83 [0.63, 1.08]	.43
Diagnosis PD: n (%)	920 (95)	381 (92)	539 (95)	1.30 [0.76, 2.20]	.49
Disease duration (years): mean (SD) [c]	6.20 (5.2)	5.68 (5.2)	6.58 (5.3)	0.18 [0.09, 0.26]	.001
Migratory background: n (%)	9 (1)	6 (1.5)	3 (0.5)	0.42 [0.09, 1.72]	.45
BMI: mean (SD)	25.6 (4.0)	25.9 (4.2)	25.4 (3.9)	-0.68 [-1.20, -0.16]	.06
Motor symptoms: mean (SD)	12.5 (7.8)	13.0 (8.2)	12.2 (7.5)	-0.53 [-1.43, 0.38]	.45
Depression: mean (SD)	11.8 (6.9)	12.1 (7.0)	11.6 (6.8)	-0.61 [-1.50, 0.29]	.43
Anxiety: mean (SD)	38.0 (9.4)	38.9 (9.5)	37.4 (9.3)	-1.63 [-2.85, -0.41]	.06
Cognition: mean (SD) [d]	18.0 (3.0)	17.2 (3.1)	18.6 (2.7)	0.06 [0.04, 0.09]	<.0001
Quality of life: mean (SD)	73.9 (13.2)	73.0 (13.3)	74.6 (13.0)	1.95 [0.33, 3.57]	.09
COVID-19 burden: mean (SD)	2.50 (0.89)	2.44 (0.92)	2.56 (0.87)	0.14 [0.01, 0.26]	.16
Disease stage: n (%) [e]					
Stage 1	282 (29)	115 (28)	167 (29)	reference	
Stage 2	336 (34)	134 (32)	202 (35)	1.11 [0.79, 1.55]	0.67
Stage 3	150 (15)	64 (16)	86 (15)	0.99 [0.64, 1.52]	0.99
Stage 4	156 (16)	70 (17)	86 (15)	1.01 [0.64, 1.57]	0.99
Stage 5	40 (4)	23 (6)	17 (3)	0.65 [0.32, 1.34]	0.45
Comorbidities: n (%) [f]					
Cardiovascular disease	224 (23)	108 (26)	116 (20)	0.89 [0.65, 1.22]	.61
Pulmonary disease	94 (10)	45 (11)	49 (9)	0.80 [0.51, 1.23]	.49
Musculoskeletal disorder	286 (29)	124 (30)	162 (28)	0.94 [0.70, 1.27]	.79
Endocrine or metabolic disorder	95 (10)	47 (11)	48 (8)	0.80 [0.53, 1.30]	.49
Neuropsychiatric disorder	87 (9)	44 (11)	43 (8)	0.66 [0.42, 1.05]	.27
Cancer	86 (9)	48 (12)	38 (7)	0.70 [0.44, 1.12]	.42
No comorbidity	406 (41)	150 (36)	256 (45)	1.31 [1.00, 1.72]	.19
Smoking: n (%)					
Smoked in the past	544 (55)	238 (57)	306 (54)	reference	
Never smoked	411 (42)	160 (39)	251 (44)	1.00 [0.76, 1.31]	.99
Current smoker	29 (3)	16 (4)	13 (2)	0.46 [0.57, 1.02]	.21
Alcohol consumption: n (%)					
Never	193 (20)	99 (24)	94 (17)	reference	
Very rarely	193 (20)	87 (21)	106 (19)	1.32 [0.87, 2.01]	.45
Occasionally	250 (25)	112 (27)	138 (24)	1.35 [0.90, 1.99]	.42
Less than 5 days a week	167 (17)	63 (15)	104 (18)	1.80 [1.16, 2.83]	.06
5 or more days a week	181 (18)	53 (13)	128 (22)	3.46 [2.18, 5.42]	<.0001

Table 3. Continued

Variables [a]		Overall (n = 984)	PRIME (n = 414)	Usual Care (n = 570)	(Log-) B-weights / odds ratio [95% CI] [b]	Adj. p
Education: n (%)						
Primary		252 (25)	154 (38)	98 (11)	reference	
Secondary		258 (26)	114 (27)	144 (25)	1.86 [1.28, 2.72]	.008
Tertiary		474 (48)	146 (35)	328 (58)	3.90 [2.77, 5.47]	<.0001
Working situation: n (%)						
Retired		681 (69)	316 (76)	365 (64)	reference	
Fulltime		26 (3)	12 (3)	14 (2)	0.57 [0.20, 1.36]	.43
Parttime		54 (5)	21 (5)	33 (6)	0.60 [0.28, 1.25]	.43
Self-employed		36 (4)	15 (4)	21 (3)	0.69 [0.34, 1.52]	.54
Incapacitated and/or receiving sickness benefit		151 (15)	38 (9)	113 (20)	0.94 [0.61, 1.99]	.80
Unemployed		25 (3)	10 (2)	15 (3)	0.59 [0.23, 1.46]	.45
Voluntary work or following education not paid by employer		11 (1)	2 (1)	9 (2)	2.69 [0.52, 12.06]	.45
Living situation: n (%)						
With partner		755 (77)	321 (77)	434 (76)	reference	
Alone		137 (14)	62 (15)	75 (13)	0.82 [0.55, 1.20]	.49
With partner and children		65 (6)	19 (5)	46 (8)	0.97 [0.51, 1.86]	.99
In an institution, assisted living or sheltered living		19 (2)	8 (2)	11 (2)	1.41 [0.52, 3.78]	.63
Living with another family member than partner		8 (1)	4 (1)	4 (1)	0.44 [0.10, 1.88]	.45
Complications in the year prior to the first questionnaire – Urinary tract infection, pneumonia, falling, hallucinations: n (%)						
Any complication reported		505 (51)	220 (53)	285 (50)	0.89 [0.67, 1.16]	.53
Specific complications – not reported/ reported/ led to hospital admission: n (%)						
Urinary tract infection	Not reported	891 (91)	374 (90)	517 (91)	reference	
	Reported	78 (8)	34 (8)	44 (8)	0.79 [0.47, 1.31]	.51
	Hospitalized	15 (1)	6 (2)	9 (1)	1.25 [0.41, 3.74]	.79
Pneumonia	Not reported	948 (97)	393 (95)	555 (97)	reference	
	Reported	23 (2)	12 (3)	11 (2)	0.74 [0.32, 1.75]	.64
	Hospitalized	13 (1)	9 (2)	4 (1)	0.41 [0.12, 1.36]	.42
Falling	Not reported	561 (57)	230 (56)	331 (58)	reference	
	Reported	399 (41)	172 (41)	227 (40)	0.93 [0.70, 1.23]	.72
	Hospitalized	24 (2)	12 (3)	12 (2)	0.61 [0.26, 1.45]	.45
Hallucinations	Not reported	858 (87)	357 (86)	501 (88)	0.13 [0.76, 1.70]	.66
	Reported	126 (13)	57 (14)	69 (12)		

[a] SD = Standard Deviation; BMI = Body Mass Index. Motor symptoms: Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part II, ranging from 0 to 52, higher score indicates a greater degree of motor symptoms. Depression: Beck Depression Inventory II (BDI), ranging from 0 to 63, higher scores indicate greater depressive severity. Anxiety: State Trait Anxiety Inventory for Adults (STAI); only the Trait Anxiety Scale was included, ranging from 20 to 80, higher score indicates a greater degree of anxiety. Cognition: Telephone Montreal Cognitive Assessment (t-MoCA), ranging from 0 to 22, higher score indicates better cognitive performance. Quality of life: Parkinson's Disease Questionnaire-39 (PDQ-39), ranging from 0 to 100, higher score indicates a better quality of life. COVID-19 burden: COVID-19 questionnaire containing 8 questions, the average is calculated and ranges from 0 to 5, higher score indicates a higher COVID-19 burden. Disease duration: Years since diagnosis of PD or parkinsonism. Disease stage: Hoehn & Yahr scale, this score was calculated on answers from other questionnaires, notably the UPDRS. Scores can range from 1 to 5 (disease stage 1 to 5) in which a higher stage indicates more severe disease. Education: Primary educated= no education, primary school, VMBO (see also Table S1); Secondary educated= HAVO, VWO, MBO; Tertiary educated= HBO, University, PhD. Hospitalized: Complication led to a hospital admission.

[b] CI = confidence interval; all continuous variables were analysed using linear regression, all binary variables were analysed using binomial logistic regression, all categorial variables with more than two categories, including ordinal variables, were analysed using multinomial logistic regression. Continuous variables that did not meet the assumptions for linear regression were log transformed before conducting linear regression. All tests between PRIME and UC were adjusted for age, sex and disease duration, excluding the tests for age, sex and disease duration. We reported odds ratios for all variables tested with binomial or multinomial logistic regression, log-b-weights for all log transformed variables tested with linear regression, and b-weights for all other variables tested with linear regression.

[c,d] Log transformed before tested with linear regression.

[e] Not 100% in total due to NAs.

[f] Not 100% in total since participants could have comorbidities in more than one category.

Table 4. Baseline characteristics of questionnaire participants from the PRIME region who were and were not recruited through their neurologist.

Variables [a]	Recruited through neurologist [b] (n = 263)	Otherwise recruited (n = 112)	(Log-)B-weights / odds ratio [95% CI] [c]	Adj. p
Age: mean (SD)	71.6 (7.5)	70.4 (8.3)	-1.41 [-3.21, 0.31]	.50
Sex (men): n (%)	172 (65)	74 (66)	1.04 [0.65, 1.68]	.87
Motor symptoms: mean (SD) [d]	12.2 (7.7)	13.8 (8.1)	0.08 [-0.06, 0.22]	.66
Depression: mean (SD) [e]	11.7 (6.6)	12.5 (7.2)	0.03 [-0.10, 0.16]	.87
Anxiety: mean (SD)	38.7 (9.3)	39.0 (9.6)	0.18 [-1.88, 2.23]	.87
Cognition: mean (SD) [f]	17.2 (3.1)	17.5 (2.9)	0.03 [-0.01, 0.07]	.57
Quality of Life: mean (SD)	73.9 (12.9)	72.4 (13.8)	-0.51 [-3.20, 2.17]	.87
Disease duration in years: mean (SD) [g]	5.36 (4.5)	6.51 (6.0)	0.13 [-0.14, 0.48]	.50
Education: n (%)				
Primary	101 (38)	34 (30)	reference	
Secondary	75 (29)	32 (29)	1.31 [0.73, 2.32]	0.66
Tertiary	87 (33)	46 (41)	1.62 [0.94, 2.80]	0.50
Disease stage: n (%) [h]				
Stage 1	77 (29)	34 (30)	reference	
Stage 2	91 (35)	34 (30)	0.80 [0.45, 1.45]	.73
Stage 3	38 (14)	18 (16)	0.91 [0.43, 1.90]	.87
Stage 4	42 (16)	15 (13)	0.66 [0.30, 1.48]	.66
Stage 5	11 (4)	8 (7)	1.60 [0.57, 4.53]	.66

[a] See table 3 footnote a.

[b] NAs: n = 39.

[c] See table 3 footnote b. All tests between recruited through neurologist and not recruited through neurologist were adjusted for age, sex and disease duration, excluding the tests for age, sex and disease duration.

[d, e, f, g] Log transformed before tested with linear regression.

[h] Not 100% in total due to NAs.

Loss to follow-up

At baseline, 984 participants completed the PRIME-NL questionnaire of whom 916 (93%) were retained at the first follow-up measurement after one year (**figure 3**). 15 participants (1.5%) had deceased before the first follow-up measurement; 8 (2%) in the PRIME region and 7 (1.2%) in the UC region. 53 participants (5.4%) dropped out of the study; 33 (8.0%) in the PRIME region and 20 (3.5%) in the UC region. The most common reasons for dropping out were disease progression (40%) and the inability to reach the participant again (17%; **supplementary table S3** also displays regional data). Within the PRIME region, the participants who were lost were older and reported a poorer quality of life than those who remained. There were no other statistically significant differences between the participants who were lost and who remained in the PRIME region. Still, the PRIME region estimates suggested that the participants lost to follow-up may have had more motor and depressive symptoms, a longer disease duration, a higher disease stage and seemed less likely to receive tertiary education than the participants who remained in the study (**table 5**). Within the UC region, the participants who were lost had more cognitive symptoms and reported a poorer quality of life than the participants who remained, but were comparable on all other outcomes (**table 5**). Noteworthy, the differences between lost and remained participants might differ between both regions. For example, the difference in motor and depressive symptoms, as well as level of education and age, seems to be more negative for the PRIME than the UC region.

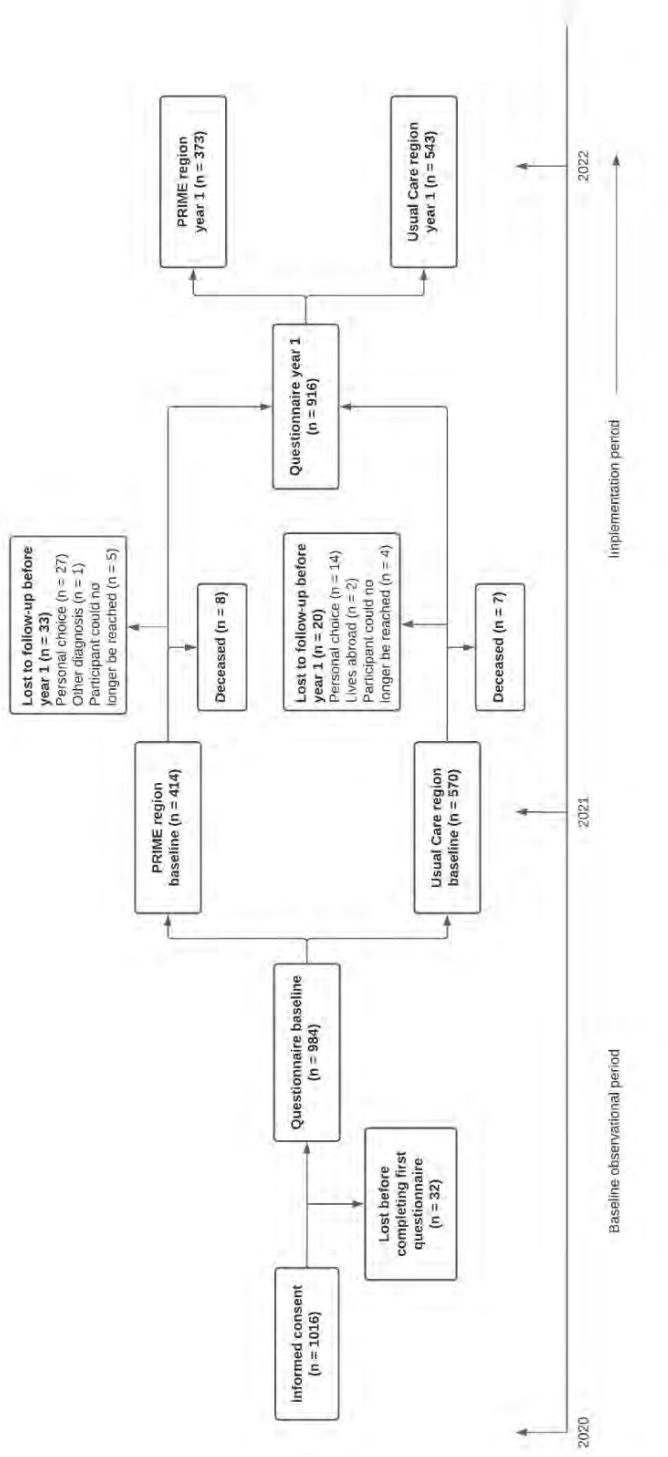

Figure 3. Illustration of the loss to follow-up during the first year of the PRIME-NL study.

Table 5. Participants who were lost to follow-up compared on baseline characteristics to participants who remained in the study, separately for the PRIME and usual care region.

Variables [a]		PRIME				Usual Care			
		Lost to follow-up (n = 33)	Remained (n = 381)	(Log-)B-weights / odds ratio [95% CI] [b]	Adj. p	Lost to follow-up (n = 20)	Remained (n = 550)	(Log-)B-weights / odds ratio[95% CI] [b]	Adj. p
Age (years): mean (SD)		76.4 (5.4)	71.3 (7.8)	4.90 [2.16, 7.64]	.01	71.5 (7.1)	73.7 (13.1)	3.12 [-0.36, 6.60]	.21
Sex (men): n (%)		21 (64)	250 (66)	0.83 [0.40, 1.80]	.62	14 (70)	316 (58)	1.54 [0.60, 4.48]	.65
Motor symptoms: mean (SD) [c]		18.9 (11.3)	12.6 (7.7)	0.21 [-0.02, 0.44]	.14	15.2 (9.4)	12.1 (7.4)	0.06 [-0.21, 0.32]	.84
Depression: mean (SD) [d]		15.0 (6.5)	11.8 (7.0)	0.20 [-0.02, 0.41]	.16	13.4 (7.2)	11.6 (6.8)	0.11 [-0.16, 0.39]	.65
Anxiety: mean (SD) [e]		41.7 (8.7)	38.7 (9.6)	2.32 [-1.17, 5.81]	.24	41.2 (8.3)	37.3 (9.3)	4.16 [0.03, 8.30]	.18
Cognition: mean (SD)		16.4 (3.2)	17.3 (3.1)	-0.02 [-0.10, 0.06]	.62	15.4 (4.0)	18.7 (2.6)	-0.19 [-0.26, -0.13]	<.0001
Quality of Life: mean (SD)		64.2 (13.4)	73.7 (13.1)	-7.29 [-11.7, -2.89]	.01	67.1 (15.9)	74.9 (12.8)	-7.76 [-13.31, -2.21]	.04
Disease duration in years: mean (SD) [f]		6.94 (4.8)	5.57 (5.2)	0.19 [-0.05, 0.44]	.17	6.75 (5.0)	6.58 (5.3)	0.04 [-0.25, 0.33]	.82
Education: n (%)									
Primary		17 (52)	137 (36)	reference		3 (15)	95 (17)	reference	
Secondary		8 (24)	106 (28)	0.64 [0.26, 1.58]	0.39	4 (20)	140 (26)	1.08 [0.23, 5.05]	.92
Tertiary		8 (24)	138 (36)	0.50 [0.20, 1.21]	0.17	13 (65)	315 (57)	1.21 [0.33, 4.44]	.84
Stage of disease: n (%) [g]	Stage 1	1 (3)	114 (30)	reference		3 (15)	164 (30)	reference	
	Stage 2	9 (28)	125 (33)	6.49 [0.79, 52.98]	0.14	3 (15)	199 (36)	0.71 [0.14, 3.63]	0.84
	Stage 3	6 (18)	58 (12)	8.25 [0.93, 72.97]	0.16	7 (35)	79 (14)	4.22 [1.00, 17.81]	0.18
	Stage 4	10 (30)	60 (16)	11.0 [1.31, 93.69]	0.10	6 (30)	80 (15)	3.67 [0.82, 16.61]	0.21
	Stage 5	4 (12)	19 (5)	14.3 [1.46, 141.17]	0.10	1 (5)	16 (3)	2.92 [0.26, 32.46]	0.65

[a] See table 3 footnote a.

[b] See table 3 footnote b. All tests between lost to follow-up and remaining participants were adjusted for age, sex and disease duration, excluding the tests for age, sex and disease duration.

[c, d, e, f] Log transformed before tested with linear regression.

[g] Not 100% in total due to NAs.

Discussion

The PRIME-NL study remotely evaluates the PRIME Parkinson care model, a multifaceted complex healthcare innovation. To determine both the generalizability of the findings and potential sources of bias in the questionnaire sample, we investigated whether the source population of people with PD differs between the PRIME and UC region, compared the combined questionnaire sample of participants from both regions to the source population and compared the PRIME and UC questionnaire sample on baseline characteristics and investigated the 1-year compliance. Examining similar questions for care partners and healthcare professionals was beyond the scope of this article.

Source population differences and generalizability

According to the available healthcare claims data, people with PD in the PRIME and UC source populations were comparable at baseline regarding age, sex, comorbidities and number of fractures and pneumonia's. Although statistically significant, the difference in disease duration between the regions is negligible. People with PD in the PRIME region had a somewhat lower socioeconomic status and fewer PRIME participants used medications for anxiety, depression and cognitive symptoms. Furthermore, the comparison of CBS data between the PRIME and UC region showed no meaningful differences between the regions. Naturally, the interpretability of the CBS data is somewhat limited as the database is not PD-specific.

Given that the source populations were highly similar, we assessed the generalizability of the questionnaire sample by comparing the combined questionnaire sample of participants from both regions to the entire source population. However, only four variables were measured in both the healthcare claims database and the questionnaire sample, limiting the breadth of our comparison. The questionnaire sample shows a slight underrepresentation of older people with PD compared to the source population. Compared to other prospective longitudinal cohort studies, the PRIME-NL questionnaire participants are indeed younger when we correct for disease duration (PRIME-NL age at diagnosis = 61.8 years, ParkWest, Oxford Discovery and CaMpaIGN range = 66.1 – 70.2 years).[13–15] This underrepresentation of elderly is not uncommon in research studies [16] and can be explained by a multitude of factors such as disease progression, cognitive state and comorbidities. Specifically, our recruitment methods typically required technological skills such as visiting a website or active engagement in the community such as attending a conference, which might be easier for younger people and people who are less affected by parkinsonism. However, since the

underrepresentation of older people with PD in the questionnaire sample is only modest, we do not think this forms a substantial limitation in generalising the eventual results of the PRIME-NL study to the broader population of people with PD. Besides the difference in age, the questionnaire sample also had a slightly longer disease duration which could partially be explained by a delay of the clinical diagnosis registration in the healthcare claims data. Finally, the questionnaire sample participants were more likely to experience a pneumonia, which could partially be due to their longer disease duration.

For future studies, we recommend to put extensive effort into recruiting people personally, both offline and online, to reach the full spectrum of the parkinsonism population. Besides our own positive recruitment experiences, another study demonstrated that one or more telephone calls recruited an additional 31% of participants who differed on several characteristics, compared to those without phone contact, such as being more frail.[17] Furthermore, online advertisements through social media platforms can be used to successfully reach underrepresented groups, including geographically distant and late stage people with PD.[18] Our study would have benefited from such additional recruitment strategies, as the questionnaire sample lacks the inclusion of people with parkinsonism with a migratory background and with a primary and secondary educational attainment (**table 2B and table 3**).

Selection and confounding bias in the questionnaire sample

Baseline characteristics and recruitment strategy

Participants in the questionnaire sample in the PRIME region were older than the participants in the UC region and were also more affected by their parkinsonism given their worse cognition, anxiety, quality of life and higher BMI (although the latter three require careful interpretation). These differences highlight the presence of selection bias, given that the source populations were similar or showed a reversed effect, e.g., more anxiety medication in the UC source population. We hypothesized that the selection bias might have been caused by the recruitment letter from the neurologist in the PRIME region. A letter, sent by the participants own treating neurologist, is more personal and could have reached older and more affected people who might well be missed by general recruitment methods. The general recruitment methods required more digital skills, which might explain why participants in the UC region were younger and completed the questionnaire more frequently online rather than on paper compared to the PRIME participants. Indeed, participants in the PRIME region recruited via their neurologist seemed to be older and less likely to receive tertiary education than participants recruited via other

recruitment strategies, although they also might have had a shorter disease duration. Note that these differences were not statistically significant, so we could not find strong evidence for our hypothesis that the letter reached a specific subgroup of people with PD, resulting in the selection bias we found. However, we have identified two alternative explanations. First, the letter has reached a subgroup but our data on recruitment method are misleading. Some PRIME participants reported to be recruited by their neurologist but had entered the study before the recruitment letters were sent out. Also, some UC participants had indicated that they had been recruited by their neurologist despite not receiving a letter, maybe because their neurologist mentioned the study during a clinical visit. We have attempted to correct such cases before the analyses, but incorrect recruitment method classifications might reside disproportionally more in the PRIME region, leading to differential measurement error and thereby information bias. Second, the beneficial effect of sending a recruitment letter on recruiting specific subgroups might be limited. For example, participants living in the PRIME region live closer to the research centre from which PRIME-NL is coordinated (Radboud university medical center), which may already create a stronger sense of involvement and readiness to participate for this 'local' initiative, reducing the additive effect of the letter.

The UC rather than the PRIME questionnaire sample seems to be diverging from the source population. For example, 58% of the participants in the UC region received tertiary education, against 35% of the participants in the PRIME region. According to the CBS data, both regions should have approximately 30% tertiary educated people, assuming that no major association between education and PD is known.[10] Furthermore, the average age of the PRIME questionnaire participants (71.8) is closer to the average age of their source population (72.9) than is the case for the UC region (sample 68.2, source 72.7). We have oversampled in the PRIME region since this region is much smaller (n = 1430) than the UC region (n = 26250). Relatively more people with PD from the PRIME region were included, making them a better representation of their source population.

We did not investigate potential sources of information bias, such as the COVID-19 pandemic or being unblinded to the study group. For example, COVID-19 could have differentially affected the PRIME or the UC region over the baseline year, regionally and temporally reducing well-being. The unblinding of participants might occur after the first innovations have been implemented. Once participants are unblinded, information bias could arise during follow-up as people in the PRIME region might answer more positively since they are aware of the additional care they are receiving.

Loss to follow-up

We retained 93% of participants after the first year of follow-up (94.6% when excluding deceased participants). This compliance percentage is remarkably high, although we are not aware of similar longitudinal healthcare model evaluations within and beyond the field of parkinson(ism) to compare our findings to. As an example, the ParkWest cohort study achieved a 1-year compliance of 98.4% [15], but investigated disease progression and therefore only recruited newly diagnosed people with PD. The PRIME-NL questionnaire participants have a higher average disease duration which is typically associated with more motor and cognitive impairments hampering research participation. We assume that these impairments also make it more difficult for people with parkinson(ism) to be retained in longitudinal research when compared to other chronic conditions such as diabetes mellitus and chronic obstructive pulmonary disease.

The retention of participants in our study is most likely due to a comprehensive series of activities developed by the assessment team for the present and also other studies.[19] These activities had been devised together with several participants to match their needs more closely and include an annual personal contact moment over telephone, newsletters with research updates, a Christmas card and the presence of a helpdesk during office hours to answer questions.[19] Despite these activities being equally implemented for both regions, we lost more questionnaire sample participants in the PRIME than in the UC region after the first year. A logical explanation would be that the PRIME participants on average were older and more affected by parkinsonism at baseline, i.e., they experienced more anxiety, cognitive impairments, and a lower quality of life. These factors increase the likelihood that people with parkinsonism will reach a stage in their disease in which they are no longer willing to complete the questionnaires. This hypothesis is also supported by our data, as the most frequently reported reason to resign from participation was disease progression. Furthermore, outcomes related to disease burden were associated with reduced compliance, including motor and cognitive symptoms and quality of life. Although we lacked power to conduct statistical tests for interaction, the PRIME region seems to have suffered more from selective attrition, i.e., more affected participants were lost compared to the UC region. Future evaluation of the participants lost to follow-up is necessary, as power might become sufficient to perform statistical tests in later years of PRIME-NL.

In conclusion, the PRIME and UC source populations are highly comparable and the questionnaire sample participants are a reasonable representation of the source populations. These findings support the generalizability of the PRIME-

NL evaluation for people with PD. However, the evaluation of the questionnaire sample data can be affected in various ways. On the one hand, the selection bias introduced at baseline led to the inclusion of older and more affected participants in the PRIME region. This selection bias could become a source of confounding as age and disease progression negatively predict several outcomes. Even when we correct for baseline differences in the final evaluation, the impact of PRIME Parkinson care could be underestimated due to increased disease progression, less room for improvement in healthcare (ceiling effect) or difficulties in reaching the participants in the PRIME region. On the other hand, selective attrition of more affected participants in the PRIME region could result in overestimating the positive effect of PRIME Parkinson care (**figure 1**). We will explore various statistical methods to account for these differences, for example through inverse probability weighting or propensity score matching. Ultimately, this study brings us closer to the final purpose of PRIME-NL: to evaluate whether PRIME Parkinson care can improve care for all people with parkinsonism.

References

1. Dorsey, E. R., Sherer, T., Okun, M. S. & Bloem, B. R. The Emerging Evidence of the Parkinson Pandemic. *JPD* **8**, S3–S8 (2018).
2. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* **397**, 2284–2303 (2021).
3. Bloem, B. R. *et al.* Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology* **19**, 623–634 (2020).
4. Tenison, E. *et al.* Proactive and Integrated Management and Empowerment in Parkinson's Disease: Designing a New Model of Care. *Parkinson's Disease* **2020**, 1–11 (2020).
5. Bodenheimer, T. & Sinsky, C. From triple to quadruple aim: care of the patient requires care of the provider. *Ann Fam Med* **12**, 573–576 (2014).
6. Berwick, D. M., Nolan, T. W. & Whittington, J. The triple aim: care, health, and cost. *Health Aff (Millwood)* **27**, 759–769 (2008).
7. Ypinga, J. H. L. *et al.* Rationale and design to evaluate the PRIME Parkinson care model: a prospective observational evaluation of proactive, integrated and patient-centred Parkinson care in The Netherlands (PRIME-NL). *BMC Neurol* **21**, 286 (2021).
8. Lithander, F. E. *et al.* Proactive and Integrated Management and Empowerment in Parkinson's Disease protocol for a randomised controlled trial (PRIME-UK) to evaluate a new model of care. *Trials* **24**, 147 (2023).
9. Centraal Bureau voor de Statistiek. *StatLine database.* Available from: https://opendata.cbs.nl/#/CBS/nl/. Accessed July 11, 2023.
10. Ben-Shlomo, Y. *et al.* The epidemiology of Parkinson's Disease. *The Lancet* **403**, 283-292 (2024).
11. Benjamini, Y. & Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)* **57**, 289–300 (1995).
12. R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.
13. Szewczyk-Krolikowski, K. *et al.* The influence of age and gender on motor and non-motor features of early Parkinson's disease: Initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. *Parkinsonism & Related Disorders* **20**, 99–105 (2014).
14. Williams-Gray, C. H. *et al.* The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry* **84**, 1258–1264 (2013).
15. Bjornestad, A., Pedersen, K. F., Tysnes, O.-B. & Alves, G. Clinical milestones in Parkinson's disease: A 7-year population-based incident cohort study. *Parkinsonism & Related Disorders* **42**, 28–33 (2017).
16. Maas, B. R. *et al.* Time trends in demographic characteristics of participants and outcome measures in Parkinson's disease research: A 19-year single-center experience. *Clinical Parkinsonism & Related Disorders* **8**, 100185 (2023).
17. Tenison, E. Capturing complexity, comorbidity and frailty in people with parkinsonism and understanding their impact. (PhD thesis University of Bristol, 2023).
18. Dobkin, R. D. *et al.* Innovative Recruitment Strategies to Increase Diversity of Participation in Parkinson's Disease Research: The Fox Insight Cohort Experience. *J Parkinsons Dis* **10**, 665–675 (2020).
19. Meinders, M. J., Marks, W. J., van Zundert, S. B. M., Kapur, R. & Bloem, B. R. Enhancing Participant Engagement in Clinical Studies: Strategies Applied in the Personalized Parkinson Project. *J Parkinsons Dis* **13**, 637–640 (2023).Figure 3. Illustration of the loss to follow-up during the first year of the PRIME-NL study.

7

General discussion

Although telemedicine and remote monitoring for persons with Parkinson's disease (PD) were being researched, tested and implemented long before the COVID-19 pandemic, COVID-19 was the spark that lighted the fire of telemedicine beyond imagination.[1] The pandemic forced us to change practices almost overnight, and telemedicine and remote monitoring have created valuable alternatives for the provision of face-to-face care. Now that the spark is gone, the question is how telemedicine can remain a vital part of the healthcare system of the future.[2] In my thesis, I have tried to contribute to this paramount question. I have researched how we can improve the care for people with PD through the development and implementation of telemedicine in general and through remote monitoring more specifically. Below, I will position my research findings within the broader developments in the field and discuss the implications of my work for clinical and research practices. I will also suggest how we should proceed in the future, and will address the limitations of my work. This discussion is centred around the three main contributions of telemedicine and remote monitoring: *maintaining access to care*, *capturing objective data at home* and *providing proactive care*.

Contribution I. Maintaining access to care for everyone

Results of this thesis in context

One of the most acclaimed benefits of telemedicine is the possibility to enhance access to care, for example for people with PD, but many other patient populations will obviously benefit from the advent of telemedicine too. In **chapter 2**, I have reviewed the literature on the state of telemedicine for people with PD published between 2019 and 2021 for three parts of telemedicine: teleconsultations, telemonitoring and teletreatments. This review included studies on telemedicine performed before and during the COVID-19 pandemic. After weighing of the benefits and challenges, my evaluation was most positive for teleconsultations, mainly because teleconsultations provide the ability to increase access to care and can thereby bring comfort to people with PD and their care partners (the alternative during the pandemic was no access to care at all). Subsequent research during the first year of the COVID-19 pandemic showed that the COVID-19 pandemic spurred predominantly the use of teleconsultations and teletreatments, with telemonitoring tools sometimes supporting the consultation or treatment.[3,4] This is in line with our and other findings which also highlight the benefits of teleconsultations, as they bring convenience, comfort and prevent contagion.[5,6] Teleconsultations create an opportunity to help anyone anywhere at any time, thereby opening up completely

new avenues for blended care models that put the person with PD at the centre of healthcare.[7] In the post-pandemic time, however, the uptake of teleconsultations seems to be reversing back to pre-pandemic levels whilst the use of wearable technology steadily grows.[2,8]

In **chapter 3**, I interviewed healthcare professionals, people with PD and their care partners to learn whether these positive findings concerning telemedicine also apply to palliative care for people with PD. Palliative care is a type of specialty care that optimizes quality of life by adopting a holistic perspective on health and well-being. Because palliative care more often concerns severely affected individuals, travel opportunities are more limited for this specific population while their care needs are versatile and complex, so the potential of telemedicine is enormous here. Although in-practice experiences with telemedicine were scarce for palliative care, our participants praised the opportunities to maintain contact with people with PD who lived far away or were home- or bedbound. Yet, many of the participants were also hesitant and uncomfortable when thinking about discussing palliative care topics digitally.[9] They feared that digital contact equals less personal contact, which is important for high-quality palliative care. Other authors have also expressed concerns about teleconsultations hollowing the relationship between healthcare professionals and people with PD, especially when deployed merely as an efficiency tool rather than a service for people who voluntarily opt for this type of care.[10,11] However, we also interviewed some healthcare professionals who had delivered palliative care through telemedicine. They told us that their experiences were not as 'bad' as they had feared. Other studies have recently shown that blended palliative care consultations (physical and remote) indeed have a positive effect on the quality of life for people with PD.[12,13] Taken together, our findings and the broader literature support the idea that teleconsultations bring more benefits than challenges, and this includes the area of palliative care.

Implications for clinical practice

Using telemedicine as a tool to maintain access to care requires careful consideration (**chapter 2 and 3**). In this section, I will first delineate how I regard the concept of *access to care* and how that affects the implementation of telemedicine in clinical practice. Second, I will discuss how access to care will be lost rather than maintained when we fail to address inequalities regarding *digital literacy* and *reimbursement issues*.

First, *access to care* is an important concept in the telemedicine literature, so we need to be clear about what it means and how it is created. Access to care can be defined as having the opportunity to timely see and talk to a medical professional

to receive the effective, safe and person-centred treatment someone needs.[14] This primarily requires healthcare services to be available to those in need, i.e., someone can physically or virtually utilise the medical treatment they require. Examples within PD care are the availability of a ParkinsonNet[a] physiotherapist close by or a referral from a healthcare professional to a tertiary centre of expertise when someone's diagnosis is unclear. However, people can still experience inadequate access to care even when these services are available. A reason for this can be a lack of experienced *candidacy* for healthcare. Candidacy refers to the constructed perception or experience of being eligible for healthcare services.[17] Simply put, when someone experiences a high level of candidacy, they feel that they can visit their doctor whenever this is needed. This perception or experience is the result of a mutually reinforcing process between people in need of medical attention and healthcare providers and services. This process includes identifying yourself as a candidate (e.g., recognizing symptoms), navigating healthcare services (e.g., being aware of offered services), permeating to those services (e.g., receiving a referral or being able to read and understand the appointment system) and appearing at the health service (e.g., articulating your issue during the consultation). Understanding access to care in terms of experienced candidacy is important because we go beyond superficially counting the number of available or utilised healthcare services. Instead, candidacy is more about understanding *why* someone experiences inadequate access. To create a high sense of candidacy in the consultation room, I argue that healthcare professionals and people with PD must rely heavily on making contact, regardless of whether they meet physically or remotely. With contact I refer to a moment of presence in which both parties have the time to meet, listen and hear each other.[18] This moment of contact is important for someone's experienced candidacy (and therefore access to care) as it signals that you and your story deserve attention, understanding and support from the healthcare professional.

The findings regarding telemedicine and in particular teleconsultations take an interesting position in light of candidacy and making contact. On the one hand, teleconsultations enhance access to care because we can reach more people and we can reach those who live further away, enabling this moment of contact and presence more frequently and more readily (**chapter 2 and 3**).[19,20] As an example,

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a. ParkinsonNet is described by Ypinga[15] as "an innovative model of care, in which allied health interventions are delivered within integrated regional community networks that consist of specifically trained therapists who work according to evidence-based guidelines and accumulate additional expertise by managing a high caseload of patients with Parkinson's disease." For additional information, see [16].

the participants in the interview study on telemedicine and palliative care praised the ability to remotely include family members into palliative care conversations (**chapter 3**). On the other hand, teleconsultations can negatively impact the possibility to make deep personal contact. Indeed, the same interview study highlighted that telemedicine contact can also be regarded as more to the point and less personal, for example because it contains less small talk and is easily ended or rescheduled. Teleconsultations can therefore be experienced as an efficiency tool to quickly work through many consultations. In that case, people will experience a lack of candidacy as the 'quick and efficient' teleconsultation signals the idea that "*the doctor does not think I am worth their full attention*". Telemedicine contact therefore requires more time and effort to establish a moment of presence in which the patient-clinician relationship can grow (**chapter 2 and 3**).

Taken together, I propose to use teleconsultations as a tool to stay in contact and be present with each other rather than as a tool to maximize efficiency.[7,10] Using teleconsultations in practice requires time to meet, to have attention for each other and to establish clear agreements upfront about how teleconsultations are embedded into the overall package of healthcare services. Importantly, the choice whether or not to deploy telemedicine consultations, and if so, at which frequency, will always be a shared decision between the affected individual with their caregiver, and the involved medical professional. That way, I am hopeful that the healing relationship between healthcare professionals and people with PD can be sustained through telemedicine.[21]

Second, telemedicine can reduce access to care when diversity issues and inequalities in the population are not addressed. According to the Universal Declaration of Human Rights article 25.1, "*everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including […] medical care*".[22] However, not everyone utilizes PD care equally, with prominent examples of underserved groups including both women and non-white people.[23–25] As outlined above, telemedicine can help to enlarge access to care, but it bears the risk that it will enlarge *unequal* access to care when we fail to address major challenges concerning the implementation of telemedicine.[26] I will highlight two of these challenges: digital literacy and reimbursement issues.

Digital literacy encompasses the skills and competencies needed to understand, navigate and use digital technology systems.[27,28] As our use of digital technology changes (rapidly) over time with our socio-cultural context, a digitally literate person is able to learn and adapt to new uses of technology. The definition and

operationalization of digital literacy varies and no study has directly assessed the digital literacy of people with PD. Three studies suggest that the digital literacy of people with PD seems to be comparable with the general elderly population, and 20-30% of the people with PD report insufficient health literacy or technological skills.[29–31] Also, specific characteristics of a person can impact digital literacy differently for different systems: cognition is important for operating a tablet app but not for operating a wearable sensor.[32] Other examples include the loss of dexterity of the hands which is very typical for persons with PD, which can hamper their ability to handle a keyboard, certainly a small one on a smartphone. A further challenge is the hypophonia and other forms of dysarthria that are typical of PD, and which may make it difficult to be adequately understood in a telemedicine consultation. Furthermore, a lack of digital literacy forms an important barrier to leveraging digital health for self-management.[33] Participants in **chapter 3** frequently raised the concern that people with PD in need of palliative care might lack digital literacy skills. We also experienced first-hand in **chapter 4**, where we studied the use of a remote monitoring system in physiotherapy practices, how important digital literacy is to keep people 'on board'. Also, we suspect that digital literacy has led to unequal recruitment of people with PD in **chapter 6** concerning the validity of the PRIME Parkinson healthcare evaluation, as the participants in the treatment as usual group had to rely more heavily on digital literacy skills to find, navigate and permeate into the study, i.e., experience candidacy. To overcome the barrier of digital literacy, we must provide extensive support to people with PD,[33] which was appreciated by our participants using the monitoring system for physiotherapy in **chapter 4**. Furthermore, we should leverage the high-pace of technological developments to create systems based on principles of co-design and user-centeredness, for example by including people with PD in the research process, designing modular systems or by taking into account non-dominant language preferences.[33,34]

Besides digital literacy, *reimbursement issues* are also important to address. During the COVID-19 pandemic, people from ethnic minorities and those with a lower socio-economic status were the first to lose access to healthcare.[24] A partial explanation for this resides in the costs associated with using telemedicine, such as paying for a computer, tablet or smartphone as well as access to telecommunication provider systems and the internet. These costs can be too burdensome for specific groups of people with PD. A possible solution would be to have system-related costs for these people covered by healthcare organizations, the technology-builder or insurance companies. For example, in **chapter 4**, Philips had lent the wearable sensor and Wi-Fi hub to the participants. Besides reimbursing technology-related costs, the

time investment by healthcare professionals must also be covered. The healthcare professionals we interviewed in **chapter 3** were generally not unwilling to adopt telemedicine systems, yet the lack of clarity surrounding the reimbursement and integration into regular healthcare made them hesitant to do so. Currently, the debate is on-going whether and how telemedicine visits should be reimbursed, with specific attention for audio-only visits as a way to reach marginalized populations.[35,36] A major question is whether telemedicine visits are cost-effective for delivering an equal quality of care, which also remains inconclusive within the PD field.[4,36–40] In the Netherlands, a first step towards full reimbursement has been made: healthcare actions can be reimbursed regardless of their place (physical or digital) when the digital version has been shown to be equally effective, such as for teleconsultations.[41] However, the costs for the systems and applications themselves are not covered within the current reimbursement policy. A more progressive approach has been adopted by Germany, which created a uniform reimbursement policy for health apps across health insurers including pre-defined criteria for app manufacturers to get an app reimbursed.[42] Furthermore, they created a singular, obligatory healthcare information technology structure to streamline communication between organizations, addressing this barrier for implementation we also identified in **chapter 3**.[43] Noteworthy, Estonia has already implemented such an integrated healthcare system in 2008 to improve the quality of healthcare. The Estonian e-health system covers every patient in the nation and tracks all of their health-related information. Healthcare providers and relatives can be given access to a patient's profile, thereby improving communication and reducing bureaucracy.

Recommendations or considerations for further research

Teleconsultations form a welcome addition to the clinician's toolbox, but more research is needed to firmly ground its effects, especially on enhancing access to care. Based on my findings from **chapter 2 and 3**, I recommend to work together with people with PD, clinicians, researchers, designers, companies, healthcare innovators and healthcare insurers to create an understandable, usable, safe system for remote consultations that addresses digital literacy and implementation gaps (see also contribution 2 for system development). Then, we should research the effect of using this system in everyday practice by observing how people with PD interact with the system and the healthcare professional on the screen. Other studies have examined the effect of teleconsultations on, e.g., quality of life[12,13] or satisfaction[3,44], but, as I have argued above, we need a deeper understanding of people's experiences whilst using telemedicine to understand why standardized metrics do or do not change.[2,45] Questions concerning presence, candidacy and connection can and should be at the foreground: what is it like to close a

conversation about the end of life by pressing a single button? Do you feel seen as a person when sitting in front of a webcam? Can you reach out to your clinician more easily through telemedicine and do you feel strengthened to do so? Only then can we start to understand the impact of telemedicine on access to care and outcomes that matter to people with PD.

At the same time, it is also important to critically reappraise the way we have practiced medicine in the past century. Do we really feel that it is a service to affected individuals to travel long distances to remotely situated hospitals, to sit in waiting rooms for a prolonged period of time, only to see your physician for 10 to 15 minutes and to offer a strongly biased perspective of your problems at home, under severe time constraints? We have to realise that the ability to make physical visits to a hospital for an in-person consultation is a reality only for a small proportion of the worldwide population, making it a luxury item that is difficult to scale globally. Obviously, when there is a choice between in-person consultations or telemedicine visits, then this should be openly discussed. But the painful truth is that telemedicine will likely be the one and only option for many patients in the world to be able to gain access to healthcare. We should still remain cognizant of the limitations of telemedicine under the circumstances, but it is very likely that a global implementation of telemedicine services leads to dramatic improvements in quality of life for many affected individuals with PD (or other healthcare conditions) who currently have no or extremely limited access to care.[7,46–48]

Contribution II. Capturing objective data at home through personalized tools

Results of this thesis in context

Chapter 4 describes the design and use of a wearable sensor system to be used within the context of PD physiotherapy. The system consisted of a necklace, which passively recorded both physical activity and falls, and a tablet or smartphone application. This latter application was used for active data collection, because people with PD could manually report medication intakes and additional activities. In prior work, we had shown that the fall detector was able to reliably capture falls in the person's own home situation.[49] Leveraging technology to support physical activity is gaining much attention in the PD field.[50–52] Whereas many studies focus on the effect of monitoring technology to increase the volume or intensity of physical activities, the study in **chapter 4** focuses on how to create such a system in the first place. Noteworthy, the people with PD participating in the study of **chapter 4**

stressed two elements that are important for the successful use of monitoring tools in practice: their usability and utility. Broadly speaking, the term 'usability' refers to *how* people use the monitoring tool, whilst the term 'utility' refers to *what* is being monitored. Below, I will discuss the implications of both elements for the way we research and develop monitoring tools to capture data at home.

Implications for research

First, the utility of the remote monitoring system varied considerably among users. In advance, we assumed that our system could bring theoretical benefits to both physiotherapists and people with PD, such as insight in risk factors for fall incidents and objective information about physical activities.[49,53,54] However, we learned that our assumptions were too generic. When people used the system in practice, some indeed experienced enhanced motivation to move more or to gain insight in fall events. Others felt burdened by the constant reminder of their disease by tracking their everyday activity or were already very physically active and therefore experienced little added value. This finding corresponds with later research stressing the need for personalized monitoring of PD.[30,55,56] The utility of our system was limited because of a lack of personalization options. Preferably, each person interested in monitoring should be able to select which outcomes matter to that individual.

Second, the usability ratings varied strongly between the passive (necklace) and active (application) monitoring parts of our system. The necklace was rated positively and posed little issues. However, the application yielded many technical errors and was error prone, as people could easily forget a medication intake or daily questionnaire about fall events.

This form of active data collection put additional burden on people with PD, although not everyone was troubled by a hampering system.[57] This finding is in line with other studies showing that passive data collection is preferred over active data collection to reduce the burden of tracking.[55,56] Furthermore, not every person is capable of operating each system, for example when tremor hampers the operation of tiny buttons on tiny screens. To account for some of the possible usability issues, we offered people in **chapter 4** with cognitive impairments the possibility to only wear the passive data recorder and omit the use of the self-report application to sustain their participation.

Taken together, our findings stress the need for personalization of tools: flexible tools that can meet individual needs. Given the importance of *personalization*,

I wish to highlight an important distinction from the term *person-centredness*. Personalization means that a tool that adds value for a large group of individuals is tailored to specific sub-groups, i.e., it is a design movement from the group-level to the person-level. For example, adjusting a body-worn sensor so that men can wear the sensor on their belt and women can wear it on their bra. On the contrary, person-centredness is a design principle that starts at the person-level. Group-level derivatives are possible but are not the goal of the approach. For example, in an unpublished study, we provided designers in-training the task to design 'something' useful for a single person with PD. This resulted in tools directly applicable to the person, such as a mirror that supports dressing in a small camper and a keyboard to sustain typing for an architect. In box 1, I discuss two tools to move between the group- and person-level.

Recommendations or considerations for further research

In **chapter 4**, we have tried to personalize the system as much as possible by taking a *design thinking* approach. Design thinking is a framework to create value with tools according to specific working mechanisms.[63] For example, with a smartwatch (tool) we wish to enhance someone's quality of life (value) by optimizing medication intake (working mechanism). The design process involves several iterations of empathizing with the users, defining the question, creating potential answers, and building and testing prototypes (**figure 1**). This framework is based on the continuous opening up to new problems, ideas and solutions (divergence) and selection of what is relevant for the problem at hand (convergence). It is no panacea to develop perfect tools, yet it provides a way of thinking that allows a constant negotiation between highly person-specific needs and relevant group-level solutions. Design thinking also heavily stresses the need for co-design and co-creation, to create solutions together with instead of for someone.[34,64] In **chapter 4**, we already incorporated some design thinking elements in our approach such as an iterative design of the system and regular feedback sessions. Going forward, I would suggest to extend this approach even more. For example, I would recommend to spend more time in the empathize and problem definition phase of the design thinking approach, as we want to understand what people want to get out of a measure of, e.g., freezing of gait, tremor or a fall incident before we dive into a technical solution. Furthermore, I recommend to perform more but shorter testing phases with fewer participants. Instead of testing two large groups yielding similar feedback, testing many small groups allows for numerous in-between system updates and thereby richer feedback.

Box 1. Personas and user profiles

Designers use various tools to move between the group- and person-level, such as persona's and user profiles (**table 1**). A persona refers to a fictional description of a user that represents a larger group. The term was first coined by psychologist Carl Jung and refers to the social role a person plays in the world, such as 'the doctor or 'the patient'.[58] According to Jung, we incorporate archetypical elements, which are universal human symbols and themes, into our personas. Designers create a persona by combining person-level data into a single fictional person, often including demographic details and a picture. The persona then serves as a role-model to tailor the system to. Conversely, a user profile is drafted from big data analytics of large amounts of people. The user profile adds specific group-level patterns to a unique, individual profile of a user (e.g., this person spends most time watching screen X). My understanding of these two concepts has changed after publication of **chapter 4**. Looking backwards, I would refer to the 'user profiles' from **chapter 4** as personas rather than user profiles because I have tried to capture the story of user groups describing goals, skills and needs. We had created these 'user profiles' to make our results more specific: next to sketching overarching conclusions, the 'user profiles' allowed us to specify what would work for what group of users. Although the 'user profiles' provided some specific claims about what would work for whom, we realized that they are not specific enough for truly person-centred design of healthcare tools. The unpublished results from our work with designers in-training led to the conclusion that even the 'user profiles' remained too generic and that conversations with individual people with PD are necessary to create something truly person-centred.

Table 1. Similarities and differences between personas and user profiles.[59–62]

	Personas	User profiles
Similarities	Personified abstractions of user groups to understand and empathize with users encompassing their goals, behaviours and needs	
Differences	Qualitative data of selected sample	Quantitative data of large group
	Bottom-up approach	Top-down approach
	Fictional, story-based role description	Aimed at describing individual users
	More abstraction	More concrete and specific

As a final recommendation for future research, I believe that considerable value lays in a special case of person-centred monitoring called *personal science*. Personal science is the idea that individuals apply scientific methods to answer their own personal health questions, typically through self-monitoring with tools relevant to their situation and question.[65,66] For example, Sara Riggare, a prominent advocate of personal science, has studied the effect of nicotine on her dyskinesias through a placebo-controlled research design.[67] Although her approach to personal science is very extensive, many people with PD are already applying some form of self-monitoring (see also **chapter 4**). These people however experience difficulties doing so, for example when deciding which tools to use and how to understand their data.[30,55,56] In my opinion, researchers and personal scientists can learn from and help each other. Researchers, leveraging their analytical skills and technical know-how, might be able to help people with PD to self-monitor, for example through sharing simple data collection systems in the form of wearable sensors. At the same time, researchers could learn from working with people with PD that pursue (elements of) personal science in the form of self-monitoring, for example by learning which personal research questions are important for people with PD and which innovative ways of monitoring suit both the person and their environment. Broadly speaking, personal scientists represent the 'person-level', whilst researchers represent the 'group-level'. There is much to learn for both groups if we can foster more conversations between them, ultimately creating monitoring tools that are person-centred, usable and useful in everyday practice.

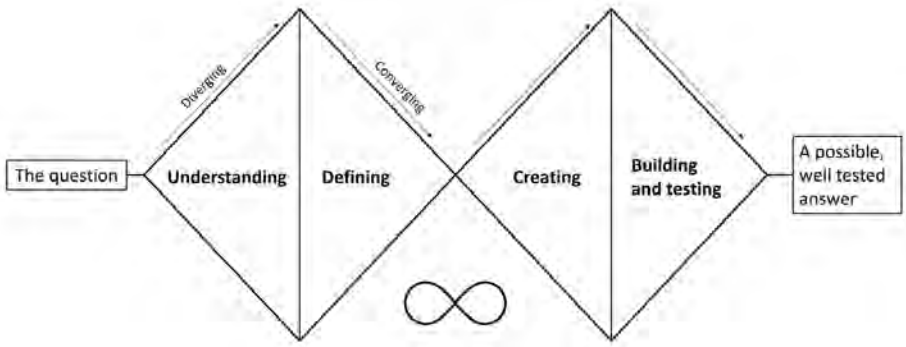

Figure 1. The double-diamond model of design represents one of many possible design processes. The double-diamond stresses iterative phases of diverging (opening up to new options) and converging (selecting and focusing on a few key options). Broadly categorized, four phases can be divided: Gaining a deeper understanding of the stakeholders' perspectives on the question; defining the question in depth and as broad as possible based on or together with stakeholders; creating numerous potential answers to the question, including broad and crazy ones; building and testing (combinations of) the most viable answers with the users in short, iterative sprints. There is no a-priori order in which to follow these phases, as the results from each phase might lead to questions only addressable by each of the other phases (represented by the infinity symbol below).

Contribution III. Providing proactive care

Results of this thesis in context

To prevent unnecessary disease burden, I contributed to the advancement of proactive care in **chapter 5 and 6**. In **chapter 5**, I propose a four-step mixed methods approach to identify relevant targets for prevention. Although the available cohort data lacked power to reach firm conclusions, our method elaborately shows how we can identify realistic prevention targets. Other research groups have already employed proactive questionnaire or telephone based screening to prevent unnecessary hospital visits and admissions.[37,68] Our findings from **chapter 5** can help to focus the content of such screening tools on symptoms that have a great likelihood of leading to medical complications. In other disciplines, such preventive monitoring applications are also being successfully used, for example to manage diabetes and inflammatory bowel disease.[69,70] In **chapter 6**, we laid the foundation for a thorough evaluation of the PRIME-NL study. One of the primary goals of PRIME-NL is to make the Dutch PD healthcare system more proactive in signalling needs and tackling problems. By scrutinizing the validity of the PRIME-NL study, we pave the way for a thorough evaluation of implemented proactive healthcare interventions.

Implications for clinical practice and research

Throughout this thesis and especially in **chapter 5,** I have argued in favour of using telemedicine to provide proactive clinical care for people with PD. Yet, the potential applications of telemedicine are manifold, ranging from medication optimization[4,71,72], to remotely supervised physiotherapy[50–52], to digital outcome measures in clinical trials[73], to early diagnostic markers[74] and more. The decision to focus on proactive care was therefore deliberate. I am aware that the direction of my research and my thesis as a whole have been influenced by my personal and professional convictions. Here, I wish to articulate these convictions by describing them in light of the implications of my research for proactive clinical care, hopefully placing both in a broader context.

First, **chapter 5** provides an overview of *what* variables are relevant to monitor to achieve a more proactive approach to care. The findings show that a broad variety of variables must be considered for complication prevention, encompassing many motor and non-motor symptoms. This is line with the movement in the field (see also **chapter 2**), in which monitoring tools are being developed for both motor and non-motor symptoms.[54,75–77] Yet, the interviews with people concerning telemedicine for palliative care (**chapter 3**) showed that monitoring might not be suitable for highly personal and less quantifiable topics. These responses

resonated with me because they aligned with my convictions acquired throughout my training as a behavioural scientist. I learned that physical constructs can often directly be counted and observed (e.g., the number of steps per day), but I hold the belief that mental constructs are the product of a dynamic interplay between a person, their history and their environment (related to constructivism). In practice, this means that we must critically reflect on which way of data collection is suitable for what variable. For example, a smartwatch can automatically detect a tremor, but depressive symptoms require person-specific momentary assessments.[78]

This is closely related to my second point, namely *how* we can develop models of proactive care that leverage telemedicine. In **chapter 1**, I proposed to use remote monitoring tools to fuel online dashboards combined with online communication software. However, the findings from **chapter 4**, where we tested a remote monitoring system in physiotherapy practices, showed that the translation of theory to practice is difficult because there is no one size fits all solution. Findings from **chapter 3** align in this regard, as the interviewed participants voiced concerns that innovative telemedicine systems lack thoughtful implementation into common routines.[79] Furthermore, the findings from **chapter 6**, where we evaluated the validity of the PRIME-NL study, showed that including a representative group of people with PD in research is challenging.[80] This latter finding is not new, as others have previously drawn attention to the fact that it can be challenging to recruit women into clinical trials,[81] and the same applies to the participants from black and minority ethnic communities.[82] Taken together, my findings stress the need for a closer alignment of our research with the people and environments we wish to support. In my earlier research, I have learned that this highly person-centred (idiographic) perspective can yield valuable insights.[83] There, in a German healthcare clinic, I learned one of the key lessons I brought to my PhD work: *nothing about me without me*. In practice, this idea is rapidly gaining traction, with many authors arguing in favour of co-creation and inclusive research and care practices by involving people with PD in every step of the way.[34,64,84]

Finally, I wish to reflect on *why* we chose to study the use of telemedicine for proactive care. Clearly, proactive care can prevent unnecessary disability and costs by tackling problems before they exacerbate. In **chapter 5**, I show that this potential for prevention is present for five major complications in PD, although the precise estimates must be interpreted carefully. These five potentially preventable complications included fall incidents, aspiration pneumonias, urinary tract infections, psychotic symptoms and mood disorders. Although not mentioned explicitly, a proactive approach to healthcare is also present in **chapter 3 and 4**,

by discussing palliative care topics early to prevent unnecessary unclarity and doubts later on and signalling fall risks to prevent future falls. Other studies in the field could also be classified as forms of proactive care, such as early detection and disease modification efforts.[85,86] My research was part of the PRIME Parkinson project, which explicitly focuses on achieving more proactive care.[87–89] Naturally, my research aimed to contribute to this vision. I am aware however, that this vision can be in conflict with individual preferences of people with PD, who might not be interested in monitoring multiple variables to potentially prevent a complication that they might have never thought of.[55,56,84] In fact, even alerting people with PD about the possible advent of such complications might be frightening, and we should carefully consider the impact of our preventive actions on people. We must take both the prevention and individual perspectives into account when offering tools in practice, for example by providing clear information about the potential utility of regular monitoring and discussing which complications might be relevant to this individual with PD.

Recommendations or considerations for further research

Following an exploration of *what* should be monitored for proactive healthcare in **chapter 5**, I evaluated an innovative healthcare infrastructure *where* such tools could be implemented in **chapter 6**. The implementation of monitoring tools in clinical practice is increasing, yet difficult for various reasons.[76,90] I highlight two in particular. First, the impact of telemedicine and remote monitoring tools on healthcare utilization remains unclear, leading to hesitant implementation and reimbursement policies.[36] On the one hand, telemedicine might alleviate pressure on the healthcare system.[91] Remote visits can reduce travel time for patients and even for healthcare professionals (who could partially deliver their services from within their own homes); this would also be attractive from an environmental perspective as it would reduce the already large carbon footprint that the healthcare system currently has on our ecosystem. Interestingly, remote monitoring tools could identify people who are stable and currently not in need of treatment, thereby preventing overtreatment. At the same time, remote monitoring tools could, in an ideal world, proactively detect the earliest warning signs and symptoms that might theoretically culminate into devastating and costly complications. Examples would include near falls that could be a harbinger of fall-related injuries, or coughing during meals which can be a predictor of aspiration pneumonia. On the other hand, the increased accessibility to healthcare might also lead to additional and sometimes unnecessary appointments.[36] And, as I pointed out earlier, continuous home-based monitoring could create an 'omnipresence' of the doctor, thereby constantly reminding patients of their disease, which may lead to heightened anxiety. There is also a realistic

concern that persons with PD might create obsessive-compulsive behaviour in relation to the collection of remote digital data. Future research should therefore establish whether telemedicine reduces or exacerbates the pressure on healthcare systems. Certainly, a personalised approach to telemedicine and remote monitoring, taking into account factors such as digital literacy, a tendency towards impulsiveness and anxiety levels, will be essential to devise the optimal solution for each affected individual. Second, monitoring tools must conform to regulatory standards before they can be used in clinical care. Although some systems have received such an approval, e.g., the PDMonitor and the Personal KinetiGraph, many tools and applications are in early development stages and it will take several years before they receive regulatory approval.[76,77] The current levels of approval are also of only limited significance. As an example, the Rune Labs Kinematics System has recently received clearance by the United States Food and Drug Administration (FDA), meaning that the system is safe to use in clinical practice, and that it is able to replicate clinical measures of tremor and dyskinesias. However, this FDA approval explicitly does not indicate whether use of such a remote monitoring device leads to improvements in healthcare, or whether the digital device can be used as an outcome in a research setting.[92] Further research is needed to prove such applications.

Methodological considerations

I have discussed the individual strengths and limitations within each respective chapter. For my thesis as a whole, I highlight three methodological considerations. First, my chapters vary widely in topic and development phase.[93] I performed fundamental research for preventive care targets in **chapter 5**, combined perspectives on telemedicine for palliative care in **chapter 3** and tested a remote monitoring system in physiotherapy practice in **chapter 4**. A strength of this approach is the rich understanding we gain of the value of telemedicine for PD healthcare. Findings from **chapter 4** also cross-fertilized other chapters, for example inspiring interview questions for **chapter 3**. However, this broad approach also hampered the progress within each topic. For example, the findings from **chapter 3 and 5** should be translated to tools that can be tested in practice, whilst the results from **chapter 4** raised important system improvement points. Also, **chapter 6** would ideally have encompassed an evaluation of implemented telemedicine systems. Yet, I experienced first-hand that the step from system development to implementation is extremely difficult with financial, ethical, value-based and practical challenges along the way.

Second, this wide variety of topics called for a diverse application of research methods. I have selected a research methodology and corresponding method to investigate each research question. This ranged from a qualitative approach to understand experiences (**chapter 3**), to a quantitative approach to ascertain PRIME-NL's validity (**chapter 6**), to combining quantitative and qualitative methods to create causal pathways (**chapter 5**). Although the methodological choices for each chapter were, in my regard, adequate for each chapter, my work lacks an overarching theoretical framework that combines the results from applying these methodologies. Such a theoretical framework should explain the assumed effects of telemedicine on PD healthcare and provide us with specific and testable hypotheses. My thesis is an attempt to combine findings on telemedicine from diverse topics, but I acknowledge that many of the theoretical assumptions remain isolated. In general, theory formation around telemedicine tools is scarce and remains fragmented, focusing only on specific aspects of telemedicine such as technology acceptance, user-centred design or behavioural change.[94,95] The field would benefit from further explicating and unifying the assumptions we hold about the benefits and burdens of telemedicine for PD healthcare.[1,7,10]

Finally, although I have carefully selected the methodologies for each chapter, my findings might have been altered if I had chosen a different methodology to answer my research questions. First, most of my studies are based on observational data (**chapter 3, 5 and 6**). An intervention study would have provided more direct answers to some of my research questions. For example, the design of **chapter 5** could have been replaced by a randomized controlled trial where we follow two groups: one tracking relevant symptoms for specific complications, and one control group. Such real life data would have given direct knowledge concerning which variables truly, instead of only theoretically, prevent complications. Second, several studies concern only cross-sectional rather than longitudinal data (**chapter 3, 5 and 6**). Following participants through time might have resulted in enhanced power and novel insights. For example, repeatedly interviewing and observing our participants from **chapter 3** might allow us to evaluate how perceptions influence uptake of telemedicine systems, and in turn how potential uptake might influence perceptions. Finally, my datasets were predominantly grounded in the Dutch healthcare context, limiting the generalizability of my findings. For example, the physiotherapists recruited in **chapter 4** were all part of the Dutch ParkinsonNet, meaning that they had received special training to treat people with PD. Healthcare systems in other countries might lack or differently organize such specialized training, meaning that the potential utility of a monitoring system could also differ (e.g., be larger because of a lack of a ceiling effect).

The future of telemedicine and remote monitoring

Above, I have delineated how my research may help to answer the question how we can best position telemedicine, and in particular remote monitoring, within our healthcare system. Important research questions remain, including how to decide when remote monitoring can best be offered to people with PD, what the impact of monitoring on people is, how remote monitoring data can support clinical decision making, whether telemedicine improves outcomes in routine clinical care, whether telemedicine is cost-effective, and how remote monitoring can be used to collect data to define an endpoint in clinical trials. Despite these open questions, telemedicine already forms an important pillar for high-quality healthcare today and will increasingly do so in the future. Going forward, close collaborations are necessary between researchers, clinicians, people with PD, designers and health insurers to optimally integrate telemedicine in routine clinical care. In 2014, the past, present and future of telemedicine were described.[1] Several predictions have in the meantime been realized and, during the three years of my PhD, the field has gained further traction.[8] I therefore wonder what the state of telemedicine will be in 2034, 10 years from now.[96] Based on my research, I would predict that most clinics will offer blended follow-up care when possible, preferably through safe video software. For those living far away and in less wealthy or less densely populated countries, telephone or video appointments will become the primary way to reach a movement disorder neurologist or specialized nurse. Numerous monitoring tools and applications will have hopefully matured, providing decision making and self-management modules for people with PD and clinicians. Especially the use of wearable sensors in preventive clinical trials will have become the 'new normal' for sensitive disease tracking. Some healthcare organizations will have adopted proactive screening dashboards, in which people are remotely monitored using wearable sensors and pre-consultation questionnaires.[97] By combining standardized and person-specific monitoring modules, these dashboards can form the epicentre of someone's personal care plan, centralizing communication between involved clinicians and people with PD.

References

1. Achey, M. *et al.* The past, present, and future of telemedicine for Parkinson's disease. *Movement Disorders* **29**, 871–883 (2014).
2. Goetz, C. G. & Stebbins, G. T. Is Telemedicine the New Normal or Is the Office Visit Still the Movement Disorder Option of Choice? *Movement Disorders* **36**, 1481–1482 (2021).
3. Hassan, A. *et al.* Global Survey on Telemedicine Utilization for Movement Disorders During the COVID -19 Pandemic. *Movement Disorders* **35**, 1701–1711 (2020).
4. Evans, L., Mohamed, B. & Thomas, E. C. Using telemedicine and wearable technology to establish a virtual clinic for people with Parkinson's disease. *BMJ Open Qual* **9**, e001000 (2020).
5. Dorsey, E. R., Okun, M. S. & Bloem, B. R. Care, Convenience, Comfort, Confidentiality, and Contagion: The 5 C's that Will Shape the Future of Telemedicine. *JPD* **10**, 893–897 (2020).
6. Dorsey, E. R. *et al.* Randomized Controlled Clinical Trial of "Virtual House Calls" for Parkinson Disease. *JAMA Neurol* **70**, 565 (2013).
7. Dorsey, E. R., Bloem, B. R. & Okun, M. S. A New Day: The Role of Telemedicine in Reshaping Care for Persons With Movement Disorders. *Movement Disorders* **35**, 1897–1902 (2020).
8. Deb, R., An, S., Bhat, G., Shill, H. & Ogras, U. Y. A Systematic Survey of Research Trends in Technology Usage for Parkinson's Disease. *Sensors* **22**, 5491 (2022).
9. May, S. *et al.* Digital technologies in routine palliative care delivery: an exploratory qualitative study with health care professionals in Germany. *BMC Health Serv Res* **22**, 1–12 (2022).
10. Mulroy, E. *et al.* Reply to: "A New Day: The Role of Telemedicine in Reshaping Care for Persons With Movement Disorders". *Movement Disorders* **35**, 1903–1904 (2020).
11. Mulroy, E. *et al.* Telemedicine in Movement Disorders: Leçons du COVID-19. *Movement Disorders* **35**, 1893–1896 (2020).
12. Kluger, B. M. *et al.* Patient and Family Outcomes of Community Neurologist Palliative Education and Telehealth Support in Parkinson Disease. *JAMA Neurol* (2023).
13. Fleisher, J. E. *et al.* IN-HOME-PD: The effects of longitudinal telehealth-enhanced interdisciplinary home visits on care and quality of life for homebound individuals with Parkinson's disease. *Parkinsonism & Related Disorders* **102**, 68–76 (2022).
14. Institute of Medicine (US) Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. 10027 (National Academies Press, Washington, D.C., 2001).
15. Ypinga, J. H. L. *et al.* Effectiveness and costs of specialised physiotherapy given via ParkinsonNet: a retrospective analysis of medical claims data. *The Lancet Neurology* **17**, 153–161 (2018).
16. Bloem, B. R. *et al.* ParkinsonNet: A Low-Cost Health Care Innovation With A Systems Approach From The Netherlands. *Health Affairs* **36**, 1987–1996 (2017).
17. Dixon-Woods, M. *et al.* Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. *BMC Med Res Methodol* **6**, 35 (2006).
18. Guité-Verret, A., Vachon, M. & Girard, D. Intentional presence and the accompaniment of dying patients. *Med Health Care Philos* **26**, 477-486 (2023).
19. Peacock, D. *et al.* Perception of Healthcare Access and Utility of Telehealth Among Parkinson's Disease Patients. *Can. J. Neurol. Sci.* **47**, 700–704 (2020).
20. Pols, J. *Care at a Distance: On the Closeness of Technology*. (Amsterdam University Press, 2012).

21. Street, R. L., Makoul, G., Arora, N. K. & Epstein, R. M. How does communication heal? Pathways linking clinician–patient communication to health outcomes. *Patient Education and Counseling* **74**, 295–301 (2009).
22. United Nations General Assembly. *Universal Declaration of Human Rights (217 A)*. (Paris, 1948).
23. Willis, A. W., Schootman, M. & Evanoff, B. A. Neurologist care in Parkinson disease. *Neurology* **77**, 851-857 (2011).
24. Nouri, S., Khoong, E. C., Lyles, C. R. & Karliner, L. Addressing Equity in Telemedicine for Chronic Disease Management During the Covid-19 Pandemic. *NEJM Catalyst* **1**, 1–13 (2020).
25. Pearson, C. *et al.* Care access and utilization among medicare beneficiaries living with Parkinson's disease. *npj Parkinsons Dis.* **9**, 108 (2023).
26. Mantri, S. & Mitchell, K. T. Falling down the digital divide: A cautionary tale. *Parkinsonism & Related Disorders* **93**, 33–34 (2021).
27. Pangrazio, L., Godhe, A.-L. & Ledesma, A. G. L. What is digital literacy? A comparative review of publications across three language contexts. *E-Learning and Digital Media* **17**, 442–459 (2020).
28. Esper, C. D., Valdovinos, B. Y. & Schneider, R. B. The Importance of Digital Health Literacy in an Evolving Parkinson's Disease Care System. *JPD*, 1–9 (2024).
29. Marxreiter, F. *et al.* The Use of Digital Technology and Media in German Parkinson's Disease Patients. *JPD* **10**, 717–727 (2020).
30. Kenny, L. *et al.* The Views and Needs of People With Parkinson Disease Regarding Wearable Devices for Disease Monitoring: Mixed Methods Exploration. *JMIR Form Res* **6**, e27418 (2022).
31. Fleisher, J. E., Shah, K., Fitts, W. & Dahodwala, N. A. Associations and Implications of Low Health Literacy in Parkinson's Disease. *Movement Disord Clin Pract* **3**, 250–256 (2016).
32. Bendig, J. *et al.* Measuring the Usability of eHealth Solutions for Patients With Parkinson Disease: Observational Study. *JMIR Form Res* **6**, e39954 (2022).
33. Nimmons, D. *et al.* Exploring the experiences of people and family carers from under-represented groups in self-managing Parkinson's disease and their use of digital health to do this. *Digit Health* **8**, 205520762211022 (2022).
34. Meinders, M. J., Marks, W. J., van Zundert, S. B. M., Kapur, R. & Bloem, B. R. Enhancing Participant Engagement in Clinical Studies: Strategies Applied in the Personalized Parkinson Project. *J Parkinsons Dis* **13**, 637–640 (2023).
35. Hughes, H. K., Hasselfeld, B. W. & Greene, J. A. Health Care Access on the Line - Audio-Only Visits and Digitally Inclusive Care. *N Engl J Med* **387**, 1823–1826 (2022).
36. Mehrotra, A. & Uscher-Pines, L. Informing the Debate about Telemedicine Reimbursement - What Do We Need to Know? *N Engl J Med* **387**, 1821–1823 (2022).
37. Wijers, A., Hochstenbach, L. & Tissingh, G. Telemonitoring via Questionnaires Reduces Outpatient Healthcare Consumption in Parkinson's Disease. *Movement Disord Clin Pract* **8**, 1075–1082 (2021).
38. McQueen, R. B. *et al.* Cost and Return on Investment of a Team-Based Palliative Care Program for Parkinson Disease. *Neur Clin Pract* **12**, 429–437 (2022).
39. Samii, A. *et al.* Telemedicine for delivery of health care in Parkinson's disease. *J Telemed Telecare* **12**, 16–18 (2006).
40. Saiyed, M., Hill, A. J., Russell, T. G., Theodoros, D. G. & Scuffham, P. Cost analysis of home telerehabilitation for speech treatment in people with Parkinson's disease. *J Telemed Telecare* **28**, 524–529 (2022).
41. Nederlandse Zorgautoriteit. *Wegwijzer bekostiging digitale zorg 2024.* Available from: https://puc.overheid.nl/nza/doc/PUC_655318_22/1/.

42. Lantzsch, H. *et al.* Benefit Assessment and Reimbursement of Digital Health Applications: Concepts for Setting Up a New System for Public Coverage. *Front. Public Health* **10**, 832870 (2022).
43. Bundesministerium für Gesundheit. *Driving the digital transformation of Germany's healthcare system for the good of patients.* Available from: https://www.bundesgesundheitsministerium.de/en/digital-healthcare-act (2019).
44. Rajapakshe, I. *et al.* Patients' Postjudice of Tele-Neurology for Movement Disorders. *Movement Disord Clin Pract* **9**, 446–451 (2022).
45. Li, W., Heng, D. L., Chia, T. H., Lim, E. & Tan, E. High Outpatient Attendance During COVID -19 Lockdown When Patients Were Given the Option to Return. *Movement Disorders* **35**, 2137–2138 (2020).
46. Schiess, N. *et al.* Six Action Steps to Address Global Disparities in Parkinson Disease: A World Health Organization Priority. *JAMA Neurol* **79**, 929 (2022).
47. Dorsey, E. R. *et al.* Moving Parkinson care to the home. *Mov Disord.* **31**, 1258–1262 (2016).
48. Dorsey, E. R. & Willis, A. W. Caring for the majority. *Mov Disord.* **28**, 261–262 (2013).
49. Silva de Lima, A. L. *et al.* Home-Based Monitoring of Falls Using Wearable Sensors in Parkinson's Disease. *Movement Disorders* **35**, 109–115 (2020).
50. Van Der Kolk, N. M. *et al.* Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *The Lancet Neurology* **18**, 998–1008 (2019).
51. Lai, B. *et al.* Exploring the uptake and implementation of tele-monitored home-exercise programmes in adults with Parkinson's disease: A mixed-methods pilot study. *J Telemed Telecare* **26**, 53–63 (2020).
52. Ellis, T. D. *et al.* Comparative Effectiveness of mHealth-Supported Exercise Compared With Exercise Alone for People With Parkinson Disease: Randomized Controlled Pilot Study. *Physical Therapy* **99**, 203–216 (2019).
53. Weiss, A., Herman, T., Giladi, N. & Hausdorff, J. M. Objective Assessment of Fall Risk in Parkinson's Disease Using a Body-Fixed Sensor Worn for 3 Days. *PLoS ONE* **9**, e96675 (2014).
54. Del Din, S., Kirk, C., Yarnall, A. J., Rochester, L. & Hausdorff, J. M. Body-Worn Sensors for Remote Monitoring of Parkinson's Disease Motor Symptoms: Vision, State of the Art, and Challenges Ahead. *JPD* **11**, S35–S47 (2021).
55. Evers, L. J. W., Peeters, J. M., Bloem, B. R. & Meinders, M. J. Need for personalized monitoring of Parkinson's disease: the perspectives of patients and specialized healthcare providers. *Front Neurol* **14**, 1150634 (2023).
56. Riggare, S., Scott Duncan, T., Hvitfeldt, H. & Hägglund, M. "You have to know why you're doing this": a mixed methods study of the benefits and burdens of self-tracking in Parkinson's disease. *BMC Med Inform Decis Mak* **19**, 175 (2019).
57. Post, E., Hall, D. A. & Bloem, B. R. Reply to "An Apple a day will not keep the (Parkinson's disease) doctor at bay!" *Annals of Neurology* **95**, 1013-1014 (2024).
58. Jung, C. G. *Two Essays in Analytical Psychology*. vol. 7 (Princeton University Press, New Jersey, 1972).
59. LeRouge, C., Ma, J., Sneha, S. & Tolle, K. User profiles and personas in the design and development of consumer health technologies. *International Journal of Medical Informatics* **82**, e251–e268 (2013).
60. Brigham, T. J. Personas: Stepping Into the Shoes of the Library User. *Medical Reference Services Quarterly* **32**, 443–450 (2013).

61. Becker, S. *et al.* User Profiles of a Smartphone Application to Support Drug Adherence — Experiences from the iNephro Project. *PLoS ONE* **8**, e78547 (2013).
62. Barrigón, M. L. *et al.* User profiles of an electronic mental health tool for ecological momentary assessment: MEmind. *Int J Methods Psych Res* **26**, e1554 (2017).
63. Dorst, K. The core of 'design thinking' and its application. *Design Studies* **32**, 521–532 (2011).
64. Wannheden, C. & Revenäs, Å. How People with Parkinson's Disease and Health Care Professionals Wish to Partner in Care Using eHealth: Co-Design Study. *J Med Internet Res* **22**, e19195 (2020).
65. Wolf, G. I. & De Groot, M. A Conceptual Framework for Personal Science. *Frontiers in Computer Science* **2** (2020).
66. Riggare, S., Hägglund, M., Bredenoord, A. L., De Groot, M. & Bloem, B. R. Ethical Aspects of Personal Science for Persons with Parkinson's Disease: What Happens When Self-Tracking Goes from Selfcare to Publication? *JPD* **11**, 1927–1933 (2021).
67. Riggare, S. *et al.* Patient-driven N-of-1 in Parkinson's Disease. Lessons Learned from a Placebo-controlled Study of the Effect of Nicotine on Dyskinesia. *Methods Inf Med* **56**, e123–e128 (2017).
68. Sennott, B. *et al.* Novel Outreach Program and Practical Strategies for Patients with Parkinsonism in the COVID-19 Pandemic. *JPD* **10**, 1383–1388 (2020).
69. Aberer, F., Hochfellner, D. A. & Mader, J. K. Application of Telemedicine in Diabetes Care: The Time is Now. *Diabetes Ther* **12**, 629–639 (2021).
70. De Jong, M. J. *et al.* Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial. *The Lancet* **390**, 959–968 (2017).
71. Woodrow, H. *et al.* A blinded, controlled trial of objective measurement in Parkinson's disease. *npj Parkinsons Dis.* **6**, 35 (2020).
72. Antonini, A. *et al.* Toward objective monitoring of Parkinson's disease motor symptoms using a wearable device: wearability and performance evaluation of PDMonitor®. *Front. Neurol.* **14**, 1080752 (2023).
73. Pagano, G. *et al.* Trial of Prasinezumab in Early-Stage Parkinson's Disease. *N Engl J Med* **387**, 421–432 (2022).
74. Arora, S., Baghai-Ravary, L. & Tsanas, A. Developing a large scale population screening tool for the assessment of Parkinson's disease using telephone-quality voice. *The Journal of the Acoustical Society of America* **145**, 2871–2884 (2019).
75. Moreau, C. *et al.* Overview on wearable sensors for the management of Parkinson's disease. *npj Parkinsons Dis.* **9**, 153 (2023).
76. Willemse, I. H. J. *et al.* Smartphone applications for Movement Disorders: Towards collaboration and re-use. *Parkinsonism & Related Disorders* **120**, 105988 (2024).
77. Janssen Daalen, J. M. *et al.* Digital biomarkers for non-motor symptoms in Parkinson's disease: The state of the art. Accepted for publication in *npj Digital Medicine* (2024).
78. Olthof, M., Hasselman, F., Oude Maatman, F., Bosman, A. M. T. & Lichtwarck-Aschoff, A. Complexity theory of psychopathology. *Journal of Psychopathology and Clinical Science* **132**, 314–323 (2023).
79. Shaw, J. *et al.* Beyond "implementation": digital health innovation and service design. *npj Digital Med* **1**, 1–5 (2018).
80. Maas, B. R. *et al.* Time trends in demographic characteristics of participants and outcome measures in Parkinson's disease research: A 19-year single-center experience. *Clinical Parkinsonism & Related Disorders* **8**, 100185 (2023).
81. Tosserams, A. *et al.* Underrepresentation of women in Parkinson's disease trials. *Movement Disorders* **33**, 1825–1826 (2018).

82. Lau, Y. H. *et al.* Does Ethnicity Influence Recruitment into Clinical Trials of Parkinson's Disease? *J Parkinsons Dis* **12**, 975–981 (2022).
83. van den Bergh, R. *et al.* The Content of Personalised Network-Based Case Formulations. *J Contemp Psychother* (2024).
84. Vlaanderen, F. P. *et al.* The Voice of the Parkinson Customer. *JPD* **9**, 197–201 (2019).
85. Tracy, J. M., Özkanca, Y., Atkins, D. C. & Hosseini Ghomi, R. Investigating voice as a biomarker: Deep phenotyping methods for early detection of Parkinson's disease. *Journal of Biomedical Informatics* **104**, 103362 (2020).
86. Schootemeijer, S. *et al.* The STEPWISE study: study protocol for a smartphone-based exercise solution for people with Parkinson's Disease (randomized controlled trial). *BMC Neurol* **23**, 323 (2023).
87. Tenison, E. *et al.* Proactive and Integrated Management and Empowerment in Parkinson's Disease: Designing a New Model of Care. *Parkinson's Disease* **2020**, 1–11 (2020).
88. Ypinga, J. H. L. *et al.* Rationale and design to evaluate the PRIME Parkinson care model: a prospective observational evaluation of proactive, integrated and patient-centred Parkinson care in The Netherlands (PRIME-NL). *BMC Neurol* **21**, 286 (2021).
89. Bloem, B. R. *et al.* Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *The Lancet Neurology* **19**, 623–634 (2020).
90. Espay, A. J. *et al.* A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Movement Disorders* **34**, 657–663 (2019).
91. O' Shea, E., Rukundo, A., Foley, G., Wilkinson, T. & Timmons, S. Experiences of health service access: A qualitative interview study of people living with Parkinson's disease in Ireland. *Health Expectations* **27**, e13901 (2023).
92. Bloem, B. R., Post, E. & Hall, D. A. An Apple a Day to Keep the Parkinson's Disease Doctor Away? *Annals of Neurology* **93**, 681–685 (2023).
93. Ministerie van Economische Zaken en Klimaat. *Technology Readiness Levels (TRL)*. Available from: https://www.rvo.nl/onderwerpen/trl.
94. Wade, V., Gray, L. & Carati, C. Theoretical frameworks in telemedicine research. *J Telemed Telecare* **23**, 181–187 (2017).
95. Gammon, D., Johannessen, L. K., Sørensen, T., Wynn, R. & Whitten, P. An Overview and Analysis of Theories Employed in Telemedicine Studies: A Field in Search of an Identity. *Methods Inf Med* **47**, 1–10 (2008).
96. Espay, A. J. Your After-Visit Summary—May 29, 2042. *The Lancet Neurology* **21**, 412–413 (2022).
97. Peerbolte, T. F., Van Diggelen, R. J. A., Meinders, M. J., Bloem, B. R. & van den Berg, S. W. If you only have 7 minutes, make them count! *Pract Neurol* **23**, 539–541 (2023).

8

English summary

The goal of this thesis was to advance the development and implementation of telemedicine, that is, the remote delivery of healthcare, for people with Parkinson's disease (PD). In particular, I have focused on remote monitoring as an important part of telemedicine. In **chapter 1**, I have provided the background of my research and explained the three overarching contributions which I envision that telemedicine – and especially remote monitoring – can make: maintaining access to care; capturing objective data at home; and providing proactive care. Within each of these domains, I have zoomed in on a complementary area of PD healthcare: maintaining access to palliative care; capturing objective data for preventive care at home; and providing proactive integrated and transmural care.

Contribution I. Telemedicine to maintain access to care

Telemedicine suddenly became the dominant way to maintain access to care when the COVID-19 pandemic erupted. This unprecedented use of telemedicine across the medical world has spurred the development and implementation of numerous telemedicine systems, also for persons with PD. Therefore, I first reviewed the current knowledge of telemedicine for persons with PD in **chapter 2** and then explored future telemedicine applications in **chapter 3**.

In **chapter 2**, I report a scoping review concerning the state of telemedicine for PD between 2019 and 2021, focusing on remote consultations, remote monitoring and remote treatments. I found that remote consultations and treatments ensure continued access to care for people with PD through digital technology. Being at home during a consultation or when receiving treatment provides comfort and convenience to people with PD, but comes at the cost of less personal contact. Remote monitoring using wearable sensors and apps is finding its way to research settings and to the clinic, but the effectiveness on clinical outcomes remains to be proven.

In **chapter 3**, I extend the findings from chapter 2 towards palliative care for PD. Palliative care is a type of specialty care that optimizes quality of life by adopting a holistic perspective on health and well-being. The quality of palliative care for people with PD is challenged, for example by a lack of access to palliative care services. Together with a team of qualitative researchers, I therefore conducted semi-structured interviews with an international sample of 15 persons with PD, six care partners and 37 healthcare professionals. Using a thematic analysis, we created four themes from the interview data that describe how telemedicine could

support palliative care. First, people with PD and healthcare professionals generally preferred to discuss palliative care topics physically when feasible, as remote consultations can create a conversational barrier to sense and feel the other. Second, remote monitoring technology can help to collect objective data at home, but healthcare professionals and people with PD had a heterogeneous perception of the utility of remote monitoring data for palliative care. Third, telemedicine systems, such as online chat messengers and video calls, can support the transfer of palliative care knowledge between healthcare professionals and towards people with PD and care partners. Finally, important requirements must be met before telemedicine can be implemented in palliative care, such as digital literacy of users and financial reimbursement of remote consultations.

Contribution II. Telemedicine to capture objective data at home

Remote monitoring technology can capture fine-grained information about the functioning at home of a person with PD. This information is highly relevant for healthcare professionals, such as physiotherapists or occupational therapists, as their treatment centres around improving functioning in daily life, in the person's own living environment. However, designing such a remote monitoring system is difficult for a variety of reasons, and choosing the best solution is challenging given the plethora of possible measures and clinical applications.

Therefore, in **chapter 4**, I describe the design and evaluation of a remote monitoring system to specifically support physiotherapy for people with PD. The monitoring system was co-designed with people with PD and physiotherapists and consisted of a smartphone and tablet app connected to a wearable sensor that recorded physical activity and falls throughout the day. In total, 46 persons with PD and 17 physiotherapists used the system in regular practice for six weeks. Based on the interview data from the users, I conclude that the usability of the system was rated positively by most, except for some who experienced cognitive impairments or lacked digital literacy. The experienced utility varied among people with PD: some became motivated to move more whilst others disliked being constantly reminded of their disease. I drafted three user profiles from the data describing how remote monitoring data could add value to PD-physiotherapy: 1) as a flagging dashboard to signal the need for renewed treatment; 2) as a motivational tool to stay physically active and 3) as a passive tracker of physical activity and falls at home to inform the physiotherapist.

Contribution III. Telemedicine to provide proactive care

Telemedicine could be used to deliver proactive care where problems are remotely identified in an early stage and tackled before they exacerbate. I propel this proactive use of telemedicine by identifying relevant variables to monitor in **chapter 5** and by evaluating the validity of a healthcare context where proactive telemedicine could be implemented in **chapter 6**.

In **chapter 5**, I identified modifiable causal factors that are relevant to monitor, with the aim of using these monitoring data as steering information to design therapeutic strategies for the prevention of PD-related complications. I focused on six complications based on their impact on people's quality of life and hospitalization and mortality rates, namely falls and related fractures, pneumonias, urinary tract infections, psychotic symptoms, mood disorders and dementia. For these complications, I performed a four-step mixed methods study to identify relevant modifiable causal factors. First, I systematically searched the literature to capture all known causal factors per complication. Second, I surveyed 99 PD healthcare professionals from 10 different disciplines to ascertain the face validity of the identified causal factors and complement the list where necessary. Third, I mapped causal pathways for each complication together with 10 healthcare professionals with expertise on that complication. Finally, I used the PRIME-NL dataset (n = 920 people with PD) to estimate the number of preventable complications if we were able to eliminate risk factors from the population, i.e., the population attributable fraction. Based on the available data, I cautiously conclude that we can theoretically prevent 60.2% of falls (95% confidence interval (CI) [33.4% - 80.4%]), 34.2% of pneumonias (95% CI [-37.3% - 75.8%]), 21.5% of urinary tract infections (95% CI [2.0% - 47.4%]), 43.1% of psychotic symptoms (95% CI [17.8% - 65.4%]), 61.9% of depressive symptoms (95% CI [35.1% - 80.3%]) and 46.6% of anxiety symptoms (95% CI [22.0% - 67.4%]). For dementia, we lacked a grounded causal pathway to estimate population attributable fractions.

In **chapter 6**, I led a team effort to examine the validity of a PD healthcare innovation called PRIME Parkinson. Over the next years, the PRIME Parkinson project will deliver proactive and integrated PD care across medical disciplines by utilizing, amongst others, telemedicine approaches. Given this upcoming implementation, this chapter identifies potential hurdles in the final evaluation of the PRIME Parkinson care model. PRIME Parkinson is being implemented in a specific region in the Netherlands and will be compared to usual care delivered in

the rest of the Netherlands. We used healthcare claims data encompassing >99% of people with PD in the Netherlands to show that the PRIME and usual care regions are similar at baseline. From both regions, a questionnaire subsample was recruited for in-depth examination. The combined questionnaire subsamples from both regions are representative of the broader PD population in the Netherlands, except for some underrepresentation of elderly. However, selection bias is present in the questionnaire subsamples, as the PRIME subsample included more affected people with PD and lost more people at follow-up compared to the usual care subsample.

In **chapter 7**, I discuss how my findings relate to the broader field of telemedicine, highlight the strengths and limitations of my work and discuss avenues for future research.

9

Nederlandse samenvatting

Het doel van dit proefschrift was om de ontwikkeling en implementatie van telemedicine, dat wil zeggen het op afstand leveren van gezondheidszorg, voor mensen met de ziekte van Parkinson te bevorderen. Ik heb me in het bijzonder gericht op monitoring op afstand als een belangrijk onderdeel van telemedicine. In **hoofdstuk 1** heb ik de achtergrond van mijn onderzoek geschetst en de drie overkoepelende bijdragen toegelicht die telemedicine - en met name monitoring op afstand - volgens mij kan leveren: het toegankelijk houden van de zorg, het vastleggen van objectieve gegevens thuis en het bieden van proactieve zorg. Binnen elk van deze domeinen heb ik ingezoomd op een complementair gebied van de gezondheidszorg voor mensen met Parkinson: het toegankelijk houden van palliatieve zorg, het vastleggen van objectieve gegevens voor preventieve zorg thuis, en het bieden van proactieve geïntegreerde en transmurale zorg.

Bijdrage I. Telemedicine om de toegang tot zorg te behouden

Telemedicine werd plotseling de dominante manier om toegang tot zorg te behouden toen de COVID-19 pandemie uitbrak. Dit ongekende gebruik van telemedicine in de hele medische wereld heeft de ontwikkeling en implementatie van talloze telemedicine systemen gestimuleerd, ook voor mensen met Parkinson. Daarom bespreek ik in **hoofdstuk 2** eerst de huidige kennis over telemedicine voor mensen met Parkinson en verken ik daarna in **hoofdstuk 3** de toekomstige toepassingen van telemedicine.

In **hoofdstuk 2** beschrijf ik een scoping review naar de huidige stand van telemedicine voor mensen met Parkinson tussen 2019 en 2021, waarbij ik me richt op consulten op afstand, monitoring op afstand en behandelingen op afstand. Ik ontdekte dat consulten en behandelingen op afstand ervoor zorgen dat mensen met Parkinson toegang blijven houden tot zorg via digitale technologie. Thuis zijn tijdens een consult of behandeling biedt mensen met Parkinson comfort en gemak, maar leidt ook tot minder persoonlijk contact. Monitoring op afstand met behulp van draagbare sensoren en apps komt steeds vaker voor in onderzoek en de kliniek, maar de effectiviteit op klinische uitkomsten moet nog worden bewezen.

In **hoofdstuk 3** breid ik de bevindingen uit hoofdstuk 2 uit naar palliatieve zorg voor mensen met Parkinson. Palliatieve zorg is een vorm van gespecialiseerde zorg die de kwaliteit van leven optimaliseert door een holistisch perspectief op gezondheid en welzijn te hanteren. De kwaliteit van palliatieve zorg voor mensen

met Parkinson staat onder druk, bijvoorbeeld door een gebrek aan toegang tot palliatieve zorg. Samen met een team van kwalitatieve onderzoekers heb ik daarom semigestructureerde interviews afgenomen bij een internationale steekproef van 15 personen met Parkinson, zes mantelzorgers of partners van mensen met Parkinson, en 37 zorgprofessionals. Met behulp van een thematische analyse hebben we vier thema's uit de interviewgegevens gecreëerd die beschrijven hoe telemedicine de palliatieve zorg zou kunnen ondersteunen. Ten eerste gaven mensen met Parkinson en zorgprofessionals er over het algemeen de voorkeur aan om onderwerpen op het gebied van palliatieve zorg indien mogelijk fysiek te bespreken, omdat consulten op afstand een barrière kunnen vormen voor het aanvoelen van de ander. Ten tweede kan technologie voor monitoring op afstand helpen om thuis objectieve gegevens te verzamelen, maar zorgprofessionals en mensen met Parkinson hadden een wisselende perceptie van het nut van monitoring voor palliatieve zorg. Ten derde kunnen systemen voor telemedicine, zoals online chatberichten en videogesprekken, de overdracht van kennis over palliatieve zorg tussen zorgverleners onderling en tussen zorgverleners en mensen met Parkinson en hun naasten ondersteunen. Tot slot moet aan belangrijke voorwaarden worden voldaan voordat telemedicine kan worden toegepast in de palliatieve zorg, zoals digitale geletterdheid van gebruikers en financiële vergoeding van consulten op afstand.

Bijdrage II. Telemedicine om objectieve gegevens thuis vast te leggen

Technologie voor monitoring op afstand kan gedetailleerde informatie vastleggen over het functioneren thuis van een persoon met Parkinson. Deze informatie is zeer relevant voor professionals in de gezondheidszorg, zoals fysiotherapeuten of ergotherapeuten, omdat hun behandeling gericht is op het verbeteren van het functioneren in het dagelijks leven, in de eigen leefomgeving van de persoon. Het ontwerpen van een dergelijk monitoringsysteem op afstand is echter om verschillende redenen moeilijk en het kiezen van de beste oplossing is een uitdaging gezien de overvloed aan mogelijke uitkomstmaten en klinische toepassingen.

Daarom beschrijf ik in **hoofdstuk 4** het ontwerp en de evaluatie van een monitoringsysteem op afstand gericht op het ondersteunen van fysiotherapie voor mensen met Parkinson. Het monitoringsysteem werd samen met mensen met Parkinson en fysiotherapeuten ontworpen en bestond uit een smartphone en tablet app verbonden met een draagbare sensor die gedurende de dag fysieke activiteit en vallen registreerde. In totaal gebruikten 46 mensen met Parkinson en

17 fysiotherapeuten het systeem zes weken lang in het dagelijks leven. Op basis van de interviewgegevens van de gebruikers concludeer ik dat de bruikbaarheid van het systeem door de meesten positief werd beoordeeld, behalve door sommigen die cognitieve beperkingen hadden of niet digitaal vaardig waren. Het ervaren nut varieerde tussen mensen met Parkinson: sommigen raakten gemotiveerd om meer te bewegen, terwijl anderen het niet prettig vonden om constant aan hun ziekte te worden herinnerd. Op basis van de interviews stelde ik drie gebruikersprofielen op die beschrijven hoe monitoring op afstand van waarde kan zijn voor Parkinson-fysiotherapie: 1) als een waarschuwingsdashboard om de noodzaak van een nieuwe behandeling aan te geven; 2) als een motiverende tool om lichamelijk actief te blijven en 3) als een passieve tracker van lichamelijke activiteit en valincidenten thuis om de fysiotherapeut te informeren.

Bijdrage III. Telemedicine om proactieve zorg te bieden

Telemedicine zou kunnen worden gebruikt om proactieve zorg te leveren waarbij problemen op afstand in een vroeg stadium worden geïdentificeerd en aangepakt voordat ze verergeren. Ik bevorder dit proactieve gebruik van telemedicine door in **hoofdstuk 5** relevante variabelen te identificeren om te monitoren en door in **hoofdstuk 6** de validiteit te evalueren van een zorgcontext waarin telemedicine zou kunnen worden geïmplementeerd voor proactieve zorg.

In **hoofdstuk 5** heb ik modificeerbare causale factoren geïdentificeerd die relevant zijn om te monitoren, met als doel deze gegevens te gebruiken als stuurinformatie voor het ontwerpen van therapeutische strategieën voor de preventie van Parkinson-gerelateerde complicaties. Ik richtte me op zes complicaties op basis van hun impact op de kwaliteit van leven van mensen en ziekenhuisopname- en sterftecijfers, namelijk vallen en gerelateerde fracturen, longontstekingen, urineweginfecties, psychotische symptomen, stemmingsstoornissen en dementie. Voor deze complicaties voerde ik een vierdelig mixed methods onderzoek uit om relevante modificeerbare causale factoren te identificeren. Ten eerste heb ik systematisch de literatuur doorzocht om alle bekende causale factoren per complicatie vast te leggen. Ten tweede heb ik 99 zorgprofessionals in de Parkinsonzorg uit 10 verschillende disciplines ondervraagd om de face validity van de geïdentificeerde causale factoren vast te stellen en de lijst waar nodig aan te vullen. Ten derde heb ik voor elke complicatie causale paden in kaart gebracht samen met 10 zorgprofessionals met expertise in die complicatie. Tot slot heb ik de PRIME-NL

dataset (n = 920 mensen met Parkinson) gebruikt om een schatting te maken van het aantal te voorkomen complicaties als we in staat zouden zijn om risicofactoren uit de populatie te elimineren, oftewel ik heb de population attributable fraction berekend. Op basis van de beschikbare gegevens concludeer ik voorzichtig hoeveel complicaties we theoretisch kunnen voorkomen: 60.2% van de valincidenten (95% betrouwbaarheidsinterval (CI) [33.4% - 80.4%]), 34.2% van de longontstekingen (95% CI [-37.3% - 75.8%]), 21.5% van de urineweginfecties (95% CI [2.0% - 47.4%]), 43.1% van de psychotische symptomen (95% CI [17.8% - 65.4%]), 61.9% van de depressieve symptomen (95% CI [35.1% - 80.3%]) en 46.6% van de angst gerelateerde symptomen (95% CI [22.0% - 67.4%]). Voor dementie konden we geen gefundeerd causaal pad maken om de population attributable fractions te berekenen.

In **hoofdstuk 6** heb ik samen met mijn team onderzoek gedaan naar de validiteit van een Parkinson zorginnovatie, genaamd PRIME Parkinson. In de komende jaren zal het PRIME Parkinson project proactieve en geïntegreerde Parkinsonzorg leveren over medische disciplines heen door onder andere gebruik te maken van telemedicine. Met het oog op deze aanstaande implementatie, identificeer ik in dit hoofdstuk mogelijke obstakels in de uiteindelijke evaluatie van het PRIME Parkinson zorgmodel. PRIME Parkinson wordt geïmplementeerd in een specifieke regio in Nederland en zal worden vergeleken met de gebruikelijke zorg in de rest van Nederland. Door middel van zorgverzekeringsdata die >99% van de mensen met Parkinson in Nederland omvatten, tonen we aan dat de PRIME en gebruikelijke zorg regio's vergelijkbaar zijn voordat de zorginnovatie wordt geïmplementeerd. Uit beide regio's werd een steekproef aan mensen gerekruteerd voor een diepgaand vragenlijst onderzoek. Gecombineerd zijn deze steekproeven representatief voor de bredere Parkinson-populatie in Nederland, met uitzondering van enige ondervertegenwoordiging van ouderen. Tussen de steekproeven uit de regio's is er echter sprake van selectiebias, aangezien de PRIME-steekproef meer mensen met Parkinson bevat die meer Parkinson-gerelateerde symptomen hebben en meer mensen verloor over tijd in vergelijking met de steekproef uit de gebruikelijke zorg regio.

In **hoofdstuk 7** bespreek ik hoe mijn bevindingen zich verhouden tot het bredere veld van telemedicine, benadruk ik de sterke punten en beperkingen van mijn werk en bespreek ik richtingen voor toekomstig onderzoek.

Appendices

Appendix 1. Research data management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants (**chapter 3, 4, 5 and 6**) and on existing data from published papers (**chapter 2**). None of the studies were subject to the Medical Research Involving Human Subjects Acts (WMO) but all were conducted in accordance with the principles of the Declaration of Helsinki. The medical ethical review committee 'METC Oost-Nederland' reviewed the study protocols for **chapter 3** (file number: 2022-15724), **4** (2017-3382), **5** (2019-5618 and 2022-13744) and **6** (2019-5618). Informed consent was obtained from research participants prior to inclusion in the studies. Technical and organizational measures were followed to safeguard the availability and confidentiality of the data, such as the use of secure data storage, access authorization and pseudonymization of the data.

Data collection and storage

The interviews for **chapter 3 and 4** were audio recorded and professionally transcribed verbatim and anonymously. For **chapter 4, 5 and 6**, we used electronic Case Report Forms using CASTOR EDC to collect questionnaire and demographic data. For **chapter 5**, we also used a secure online questionnaire platform (ParkinsonNEXT) to collect questionnaire data from healthcare professionals. All digital data were pseudonymized and stored on a secure server of the Radboudumc department of Neurology and were only accessible by members of the research team working at the designated projects within the Radboudumc. Pseudonymization was arranged on a project-level for **chapter 4, 5 and 6**. For **chapter 3 and 4**, the privacy of the participants was warranted by the use of the Radboudumc pseudonymization tool PIMS, with the respective keyfiles named "*PD_PAL telemedicine interviews*" and "*Monitoring PD physiotherapy*". All quantitative data was analysed using R Studio. All qualitative data was analysed using Atlas.ti. Hardcopies of informed consent forms were archived at the department.

Availability of the data

All studies in this thesis are published open access. The data will be archived for 15 years after termination of the study. The pseudonymized interview data of **chapter 3 and 4** as well as the pseudonymized questionnaire data from ParkinsonNEXT from **chapter 5** can be made available by the corresponding author upon reasonable request and under restricted access. The other questionnaire data from **chapter 5 and 6** is part of the PRIME Parkinson study and will adhere to the corresponding data sharing guidelines.

Appendix 2. About the author

Robin van den Bergh was born on October 30, 1996 in Roosendaal and Nispen, the Netherlands. After obtaining his secondary education in 2014 from Gymnasium Bernrode in Heeswijk-Dinther, he studied Psychology at the Radboud University in Nijmegen. During his bachelor, he was most fascinated by the broad range of methodological and analytical approaches within the field. He solicited for the honours program in Psychology through which he gained experience with behavioural experiments leveraging eye-tracking and priming techniques. From 2018 to 2020, he completed a research master in Behavioural Science at the Behavioural Science Institute in Nijmegen. There, he focused on a variety of quantitative and qualitative research methodologies. Interested in human psychopathology, he completed his master thesis on a qualitative exploration of the content of personalized network-based case formulations. During his master, he served as a board member of Maizena, the study association of the research master. He started his PhD trajectory in 2021, studying the meaningful application of telemedicine tools in diverse topics, ranging from palliative care to physiotherapy to complication prevention. His research is driven by the wish to facilitate insight and changes in the behaviour of people with Parkinson's disease.

Appendix 3. List of publications

Scientific articles published in this thesis

Van den Bergh R, Bloem BR, Meinders MJ, Evers LJW (2021). *The state of telemedicine for persons with Parkinson's disease.* Current Opinion in Neurology, 34(4), 589–597.

Van den Bergh R, Evers LJW, de Vries NM, Silva de Lima AL, Bloem BR, Valenti G, Meinders MJ (2023). *Usability and utility of a remote monitoring system to support physiotherapy for people with Parkinson's disease.* Frontiers in Neurology, 14, 1251395.

Gelissen LMY, **van den Bergh R**, Talebi AH, Geerlings AD, Maas BR, Burgler MM, Kroeze Y, Smink A, Bloem BR, Munneke M, Ben-Shlomo Y, Darweesh SKL (2024). *Assessing the validity of a Parkinson's care evaluation: the PRIME-NL study.* European Journal of Epidemiology, doi: 10.1007/s10654-024-01123-7.

Van den Bergh R, van Barschot P, Bloem BR, Muente C, Meinders MJ (2024). *In-person when necessary and available, remotely when possible: How telemedicine can support palliative care for persons with Parkinson's disease.* Submitted for publication.

Van den Bergh R, Meinders MJ, Bloem BR, Munneke M, Darweesh SKL (2024). *A route towards prevention: A mixed methods study of modifiable causal factors, causal pathways and population attributable fractions for complications in Parkinson's disease.* Submitted for publication.

Other scientific articles

Möbius M, Ferrari GRA, **van den Bergh R**, Becker ES, Rinck M (2018). *Eye-Tracking Based Attention Bias Modification (ET-ABM) facilitates disengagement from negative stimuli in dysphoric individuals.* Cognitive Therapy and Research, 42(4), 408–420.

Van den Bergh R, Olthof M, Goldbeck F, Hegewald K, Pommerien-Becht F, Daniels-Wredenhagen N, Weggemans RJ, Scholz S, Daalmans S, Otten R, Aas BG, Lichtwarck-Aschoff A (2024). *The content of personalised network-based case formulations.* Journal of Contemporary Psychotherapy, doi: 10.1007/s10879-023-09613-7.

Willemse IHJ, Schootemeijer S, **van den Bergh R**, Dawes H, Nonnekes JH, van de Warrenburg BPC (2024). *Smartphone applications for Movement Disorders: Towards collaboration and re-use.* Parkinsonism & Related Disorders, 120, 105988.

Janssen Daalen J, **van den Bergh R**, Prins E, Chenarani Moghadam MS, van den Heuvel R, Veen J, Mathur S, Meijerink H, Mirelman A, Darweesh SKL, Evers LJW, Bloem BR (2024). *Digital biomarkers for non-motor symptoms in Parkinson's disease: the state of the art.* Accepted for publication in npj Digital Medicine.

Maas BR, **van den Bergh R**, van den Berg SW, Hulstein E, Stadhouders N, Jeurissen PPT, de Vries NM, Bloem BR, Munneke M, Ben-Shlomo Y, Darweesh SKL (2024). *The PRIME-NL study: Evaluating a complex healthcare intervention for people with Parkinson's disease in a dynamic environment.* Accepted for publication in BMC Neurology.

Appendix 4. Portfolio

Year	Activity
2021	Course: Radboudumc eBROK
2021	Course: Scientific writing for PhD candidates
2021	Course: Project management for PhD candidates
2021	Course: Qualitative research methods and analysis
2021	Course: Design and illustration
2022	Course: Scientific integrity
2022	Course: The next step in my career
2022	Course: Achieving your goals and performing more successfully in your PhD
2022	Supervised MSc thesis of LMY Gelissen
2023	Workshop: Presentation skills for PhD candidates
2023	Poster presented at the World Parkinson Congress in Barcelona
2023	Course: Analysing longitudinal and multilevel data using R
2023	Summer school: R for advanced users
2023	Course: Effective writing strategies
2024	Course: Methods for design of applied clinical research

Appendix 5. Donders Graduate School

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 600 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher

education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit:

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Appendix 6. Acknowledgements | Dankwoord

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Appendix 7. Supplementary material

Chapter 3. In-person when necessary and available, remotely when possible: How telemedicine can support palliative care for persons with Parkinson's disease

Supplementary table S1. Characteristics of researchers involved in the thematic analysis

Initials	Gender	Age	Occupation and experience
R.B.	Male	27	PhD candidate, master degree in Behavioural Science. 2 years of experience on multiple PD telemedicine projects, 3 years of experience on various qualitative research projects
P.B.	Female	26	PhD candidate, master degree in speech and language therapy. 1 year of experience as qualitative research assistant. Treated people with PD in a rehabilitation centre for 2 years.
C.M.	Female	38	PhD candidate in palliative care for PD, master degree in Sociology. Over 10 years of experience in qualitative research projects. Experience in research projects on Parkinson's disease, palliative care and telemedicine for 4 years.
M.J.M.	Female	54	Senior researcher person-centred healthcare. PhD in Veterinary Sciences. Over 10 years of research experience in PD, shared decision making, palliative care and qualitative research.

Supplementary table S2. Interview guide

Introductory themes

Experiences with palliative care

First, we would like to gain an initial understanding of your experiences with palliative care.

Questions	Follow-up questions
Q1: Could you share something about your experience with palliative care?	1. For how many years have you been providing care to people with PD? 2. For how many years have you been providing *palliative care* to people with PD?

Experiences with telemedicine

We would like to gain an initial understanding of your experiences with telemedicine.

Questions	Follow-up questions
Q1: Do you have any experience with telemedicine? Could you share something about this experience?	1. What did you have to do? 2. How did that go? 3. For what reason did you do it? 4. What were your thoughts on this experience? 5. What advantages and disadvantages do you see for the utilization of telemedicine? 6. Did you need support from others to use telemedicine successfully? From whom and for which aspect(s) did you receive support?
Q2: How would you describe your proficiency in using a computer, telephone, or tablet?	1. Are you able to navigate this device easily? Or do you receive support?
	Questions only for person with PD & care partner
	1. Could you provide an example of what you do on your computer, telephone or tablet? For instance, video calling? 2. Have you experienced any problems? Which problems? 3. Do you receive support from others if you need it?

Communication with people with Parkinson's disease

We would like to gain an understanding of your thoughts on remote contact with [people with PD / healthcare professionals], for instance via remote consultations, telephone or email.

Questions	Follow-up questions
Q1: In what manner do you prefer to have contact with [people with PD / healthcare professionals]?	1. In what manner do you currently have contact with [people with PD / healthcare professionals]? 2. What are the advantages and disadvantages for physical contact? 3. What are the advantages and disadvantages for remote contact? 4. Are there barriers to utilizing technology for remote communication?
Q2: Palliative care focuses on physical, psychological, and social well-being, as well as on finding meaning and addressing what is important in life. Additionally, discussing care in the future is a crucial component. We are curious about whether communicating about this topic is different through technology. What are your thoughts on this?	1. Are there topics that you prefer to discuss in person or digitally? 2. Which topics are those and why do you prefer this? 3. What are important boundary conditions for having such a conversation? For instance, a connection with the person, prior physical contact, etc.
Q3: What do you believe the impact of telemedicine is on the relationship you have with a [person with PD / healthcare professional]?	1. How do you experience the communication now? What aspects do you perceive as pleasant and less pleasant about it? 2. Did the relationship change when care was provided through telemedicine? In what manner? 3. If not applicable 'Imagine that…' 4. How personal do you find remote contact with [person with PD / healthcare professional]?

Alignment between healthcare professionals

Questions for person with PD & care partner	Follow-up questions
Q4: Various healthcare professionals are involved in the provision of care, such as the general practitioner, nurse, physiotherapist, and other specialists. Do you feel that your healthcare professionals are well-aligned with each other and attuned to your needs?	1. Which healthcare professionals are and are not well-aligned? Could you give an example of a situation when that did or did not occur? 2. Who ensures that the healthcare professionals align their care with each other? 3. Can telemedicine support the alignment? How? 4. For instance, video calling with a care team instead of 1-to-1? Or an online collaboration platform?

Communication with other healthcare professionals

Questions for healthcare professional	Follow-up questions
Q5: Various healthcare professionals are involved in the provision of care, such as the general practitioner, nurse, physiotherapist, and other specialists. Do you feel that you and other healthcare professionals are well-aligned with each other and attuned to the needs of the person with PD and the care partner?	1. With which healthcare professionals do you collaborate to deliver palliative care? 2. With which healthcare professionals are you (not) well-aligned? Could you give an example of a situation when that did or did not occur? 3. Who ensures that the healthcare professionals align their care with each other? 4. Can telemedicine support the alignment? How? 5. For instance, video calling with a care team instead of 1-to-1? Or an online collaboration platform?

Remote monitoring

We are interested in understanding your perspective on monitoring at home. At home monitoring involves [you / people with Parkinson's disease] tracking certain symptoms from home for a period of time. For instance, this could involve monitoring of issues related to walking, communication, swallowing, fatigue, or hallucinations, as well as monitoring the effects of medications. [You / Healthcare professionals] can then discuss this information during a consultation.

Questions	Follow-up questions
Q1: Have you ever monitored the progression of Parkinson's symptoms / had someone monitor the progression of Parkinson's symptoms?	1. What are the experiences related to this? What is being measured and why? 2. In what manner was it done? 3. What are the advantages and disadvantages?
	Questions for person with PD & care partner
	1. Would you recommend others to use remote monitoring? Why or why not?
Q2: Would you find it useful to have the progression of Parkinson's symptoms monitored? What would be your reasons for deciding to do so or not?	1. What aspects would be most useful for you to monitor? What areas do you think you would like to explore or monitor more closely (care goal, what is important in life); and why? 2. What other aspects would be useful for you to monitor? For example, medication, stress, physical activity, diet? 3. What would be your primary motivation for monitoring? For instance, reassurance, gathering information, tracking progress, aligning treatment strategies, gaining more control, or early intervention in case of deterioration. 4. What would be your main reason for not monitoring the symptoms? For example, concerns about burden, digital literacy, impersonal care? 5. When would the collected information be relevant?
Questions for healthcare professional	**Follow-up questions**
Q3: An example of remote monitoring is when your patient wears a watch that measures movements and tremors. This enables you and the patient to assess whether medication is effectively tailored to the patient.	1. What are your thoughts on this example? 2. Would you be willing to participate in such monitoring? 3. Do you consider this as a valuable approach? 4. What disadvantages do you foresee?
Q4: Another example of remote monitoring is when your patient keeps a record on paper of their fatigue levels and activities for the day. This allows you to identify what activities are energizing or draining, which can help to effectively distribute the energy.	1. What are your thoughts on this example? 2. Would you be willing to participate in such monitoring? 3. Do you consider this as a valuable approach? 4. What disadvantages do you foresee?

Information and education

We sometimes hear that people with Parkinson's disease and their care partners feel inadequately informed, for instance, about the course of the disease, treatment options, or the various healthcare professionals who can help them.

Questions for healthcare professional	Follow-up questions
Q1: Do you provide information to people with PD in the advanced stage and their care partners about these topics?	1. Could you describe your experiences? 2. In what manner do you provide information? 3. Is this way of information provision sufficient? What improvements can be made? 4. What could help you in better informing people with PD and their care partners?
Questions for person with PD & care partner	**Follow-up questions**
Q1: What are your experiences concerning receiving information about the progression of the disease?	1. Do you have a need for information? 2. What kind of information has been helpful? 3. From whom did you receive information? 4. Which healthcare professionals can you approach with questions and through what means? Telephone, email, etc.
Q2: Can telemedicine contribute to improved education and enhanced information provision?	1. How can telemedicine contribute to this? 2. What do you foresee as advantages and disadvantages? 3. If no idea: consider interactions like chatting with a nurse, calling a helpdesk or obtaining information from a website.

We also hear that some healthcare professionals feel they lack the expertise or skills to deliver palliative care. They would like to receive education or training in this regard.

Questions for healthcare professional	Follow-up questions
Q3: Do you recognize this situation in practice?	1. Do you or your colleagues require more education or information regarding palliative care? 2. On which topics would you like to receive education or information? 3. Which healthcare professionals can you consult if you have questions about palliative care?
Q4: Can telemedicine contribute to improved education and enhanced information provision?	1. How can telemedicine contribute to this? For example, online consultations with palliative specialists, online discussion groups/lectures, reference materials on a website, or reminders to systematically assess palliative care domains. 2. Which advantages and disadvantages do you foresee?

Chapter 5. A route towards prevention: A mixed methods study of modifiable causal factors, causal pathways and population attributable fractions for complications in Parkinson's disease

Supplementary file S1. Literature search strategy

The goal of this supplementary file is to describe the decisions that we made and the search strategy that we used to identify causal factors in the literature.

Description of search strategy process

First, we searched the PubMed and Cochrane Review databases for systematic reviews and meta-analyses published up until March 2022. We have outlined the search strategies below. The goal of this search strategy was to find articles that describe causal factors that are relevant to each complication within the Parkinson's disease population. An article should therefore at least describe one or more causal factors and investigate one or more of the six complications. Otherwise the article was excluded from the selection.

PubMed review search strategy

(Parkinson Disease [MesH] OR Parkinson* [tiab])

AND

(fall*[tiab] OR fracture*[tiab] OR fractures, bone [Mesh] OR
pneumonia* [tiab] OR pneumonia [Mesh] OR
urinary tract infection* [tiab] OR urinary tract infections [Mesh] OR
Hallucination*[tiab] OR hallucination [Mesh] OR psychosis*[tiab] OR psychotic disorders[Mesh] OR delirium [tiab] OR delirium [Mesh] OR
depressi*[tiab] OR depression [Mesh] OR anxi*[tiab] OR anxiety [Mesh] OR
(social*[tiab] AND isolat*[tiab]) OR functional declin*[tiab] OR dementi*[tiab])

AND

(meta-analysis[Filter] OR systematicreview[Filter]) AND (english[Filter])

Cochrane review search strategy

(Parkinson*):ti,ab,kw OR MeSH descriptor: [Parkinson Disease] explode all trees

Findings of the review search

This resulted in 662 PubMed systematic reviews (SR) and meta-analyses (MA) and 81 Cochrane reviews. We processed all articles by first reading the titles, excluding those who were not relevant. For the remaining articles, we read the abstract. If still relevant for the goal of the study, we read the full-text version of an article. This resulted in:

- 3 relevant reviews/MAs for falls and hip fractures;
- 1 review for pneumonia that examined frail older people but not people with Parkinson's disease, but given the limited research on causal factors we decided to include it unless a more fitting article was found;
- 0 reviews/MAs for urinary tract infections (UTI);
- 2 reviews on psychotic symptoms and delusions in PD, one of which focused mostly on prevalence and the other on some moderating variables;
- 2 reviews for mood disorders, of which one focused on psychological predictors and the other examined factors associated with the prevalence;
- 7 reviews/MAs for dementia, 2 were focused on genetic predispositions, 1 on CSF-biomarkers, 2 on sleep disorders, 1 on subjective cognitive decline and 1 on the prevalence of dementia;

Given the limited findings for all complications except for falls and fractures, we decided to broaden our search strategy. We removed the restriction of an article being a SR or MA, but added the requirement that there should be one of the following words in the title: risk*, factor*, predict*, occurrence, or epidemiolog*. This line was added to somewhat confine our search to articles covering relevant topics. The asterisk (*) signals that the ending of the word may vary.

We operationalized 'causal factors' as 'risk factors' here to align with the more commonly used wording. Also, we did not include words like 'mediator' or 'modifier' in the search, as these were not likely to result in additional relevant search results. We kept the line searching for falls and fractures to be comprehensive and see whether we accidentally missed highly relevant papers. However, we did not examine these in detail because we already found adequate reviews for this topic. Furthermore, we conducted this search only on PubMed because Cochrane is a review and trial database. Additionally, for dementia, we confined the search to title only because title-abstract resulted in many irrelevant papers earlier. This resulted in the following search strategy:

PubMed regular article search strategy
(Parkinson Disease [MesH] OR Parkinson* [tiab])

AND

(fall*[tiab] OR fracture*[tiab] OR fractures, bone [Mesh] OR
pneumonia* [tiab] OR pneumonia [Mesh] OR
urinary tract infection* [tiab] OR urinary tract infections [Mesh] OR
hallucination*[tiab] OR hallucination [Mesh] OR psychosis*[tiab] OR psychotic disorders[Mesh] OR delirium [tiab] OR delirium [Mesh] OR
depressi*[tiab] OR depression [Mesh] OR anxi*[tiab] OR anxiety [Mesh] OR
(social*[tiab] AND isolat*[tiab]) OR functional declin*[tiab] OR dementi*[title])

AND

(risk*[title] OR factor*[title] OR predict*[title] OR occurrence[title] OR epidemiolog*[title])

Findings of the regular article search

Falls and fractures
We left the falls and fractures line in this search strategy to be comprehensive. However, none of the articles that were found because of these search terms were incorporated in the final selection of papers. We did include 2 review articles identified in our personal database as these reviews were highly specific towards falls in Parkinson's disease *and* included relevant causal factors.

Pneumonia
For pneumonia, we identified 6 studies in total. Two studies were conducted by the same Korean group that used roughly the same nationwide healthcare claims data to identify causal factors for pneumonia in PD. Another 2 studies examined the same type of database, but now situated in Taiwan. These were the only studies specifically examining PD, but were somewhat limited because they used the same database from two countries. These studies were included.

We also found one systematic review, one literature review, and one large case-control study all examining pneumonia causal factors in the general (elderly) population. Given the limited PD specific evidence, we were willing to incorporate findings from the general population as long as the articles were (systematic) reviews. Therefore, we included 2 articles. However, we realized that our search

strategy did specifically search for Parkinson's disease, possibly leaving out other systematic reviews that have been conducted in the general population. To be thorough, we therefore searched PubMed again for systematic reviews or MAs that have been conducted in the general population. We searched PubMed with: ("risk factor*"[tiab] AND "pneumoni*"[tiab]) AND (meta-analysis[Filter] OR systematicreview[Filter]).

This resulted in 233 articles of which 10 were relevant. This included one review we already identified in the PubMed review and regular article search and one systematic review written in German from which we only read the abstract.

This resulted in 15 articles in total. Four were PD specific nationwide healthcare claims studies, 11 were systematic or literature reviews from the general population.

Urinary tract infection (UTI)

For UTIs, we did not find any relevant articles covering UTIs and PD with the search mentioned under "PubMed regular article search strategy". Given that there were also no reviews found in the first step, we decided to broaden our search strategy for UTI's considerably. We created a new strategy consisting of two parts:

((Parkinson Disease [MesH] OR Parkinson* [tiab]) AND
(urinary tract infection* [tiab] OR urinary tract infections [Mesh]))
OR
((urinary tract infection* [tiab] OR urinary tract infections [Mesh]) AND (risk factor*[tiab]) AND
(meta-analysis[Filter] OR systematicreview[Filter]) AND (english[Filter]))

Part 1 (above the single line OR) is essentially the same search strategy as outlined underneath "PubMed regular article search strategy", except for removing the final, epidemiological line. This search thus covers regular articles mentioning Parkinson's disease and UTI.

Part 2 (underneath the single line OR) searches for English systematic reviews or meta-analyses in the general population UTI literature on causal factors. Similarly to pneumonia, we decided to look beyond the Parkinson-specific literature with the constraint of only including systematic reviews or meta-analyses.

This search resulted in 186 articles, of which 10 were relevant to our study and therefore included. For one of the articles we could not get access to the full PDF so therefore relied solely on the info in the abstract.

Psychotic symptoms

We divide psychotic symptoms 2 main categories: hallucinations and delirium. When searching for reviews, we identified only 1 relevant article that very broadly covered delusions. Therefore, we added the search results from the regular article search as outlined above. This included 17 relevant articles.

Mood disorders

We identified 21 Parkinson specific articles covering various causal factors for depression and anxiety disorders. Therefore, no further searches were warranted beyond the one described under "Pubmed regular article search strategy".

Dementia

We identified 1 article highly relevant for functional decline. For dementia, we focused on papers identifying causal factors not already known from the systematic review search earlier. We identified 9 relevant papers.

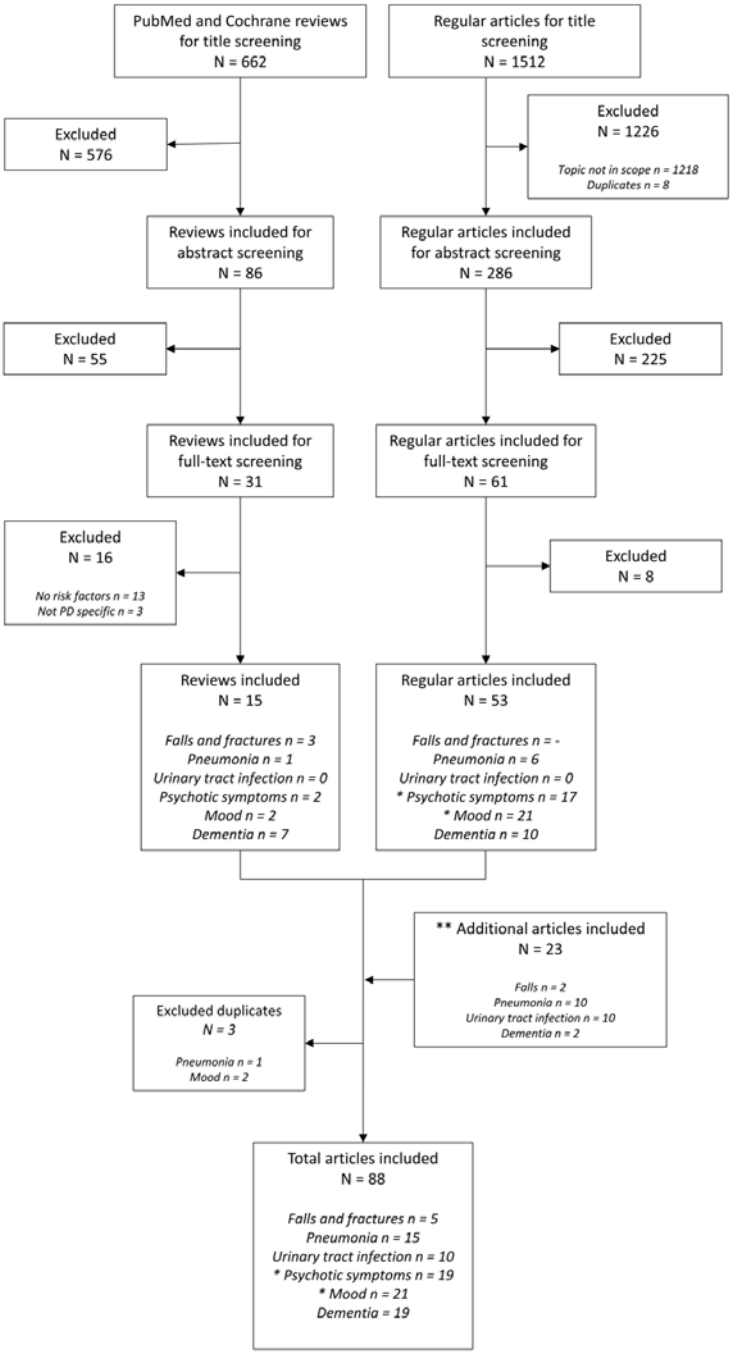
Whilst reading the literature, we encountered 2 articles that were of further interest because they either estimated the population attributable fractions for causal factors for dementia or because they tracked persons with PD over prolonged periods of time and assessed causal factors for cognitive decline.

Conclusion

We included the following number of articles per complication:

	Falls and fractures	Pneumonia	UTI	Psychotic symptoms	Mood	Dementia
PD specific SR + MA	3	0	0	2	2	7
PD regular articles		6	0	17	21	10
SR + MA general population		10				
PD + UTI | SR + MA causal factors general population			10			
Serendipitous finds	2					2
Final selection	5	15*	10	19	21*	19
		* 1 duplicate			* 2 duplicates	

Supplementary file S2. Article flowchart figure



* One article covered risk factors for both psychotic symptoms and mood disorders.
** Additional articles were included, see file S1.

Supplementary file S3 and S4

Due to their size, supplementary files S3 and S4 are only accessible upon request. Please reach out to: secretariaatexpertisecentrumvoorparkinsonenbewegingsstoornissen@radboudumc.nl for more information.

Supplementary file S5. Operationalisation of causal factors for estimating population attributable fractions

	Causal factors	Definition / operationalization
Falls	Hypokinetic rigid gait	Sum of MDS-UPDRS part III bradykinesia (left and right) and rigidity questions is 15 or lower (maximum score is 30). We created a self-report scale (1-10) for people to indicate their symptom severity, with 1 being high and 10 none.
	Freezing of gait	Reported freezing episode in the last month based on the NFOG-Q item 1.
	Balance impairments	Reported mild to moderate but not severe problems in the past week with maintaining balance or walking based on item 12 from the MDS-UPDRS part II. We excluded severe problems with balance as that answer option details that someone aids you while walking, eliminating the fall risk.
	Orthostatic hypotension	Reported at least frequent symptoms of orthostatic hypotension based on the SCOPA-AUT cardiovascular dysfunction subscale. Score needs to be 6 or higher out of the maximum of 9.
	Cognitive impairments	t-MOCA score lower than 18 out of 22.
	Hallucinations	Reported hallucinations in the past year.
	Alcohol abuse	Drinking alcohol for 5 or more days per week.
	Depression	Sum score of BDI is 19 or higher, indicating moderate to severe depression.
	Cardiovascular disease	Reported to have any of the following cardiovascular diseases: angina pectoris, heart failure, heart attack, cardiac arrhythmia, brain infarct/haemorrhage.
	Arthrosis	Reported to have arthrosis.
	Reduced physical activity	Reported to perform no light (30 minutes) or heavy (20 minutes) physical activities on a typical week, thereby leaving only the moderately physically active participants (see moderation explanation of causal pathway).
	Fear of falling	Reported frequent or constant anxiety and worries about falling in the presence of others based on item 9 from the PDQ-39.
	Not available in current dataset:	*Dyskinesias, festination, postural abnormality, impulse control disorder, visual impairments, neuropathy, benzodiazepine use.*

Supplementary file S5. *Continued*

	Causal factors	Definition
Pneumonia	Cardinal motor symptoms	Sum of MDS-UPDRS part III cardinal motor symptom questions including tremor, bradykinesia (left and right), rigidity and freezing is 25 or lower (maximum score is 50). We created a self-report scale (1-10) for people to indicate their symptom severity, with 1 being high and 10 none.
	Cognitive impairments	t-MOCA score lower than 18 out of 22.
	Lung disease	Reported to have any of the following lung diseases: asthma, COPD or pulmonary hypertension
	Cardiovascular disease	Reported to have any of the following cardiovascular diseases: angina pectoris, heart failure, heart attack or cardiac arrhythmia. Included cerebrovascular accidents as that yielded insufficient power when analysed alone.
	Smoking history	Reported to have smoked in the past.
	Dysphagia	Reported frequent to often problems in the past month with swallowing based on the SCOPA-AUT item 1.
	Dystussia	Reported frequent to often problems in the past month with food getting stuck in the throat based on the SCOPA-AUT item 3.
	Immunodeficiency	Defined as people with diabetes because of data availability. Diabetes serves as an example.
	Removed after analysis:	*Poor oral hygiene was such a rare determinant that we could not estimate a reliable risk ratio.*

	Causal factors	Definition
Urinary tract infection	Underactive bladder	Reported regular or frequent difficulties in the past month to clear the bladder of urine based on SCOPA-AUT items 10, 11 and 12, excluding participants with a catheter.
	Overactive bladder	Reported regular or frequent difficulties in the past month to retain urine based on both SCOPA-AUT items 8 and 9, excluding participants with a catheter.
	Impaired mobility	A score of 75 or higher on the PDQ-39 mobility subscale indicating a large impact of mobility on quality of life.
	Diabetes	Reported to have diabetes mellitus.
	Having a catheter	Reported to have a catheter in the SCOPA-AUT questionnaire.
	Cardinal motor symptoms	Sum of MDS-UPDRS part III cardinal motor symptom questions including tremor, bradykinesia (left and right), rigidity and freezing is 25 or lower (maximum score is 50). We created a self-report scale (1-10) for people to indicate their symptom severity, with 1 being high and 10 none.
	Cognitive impairments	t-MOCA score lower than 18 out of 22.
	Not available in current dataset:	*Not drinking enough and urolithiasis.*

Supplementary file S5. *Continued*

	Causal factors	Definition
Psychosis	Disease severity	Hoehn and Yahr score of 3 or higher.
	Dopamine agonists	Person takes one of the following dopamine agonists: pergolide, pramipexol, ropinirol, apomorfine, rotigotine or bromocriptine. Irrespective of dose.
	Cognitive impairments	t-MOCA score lower than 18 out of 22.
	Neuropsychiatric complaints	Reported substance abuse, depression (BDI > 18) or anxiety (STAI trait > 40).
	Not available in current dataset:	*Traumatic life events, delirium, sleep deprivation, vision and hearing impairments, stress.*

	Causal factors	Definition
Depression and anxiety	Dyskinesias, response fluctuations and wearing off	Not readily available so substituted with cardinal motor symptoms in general, see for example pneumonia.
	Impaired mobility	A score of 75 or higher on the PDQ-39 mobility subscale indicating a large impact of mobility on quality of life.
	Balance impairments	Reported mild to moderate but not severe problems in the past week with maintaining balance or walking based on item 12 from the MDS-UPDRS part II. We excluded severe problems with balance as that answer option details that someone aids you while walking, eliminating the fall risk.
	Cognitive impairments	t-MOCA score lower than 18 out of 22.
	Autonomic dysfunction	Reported autonomic dysfunction based on the SCOPA-AUT sum score above 31. We use an adjusted version without the sexual dysfunction questions so the maximum is 63.
	Hallucinations	Reported hallucinations in the past year.
	Coping style	Reported a passive rather than an active coping style. We calculated subscale averages of the 5-factor structure of the Ways of Coping Questionnaire, where taking action, goal orientation and social support were considered active and distancing and avoidance and acceptance were considered passive coping styles. People were considered to have a passive coping style when their passive coping subscale average was higher than the active coping subscale average.
	Not available in current dataset:	*Poor sleep quality / fatigue.*

Supplementary file S5. *Continued*

Definition / operationalization of complications	
Fall	Reported a fall in the past year.
Pneumonia	Reported a pneumonia in the past year.
Urinary tract infection	Reported a urinary tract infection in the past year.
Psychosis	Reported to have had at least 1 hallucination in the past year, e.g. visual, auditory, olfactory.
Depression and anxiety	BDI score above 18 or STAI-trait score above 40.

Supplementary file S6. Analytical approach to estimating the population attributable fractions

Initially, we used Levin's formula to calculate population attributable fractions [1]:

$$PAF_e = \frac{P_e(RR_e - 1)}{1 + P_e(RR_e - 1)}$$

where PAF_e is the population attributable fraction for each exposure, i.e., causal factor, P_e is the prevalence of the causal factor and RR_e the relative risk of the complication because of the causal factor. We calculated the prevalence of each causal factor based on the PRIME-NL data. We decided to use odds ratio's as measure for relative risk due to the rareness of our events. We calculated the odds ratio using logistic regression with the complication as outcome and the causal factor as predictor, correcting all estimates for age, sex and disease duration.

The Levin's population attributable fraction formula typically overestimates population attributable fractions as it assumes independence between causal factors, i.e., the formula estimates each causal factor's population attributable fraction assuming no shared variance between causal factors. In reality, many causal factors are associated with each other (non-independence) and share some variance in explaining the outcome. Therefore, we adjusted the Levin's population attributable fraction formula to take this shared variance into account. In line with other studies [2–4], we performed a principal component analysis on the causal factors per complication. We used the Kaiser-Guttman criterium to determine the number of components, i.e., we retained as many components as there are eigenvalues above 1. From the principal component analysis, we retrieved the communality of each causal factor which is a measure of shared variance with other causal factors. Subsequently, the weight of each causal factor's population attributable fraction was defined as the remaining unique variance:

$$Weight\ (w_e) = 1 - \ communality_e$$

Using this weight, we adjusted both individual (PAF_e) and overall PAF estimates:

$$Adjusted\ PAF_e = w_e * PAF_e$$

$$Adjusted\ PAF = 1 - \prod(1 - w_e * PAF_e)$$

$$Adjusted\ PAF = 1 - [(1 - w_1 * \ PAF_1) * (1 - \ w_2 * PAF_2) \ldots * (1 - w_e * PAF_e)]$$

References

1. Levin, M. L. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* **9**, 531–541 (1953).
2. Mukadam, N., Sommerlad, A., Huntley, J. & Livingston, G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *The Lancet Global Health* **7**, e596–e603 (2019).
3. Nianogo, R. A. *et al.* Risk Factors Associated With Alzheimer Disease and Related Dementias by Sex and Race and Ethnicity in the US. *JAMA Neurol* **79**, 584 (2022).
4. Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K. & Brayne, C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *The Lancet Neurology* **13**, 788–794 (2014).

Supplementary file S7. Causal pathways and population attributable fractions for each complication

In general, we have inserted the missing causal factors into the tables only for falls and urinary tract infections to illustrate the factors missing from the PRIME-NL dataset; for the other complications we have omitted these missing factors for conciseness.

Falls and fractures

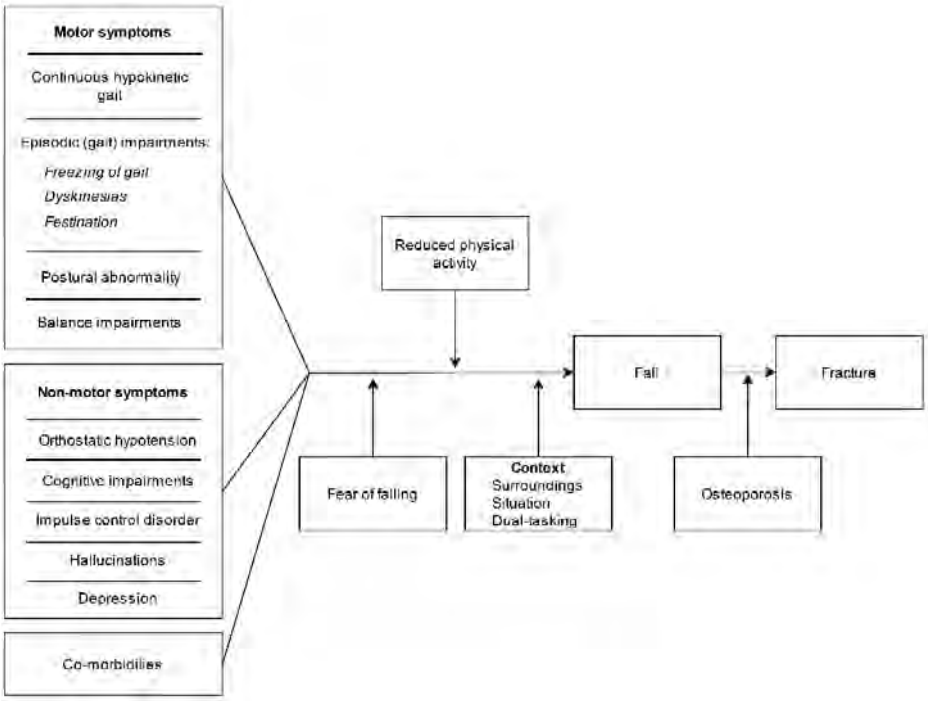


Figure 1. The causal pathway for falls and fractures.

The risk of falling is increased by motor symptoms, non-motor symptoms and co-morbidities. Important motor symptoms include the **hypokinetic gait** of people with PD, such as reduced arm swing, step-length and -height. Episodic (gait) impairments such as **freezing of gait**, **dyskinesias**, and **festination** are commonly related to fall-incidents because of an inability to move or control movements. These episodic gait impairments do not happen to everyone and are context-dependent. **Postural abnormalities** such as pisa syndrome or camptocormia also heighten fall chance because the centre of gravity of the person shifts towards the edges of the base of support, and lower limb dystonia impairs the ability to maintain

balance and hampers stability. Finally, fall risk is increased when people have **balance impairments,** such as smaller, slower or even absent balance correcting steps. Important non-motor symptoms include **orthostatic hypotension** which can cause fainting after standing up. **Cognitive impairments** can cause reduced disease insight, leading to overestimation of one's own physical capabilities. An **impulse control disorder** can lead to a lack of inhibition of movement in risk full situations. **Hallucinations** can increase fall-risk because people can react to their hallucinations, e.g. approaching a visual hallucination without noticing the table that stands in front of them. Finally, **depression** and medications associated with treatment thereof have a complex negative relation with falls, including motor and cognitive pathways such as impaired attention. Important **co-morbidities** include visual impairments, neuropathy, different leg-length, arthrosis, polypharmacy such as many benzodiazepines causing drowsiness, alcohol abuse, cardiovascular problems which reduce stamina to move, or muscle-weakness. These co-morbidities all lead to a greater fall risk. These motor symptoms, non-motor symptoms and co-morbidities have a joint effect on fall risk, for example when someone has both orthostatic hypotension and postural abnormalities where the light-headedness makes it especially difficult to maintain balance given the postural abnormalities.

The effect of these causal factors is modified by three factors. First, **physical activity** is thought to have a reversed U-shape effect on fall-risk. When someone is almost not physically active, their fall-chance increases because their physical capacities are reduced. When someone is very physically active, their fall-chance also increases simply because they more often encounter the possibility to fall. The strength of the U-shape effect of physical activity on fall-risk depends on the severity of motor symptoms, non-motor symptoms and co-morbidities. When symptoms are mild, the negative effects of physical activity on fall-risk are flattened out. When symptoms are more severe, the association becomes stronger. Second, the **fear of falling** follows a similar reversed U-shape effect on fall-risk, depending on whether the fear is proportional to someone's own abilities. When someone has very mild symptoms, the absence of the fear of falling is justified and does not enhance fall-risk. However, if the person's fear of falling is disproportionally large, they might stop becoming physically active or become tensed and stressed while moving, heightening fall-risk. When someone has more severe symptoms, the absence of the fear of falling enhances fall-risk because they overestimate their abilities. A justified fear of falling would protect this person from a fall-incident. Third, **contextual** factors play an important role in enhancing fall-risk, but only do so when motor symptoms, non-motor symptoms or co-morbidities are present. Examples of contextual causal factors include: people's surroundings such as small

doors that elicit freezing of gait or having thick rugs and loose cables in the house; common situations requiring immediate and fast action such as the doorbell ringing or when someone needs to void during the night; or dual-tasking such as carrying something while another person starts talking to you.

Finally, not every fall-incident leads to a fracture. A main modifier of this effect is **osteoporosis**, which is more common in older people.

Table 1. Population attributable fractions for falls and fractures.

Causal factor	Causal factor prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					**37.1%**
Balance impairments	25.2%	3.65 [2.59; 5.17]	50%	40% [28.5; 51.2]	14.8% [8.2; 19.8]
Hypokinetic rigid gait	68%	1.85 [1.35; 2.55]	38%	36.6% [19.1; 51.4]	13.6% [7.5; 18.2]
Freezing of gait	22.8%	2.34 [1.65; 3.33]	50%	23.4% [13; 34.7]	8.7% [4.8; 11.6]
Dyskinesias					NA
Festination					NA
Postural abnormalities					NA
Non-motor symptoms					**15.1%**
Depression	13.8%	2.34 [1.56; 3.54]	29%	15.6% [7.1; 25.9]	5.8% [3.2; 7.7]
Hallucinations	12.8%	2.38 [1.55; 3.69]	50%	15% [6.5; 25.5]	5.6% [3.1; 7.4]
Cognitive impairments	35.9%	1.27 [0.94; 1.71]	41%	8.8% [-2.2; 20.3]	3.3% [1.8; 4.4]
Orthostatic hypotension	0.6%	3.02 [0.39; 61.85]	49%	1.1% [-0.3; 25.7]	0.4% [0.2; 0.6]
Impulse control disorder					NA
Other					**8.0%**
Arthrosis	18.8%	1.67 [1.17; 2.38]	71%	11.1% [3; 20.7]	4.1% [2.3; 5.5]
Alcohol abuse	18.1%	1.4 [0.98; 2.01]	84%	6.8% [-0.4; 15.5]	2.5% [1.4; 3.4]
Heart disease	22.2%	1.17 [0.83; 1.66]	51%	3.7% [-3.9; 12.7]	1.4% [0.8; 1.9]
Osteoporosis					NA
Total					**60.2% [33.4; 80.4]**

CI = Confidence interval; PAF = Population attributable fraction; NA = Not available in the PRIME dataset.

Effect modification for falls and fractures

For both fear of falling and physical activity, we examined effect modification as outlined in the methods. The initially estimated total population attributable fraction remained similar when we examined only the participants with a moderate amount of physical activity (total population attributable fraction = 60.7%, 95% confidence interval = 33.2% - 80.9%); yet the total population attributable fraction decreased when examining only the participants without a fear of falling (total population attributable fraction = 50.6%, 95% confidence interval = 24.0% - 71.2%).

Pneumonia

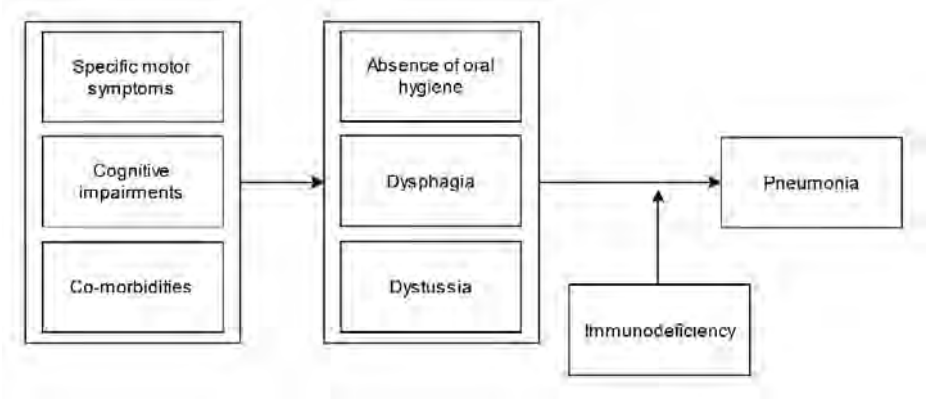


Figure 2. The causal pathway for a pneumonia.An aspiration pneumonia is caused when virulent bacteria enter the lungs and infect the air sacs.

The risk of a pneumonia is increased by several causal factors. First, **specific motor symptoms** such as hypokinesia in the respiratory muscles can cause dysphagia and dystussia which we explain below. **Cognitive impairments** including dementia impair the autonomic control over, e.g., swallowing and coughing, and reduce the ability to concentrate and learn new ways of eating and drinking that prevent aspiration, for example to remember to eat slow and with small bites or use the chin-down posture during swallowing. **Co-morbidities** include a lung disease such as chronic obstructive pulmonary disease or asthma that reduce the capacity of the lungs to sustain the impact of infections. Although people with a chronic lung disease frequently cough, assessing the quality of their cough is important (see dystussia). Similarly, having smoked in the past or currently smoking deteriorates the health of the lungs and their condition to sustain infections. Also, cerebrovascular accidents impair the autonomic control over, e.g., swallowing and coughing. Furthermore, chronic heart failure impairs the stamina and physical condition of a person, reducing their ability to cough with strength.

These causal factors are mediated by several factors that heighten the risk of a pneumonia. When people have problems maintaining **oral hygiene**, it can cause food to remain in the mouth causing bacterial infections that can transfer into the lungs. The risk of insufficient oral hygiene is especially high when people become dependent on others for oral hygiene. **Dysphagia** (difficulties swallowing) and **dystussia** (reduced coughing strength and effectiveness) play a combined role in the occurrence of a pneumonia. When people have difficulties swallowing their food or drinks, the likelihood is increased that some of the food or liquid will enter the respiratory tract and lungs. However, the food will only enter the lungs when people are unable to cough effectively. Dysphagia can, for example, be caused by hypokinesia of the swallowing muscles. Dystussia can, for example, be caused by hypokinesia in the respiratory muscles which are also associated with dyspnea (impaired breathing). Dyspnea can hamper effective coughing due to insufficient air available in the lungs to cough.

Finally, the strength of someone's **immunodeficiency** has a modifying effect on the risk of a pneumonia. When someone's has a poor immunodeficiency, they have more difficulties to fight off any viral or bacterial infections in the lungs. Someone's immunodeficiency is influenced by, for example, their mobility levels, their physical capacities and the presence of co-morbidities such as HIV or diabetes.

Effect modification for pneumonia

We examined effect modification for diabetes as example of an impaired immunodeficiency. The initially calculated total population attributable fraction remained similar when we examined only the participants without diabetes (total population attributable fraction = 36.9%, 95% confidence interval = -31.3 % - 76.3%).

Table 2. Population attributable fractions for pneumonias.

Causal factor	Causal factor prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					**4.2%**
Card. motor symptoms*	23%	1.26 [0.53; 2.78]	38%	5.6% [-12.1; 29.1]	2.3% [-2.8; 5.2]
Dysphagia	6.9%	1.37 [0.32; 4.06]	73%	2.5% [-5; 17.5]	1% [-1.2; 2.3]
Dystussia	4.3%	1.53 [0.24; 5.46]	68%	2.2% [-3.4; 16.2]	0.9% [-1.1; 2.1]
Non-motor symptoms					**13.4%**
Cognitive impairments	35.9%	2.35 [1.1; 5.2]	52%	32.7% [3.5; 60.1]	13.4% [-16; 30.3]
Other					**15.7%**
Lung disease	10.1%	2.7 [1.04; 6.21]	83%	14.7% [0.4; 34.6]	6% [-7.2; 13.6]
Heart disease	22.2%	1.73 [0.78; 3.73]	45%	14% [-5.3; 37.7]	5.7% [-6.9; 13]
Smoking	56.7%	1.19 [0.57; 2.64]	21%	9.9% [-32.6; 48.2]	4% [-4.8; 9.2]
Total					**33.4% [-40; 75.6]**

CI = Confidence interval; PAF = population attributable fraction.* Card. motor symptoms = cardinal motor symptoms, including tremor, bradykinesia, rigidity and freezing, used as proxy for the specific motor symptoms mentioned in the description.

Urinary tract infection

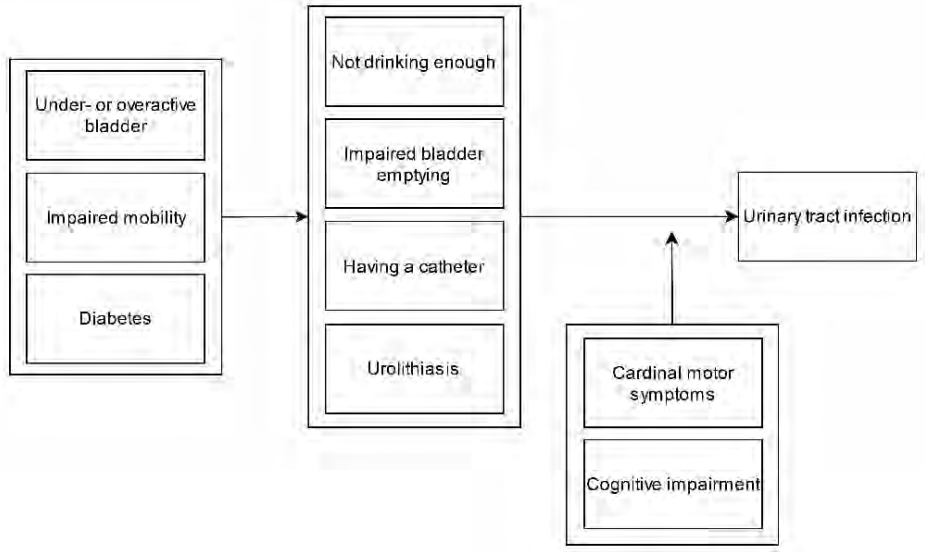


Figure 3. The causal pathway for a urinary tract infection.

A urinary tract infection can only be caused when the concentration of specific virulent bacteria in the urine and urinary tract is high enough. The concentration of bacteria depends on the multiplication speed of the bacteria, the amount of urine produced influencing the concentration and the voiding frequency as this flushes the bacteria out of the urinary tract and thereby resets the multiplication of bacteria. Several causal factors increase the risk of a urinary tract infection. First, an **underactive bladder** can cause impaired bladder emptying, whist an **overactive bladder** can cause wetting of clothes or incontinence material in which bacteria can grow, increasing the chance of infections. Second, **impaired mobility** increases the chance that people cannot reach the toilet on time, especially when someone has incontinence difficulties. Besides the possibility of wetting of clothes, this also increases the chance that people start drinking less. Finally, having **diabetes** changes the composition of the urine and heightens the pH level, making it more likely that bacteria can grow. Diabetes can also make bladder emptying more difficult.

Mediators for the occurrence of a urinary tract infection include **not drinking enough.** If people do not drink enough, less urine is produced raising the concentration of bacteria in the urinary tract. Also, **impaired bladder emptying** is important. If urine is retained in the urinary tract after voiding, some of the (contaminated) urine including the bacteria will not leave the bladder, allowing

the bacteria to multiply inside the urinary tract. Bladder emptying problems can also cause people to start drinking less, creating a downward spiral. Furthermore, **having a catheter** increases the risk of infection when people touch the sterile catheter with their skin or meatus while inserting. The bacteria present on the skin and meatus are then inserted directly into the bladder. Also, an indwelling catheter increases the chance of urolithiasis especially when used for a longer period. Finally, **urolithiasis** can form anywhere in the urinary tract, creating a place for the bacteria to grow. This also works the other way around, as bacteria causing a urinary tract infection can also cause urolithiasis.

We identified two effect modifiers. First, **cardinal motor symptoms** can hamper self-care. PD symptoms such as tremor or dyskinesias can hamper the (re)placement of a catheter, for example making the sterile insertion more difficult. Second, **cognitive impairment** can also hamper self-care, for example by forgetting to drink or not remembering the catheter replacement procedures.

Effect modification for urinary tract infection

For both cardinal motor symptoms and cognitive impairment, we examined effect modification. The initially calculated total population attributable fraction changed slightly when we examined only the participants without severe cardinal motor symptoms (total PAF = 15.1%, 95% confidence interval = -4.0% - 47.8%) as well for the participants without cognitive impairments (total PAF = 16.7%, 95% confidence interval = -6.1% - 57.3%).

Table 3. Population attributable fractions for urinary tract infections.

Causal factor	Causal factor prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					**14.6%**
Overactive bladder	13.2%	2.36 [1.33; 4.11]	56%	15.2% [4.2; 29.1]	6.2% [0.6; 13.8]
Underactive bladder	10.8%	2.32 [1.09; 4.71]	51%	12.5% [0.9; 28.6]	5.1% [0.5; 11.3]
Impaired mobility	6%	2.48 [1.14; 5.16]	58%	8.1% [0.9; 20]	3.3% [0.3; 7.4]
Impaired bladder emptying					NA
Other					**6.7%**
Having a catheter	1.2%	13.83 [3.01; 56.63]	60%	13.3% [2.4; 40]	5.4% [0.5; 12]
Diabetes	5.1%	1.66 [0.53; 4.34]	37%	3.3% [-2.5; 14.6]	1.3% [0.1; 3]
Not drinking enough					NA
Urolithiasis					NA
Total					**21.5% [2.0; 47.4]**

CI = Confidence interval; PAF = Population attributable fraction; NA = Not available in the PRIME dataset.

Psychotic symptoms

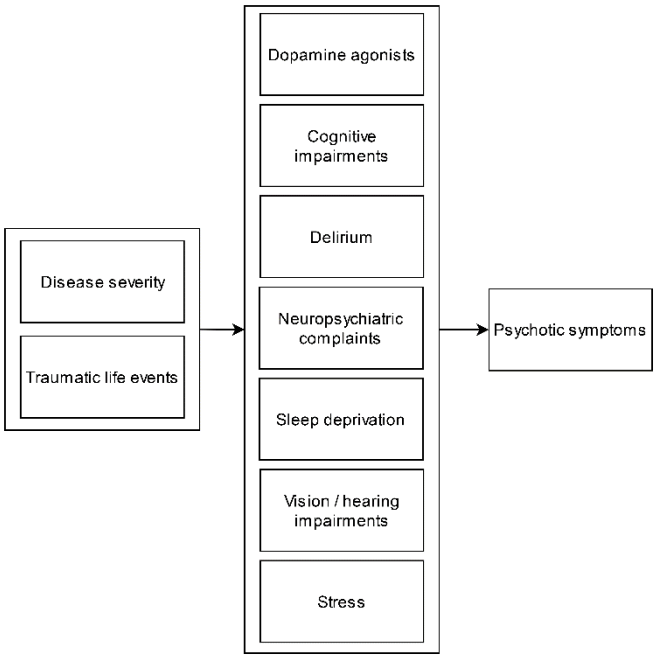


Figure 4. The causal pathway for psychotic symptoms.

Psychotic symptoms can encompass sensory observations or a belief/conviction that does not match with reality. Sensory observations can include visual, auditory or haptic hallucinations. Convictions can include severe confusion or disordered thinking and delusional or paranoid beliefs. Mapping a causal pathway for psychotic symptoms was difficult due to the many connections between causal factors. There seems to be no clearly distinct pathway towards psychotic symptoms, leading us to include both longer **disease severity** and having experienced **traumatic life events** that caused extreme stress as non-modifiable causal factors.

We identified several mediators. **Dopamine agonists** and levodopa are primarily prescribed to treat the motor symptoms of PD. At the time of clinical diagnosis, people with PD still have some nigrostriatal dopamine-producing neurons, which means that they are only partially dependent on extrinsic dopamine (agonist) treatment. As the disease progresses, the remaining nigrostriatal dopamine-producing neurons gradually diminish, which means that people with PD become almost completely dependent on dopamine (agonist) treatment. Thus, a minor

increase or decrease in the dose of dopamine (agonist) treatment can induce considerable fluctuations in motor functioning. As a consequence, it becomes increasingly difficult to prevent an overdose or underdose of dopamine in the brain. As a side effect of overdosing dopamine (agonist) treatment is that the medication can elicit psychotic symptoms. We focused specifically on the dopamine-agonists as they are notorious for causing psychotic symptoms at a considerably higher rate than levodopa. Also, **cognitive impairments** including dementia can result in psychotic symptoms due to the chemical and physical changes in the brain. Furthermore, a **delirium,** a small acute confusion that is reversible, can be caused by, for example, a urinary tract infection or pneumonia. The physical inflammatory reaction causing the delirium can lead to psychotic symptoms such as disorganized thinking and hallucinations. Finally, other causal factors are important such as **neuropsychiatric complaints** including mood disorders and substance abuse; **sleep deprivation** including reduced sleep quality, REM-sleep behaviour disorder and excessive daytime sleepiness; **vision and hearing impairments** hampering the ability to distinguish real and unreal observations and finally **stress**.

Table 4. Population attributable fractions for hallucinations.

Causal factor	Causal factor prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Non-motor symptoms					**33.6%**
Anxiety	36.2%	2.74 [1.81; 4.16]	59%	38.6% [22.7; 53.3]	16.2% [6.7; 24.6]
Cognitive impairments	35.7%	1.74 [1.14; 2.66]	29%	20.9% [4.8; 37.2]	8.8% [3.6; 13.4]
Depression	13.8%	2.85 [1.74; 4.59]	64%	20.4% [9.3; 33.2]	8.6% [3.5; 13]
Other					**9.4%**
Disease severity	18.7%	2.44 [1.52; 3.89]	35%	21.2% [8.8; 35.1]	8.9% [3.7; 13.5]
Substance abuse	0.6%	5.37 [0.68; 34.29]	43%	2.4% [-0.2; 15.9]	1% [0.4; 1.5]
Dopamine agonists	8.8%	0.88 [0.42; 1.7]	48%	-1.1% [-5.4; 5.8]	-0.5% [-0.2; -0.7]
Total					**43.1% [17.8; 65.4]**

CI = Confidence interval; PAF = Population attributable fraction.

Mood disorders: depression and anxiety

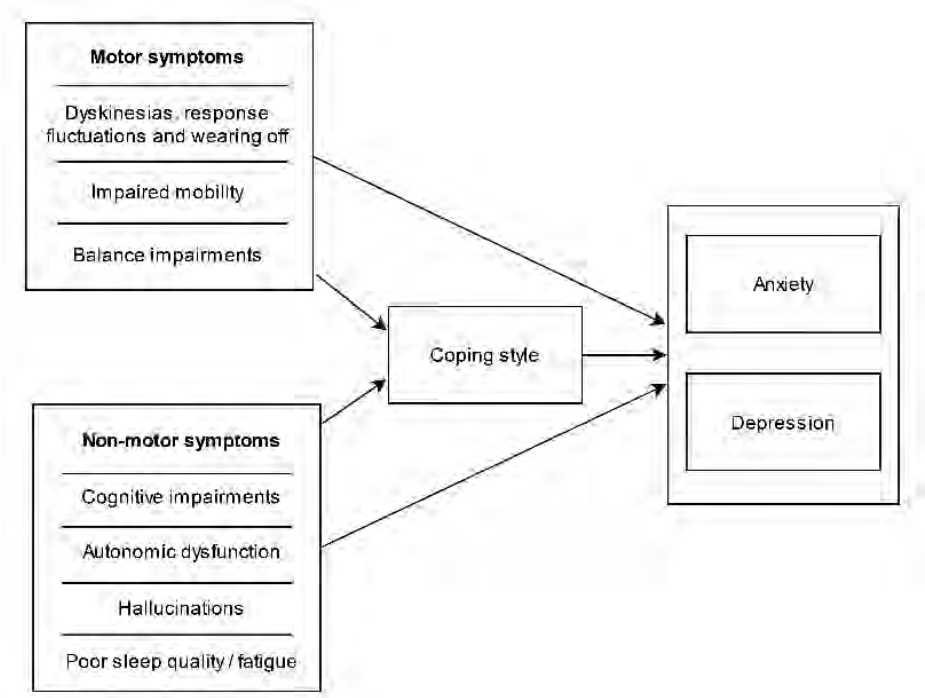


Figure 5. The causal pathway for depression and anxiety.

Anxiety and depression often co-occur and can influence each other. We have drafted one causal pathway for both disorders due to their shared aetiology and relevant causal factors. We identified three important (groups of) causal factors for the development of depression and anxiety. First, **motor symptoms** such as dyskinesias as well as the wearing off of medication or fluctuating motor responses to medication intake can create feelings of anxiety and depression. People can become anxious about the unpredictability of the expression of the disease. Such feelings can be further facilitated by not knowing how the disease will progress in the future. Some motor symptoms are also visible to other people, such as tremor or gait impairments, which can lead to feelings of shame and avoidance of going outside. Also, **mobility** and **balance impairments** might increase the fear of going outside because of the risk of a fall, hampering social connections.

Second, **non-motor symptoms** can also increase the risk of anxiety and depression because they instil feelings of a loss of control, uncertainty about the future and signal the progression of the disease. Typical non-motor symptoms that can lead to

anxiety and depression include cognitive impairments, autonomic dysfunction and hallucinations. Furthermore, having a poor sleep quality could increase fatigue and hamper concentration, which in turn could lead to inactivity and a risk of worrying which enhances the risk of anxiety and depression.

Finally, how a person deals with the occurrence of these symptoms is important in mediating the development of anxiety or depression. A person's **coping style** describes how people deal with and adapt to issues in their life. Coping styles can be broadly categorized in active and passive styles. An active coping style is characterized by dealing with an issue, for example by taking goal-directed action and seeking social support. Passive coping styles involve avoidance and denial of the problem and an attempt to detach oneself from the issue. An active coping style rather than a passive coping style is associated with lower chances of developing anxiety or depression. Personality traits like neuroticism, i.e., emotional instability, and low self-efficacy, i.e., the absence of belief in one's own abilities, can stimulate passive coping strategies.

Table 5. Population attributable fractions for depressive symptoms.

Causal factor	Causal factor prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					**30.7%**
Spec. motor symptoms	22.8%	3.11 [2.03; 4.73]	53%	32.5% [19.1; 46]	13.1% [7.4; 16.9]
Balance impairments	25.3%	2.64 [1.71; 4.08]	45%	29.4% [15.3; 43.8]	11.8% [6.7; 15.4]
Impaired mobility	5.7%	3.97 [2.06; 7.53]	42%	14.4% [5.7; 27]	5.8% [3.3; 7.5]
Non-motor symptoms					**20.2%**
Cognitive impairments	35.5%	1.9 [1.27; 2.86]	49%	24.3% [8.7; 39.8]	9.8% [5.5; 12.7]
Hallucinations	12.8%	2.9 [1.77; 4.68]	46%	19.6% [9; 32.1]	7.9% [4.5; 10.2]
Autonomic dysfunction	2.8%	3.37 [1.36; 7.9]	32%	6.2% [1; 16.1]	2.5% [1.4; 3.2]
Other					**11%**
Passive coping style	29.2%	2.29 [1.54; 3.41]	20%	27.4% [13.6; 41.3]	11% [6.2; 14.3]
Total					**61.9% [35.1; 80.3]**

CI = Confidence interval; PAF = Population attributable fraction.* Spec. motor symptoms = specific motor symptoms mentioned in the description.

Table 6. Population attributable fractions for symptoms of anxiety.

Causal factor	Causal factor prevalence %	Odds ratio for complication [95% CI]	Communality	PAF [95% CI]	Adjusted PAF [95% CI]
Motor symptoms					
Spec. motor symptoms	22.8%	2.63 [1.88; 3.69]	53%	27.1% [16.7; 38]	11.6% [5.5; 16.9]
Balance impairments	25.3%	1.83 [1.31; 2.56]	45%	17.4% [7.3; 28.3]	7.5% [3.5; 10.8]
Impaired mobility	5.7%	3.4 [1.84; 6.55]	42%	12% [4.5; 23.9]	5.2% [2.4; 7.5]
Non-motor symptoms					
Cognitive impairments	35.5%	1.72 [1.28; 2.32]	49%	20.3% [9; 31.8]	8.8% [4.1; 12.7]
Hallucinations	12.8%	2.71 [1.79; 4.14]	46%	18% [9.2; 28.7]	7.8% [3.7; 11.2]
Autonomic dysfunction	2.8%	2.61 [1.13; 6.32]	32%	4.3% [0.4; 12.9]	1.8% [0.9; 2.7]
Other					
Passive coping style	29.2%	1.35 [0.99; 1.82]	20%	9.1% [-0.2; 19.3]	3.9% [1.9; 5.7]
Total					**46.6% [22; 67.4]**

CI = Confidence interval; PAF = Population attributable fraction.* Spec. motor symptoms = specific motor symptoms mentioned in the description.

Chapter 6. Assessing the validity of a Parkinson's care evaluation: the PRIME-NL study

Supplementary file S1. Information on the extraction and processing of data on the general population from the Central Bureau of Statistics (CBS)

We extracted data on a provincial level, coding the province Noord-Brabant, Gelderland and Limburg as the PRIME region and the other nine provinces as the UC. We gathered the data from the StatLine database of the CBS, weighing all outcomes based on the number of inhabitants of each province where necessary. Where possible, we collected data of people >60 years to best resemble our PD population as well as data as close to the year 2020 which was the PRIME-NL baseline year.

We gathered the **number of people** in the UC and PRIME region from the official registry of citizens of the Netherlands. These data were used when the CBS database only provided percentages. When we had access to more precise estimates of the total group size, we used those, e.g. migratory background. We selected the average amount of people across the year, classified by age depending on which age group and database year was most appropriate:

https://opendata.cbs.nl/#/CBS/nl/dataset/03759ned/table?dl=39E0B

For **migratory background** we used the variable 'herkomstland', with the country of origin defined as outside the Netherlands when the person or someone's parents are not born in the Netherlands. Closest data was only available of the year 2022. We used the number of people provided by this specific table: PRIME n = 1,547,290; UC n = 2,649,563

https://opendata.cbs.nl/statline/#/CBS/nl/dataset/85458NED/table?ts=1689069161114

For **BMI**, we used overweight (BMI >= 25) as a replacement because BMI was not available. We used the data of people >65 years because >60 was unavailable; data is from the 2022 Gezondheidsmonitor. This dataset also includes current **smoking** behaviour and people who consume more **alcohol** than regular (>21 drinks for men and >14 drinks for women). Here, we used the number of people calculated in the first step: PRIME n = 1,174,546; UC n = 2,016,678

https://opendata.cbs.nl/statline/#/CBS/nl/dataset/85563NED/table?ts=1687260675027

For **COVID-19**, we used the registry of hospitalizations from 2020, specifically for age >65. We used the number of people calculated in the first step: PRIME n = 1,262,229; UC n = 2,268,434

https://opendata.cbs.nl/statline/#/CBS/nl/dataset/84523NED/table?ts=1687265201092

For **education**, no provincial data was accessible for people >60. We had to resort to data from 2018 of people >18 years. Therefore, we used the number of people calculated in the first step: PRIME n = 4,620,529 ; UC n = 9,135,511

https://www.cbs.nl/nl-nl/maatwerk/2019/19/percentage-mensen-in-opleidingsniveau-en-leeftijdgroep

For **living situation**, we classified people either as living alone or with someone, i.e. partner or children. We used the 2020 data for all people >60. Since this concerned household data, we used the n provided by this specific topic's table: PRIME n = 1,029,544; UC n = 1,923,901

https://opendata.cbs.nl/#/CBS/nl/dataset/71486ned/table?ts=1689166648244

Supplementary table S1. Overview on operationalization of the variables.

Measurement tool	Variable	Explanation
	Region	**PRIME or Usual Care region**
	Sex	Man, woman, other
	Age	In years
	Diagnosis	Diagnoses were verified via a letter from the general practitioner or neurologist.
	Disease duration	In questionnaire: Participants entered age of diagnosis. In healthcare claims data: the number of years from first DBC 501 code.
	Migratory background	Participants could indicate which ethnic group they considered themselves to belong to. Options: Dutch, Turkish, Moroccan, Surinamese, Antillean / Aruban, other.
	Recruitment procedure	Options: via my neurologist, via ParkinsonNEXT, via the Parkinson Association, via family/friends, via the person with parkinsonism I am taking care of, via other carers, via social media, via ParkinsonNet, other.
	Education (diploma obtained)	Options[a]: no education, primary school, VMBO, HAVO, VWO, MBO, HBO, University, PhD, other.
General PRIME questionnaire	Living situation	Options: alone, with partner, with partner and children, in an institution, assisted living[c], sheltered living[d], living with another family member than partner.
	Work situation	Options: fulltime, parttime, self-employed, education following not paid by employer, retired, unemployed, incapacitated, active in household caring for children or other people, unemployed and receiving sickness benefit, voluntary work.
	Smoking	Contains two questions: currently smoking? (Yes/no) Smoked in the past? (Yes/no).
	Alcohol consumption	Options: never, very rarely on special occasions, occasionally, on less than 5 days a week, on 5 or more days a week.
	BMI	Body Mass Index calculated from length and weight from questionnaire.
	Comorbidities: 5 unique variables	Cardiovascular disease, pulmonary disease, musculoskeletal disorder, endocrine or metabolic disorder, neuropsychiatric disorder, cancer, none of the above.
	Complications: 4 unique variables	Urinary tract infection, pneumonia, falling, neuropsychiatric disorders (hallucinations) in the past year: recoded to not reported, reported, reported and led to hospital admission.

	Data processing
	Created two groups: people with Parkinson's disease or with atypical parkinsonism
	Recoded to 1 = Dutch, 2 = other. If a combination of Dutch and another ethnicity was reported, then this was scored as 'other'.
	Recoded to two options: via my neurologist and not via my neurologist. Few people chose 'other' and gave an explanation as 'a letter from the hospital'; this was recoded to via my neurologist.
	Three groups[b]: 1= primary educated (no education, primary school, VMBO) 2= secondary educated (HAVO, VWO, MBO), 3= tertiary educated (HBO, University, PhD) Participants explained 'other' in the questionnaire, and this was recoded to one of the education levels.
	Recoded to 0 = never, 1 = in the past, 2 = current smoker.
	BMI = weight in kg / (length in centimetres/100)^2 .
	0= I don't have a disease in this category, 1= I do have a disease in this category.
	Recoded to 0= not had, 1= had, 2= had and led to hospital admission.

Measurement tool	Variable	Explanation
Parkinson's Disease Questionnaire-39 (PDQ-39)	Quality of Life	Contains questions in eight domains: mobility, general daily living tasks, emotional, stigma, support, cognition, communication, discomfort.
Beck Depression Inventory II (BDI)	Depression	The score of the BDI reflects the intensity of depression. Scores from 0 through 9 indicate no or minimal depression, scores from 10 through 18 indicate mild to moderate depression, scores from 19 through 29 indicate moderate to severe depression, scores from 30 through 63 indicate severe depression.
State Trait Anxiety Inventory for Adults (STAI)	Anxiety	There are 2 subscales within this measure. The State Anxiety Scale evaluates the current state of anxiety, the Trait Anxiety Scale evaluates relatively stable aspects of "anxiety proneness," including general states of calmness, confidence, and security. For this research, only the Trait Anxiety Scale was included as we are interested in the anxiety in general, not during the specific moment of filling in the questionnaire.
Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS): Part II	Motor symptoms	Only part II of the complete questionnaire is used. These questions address the extent to which a person is limited in daily activities as a result of motor symptoms.
Telephone Montreal Cognitive Assessment (t-MoCA)	Cognitive performance	Several cognitive tasks are performed through a telephone interview. The item concerning location (place and city) could not be verified via telephone and was therefore not asked. Every participant got +2 on their score for this missing question. Furthermore, the day of the week was not asked for by some of the participants. These participants got +1 on their score to correct for this missing question.
Hoehn & Yahr	Stage of disease	The Hoehn and Yahr scale is a system to describe in what stage of Parkinson's disease a person is. Scores can range from 1 to 5 (disease stage 1 to 5) in which a higher stage indicates more severe disease.
COVID-19 questionnaire	COVID-19 burden	This questionnaire contains 8 questions about the personal social impact of COVID-19, as well as the impact participants have experienced on access to healthcare. Every question could be answered with a scale from 0 (not experienced) to 5 (often experienced).

[a] VMBO, HAVO and VWO are types of education during high school, where VMBO is re-vocational secondary education, HAVO is senior general secondary education and VWO is pre-university education. MBO is secondary vocational education training, HBO is higher professional education.

[b] Recoded based on how CBS (Central Bureau of Statistics) classifies education in the Netherlands.

[c] Independently living and receiving outpatient support from a housing or welfare organisation.

[d] Living in a house belonging to a housing or welfare organisation.

	Data processing
	The total scores of all domains were summed up and averaged. Scores can range from 0 to 100, in which zero is the best and 100 the worst quality of life. The values were recoded into a reversed scale.
	Questions can be answered with ratings from 0 to 3 and are summed, with a total maximum score of 63, in which higher scores indicate greater depressive severity. We used the total score for analysis.
	Scores can range from a minimum of 20 to a maximum of 80 in a linear scale, in which a higher score indicates a greater degree of anxiety. We used the total score of trait anxiety for analysis.
	Scores can range from 0 to 52, in which a higher score indicates a greater degree of motor symptoms. We used the total score for analysis.
	Scores can range from 0 to 22, in which a higher score indicates better cognitive performance. We used the total score for analysis.
	We calculated H&Y based on answers from other questionnaires notably the UPDRS, e.g., for the presence of bilateral impairments or mobility aids. 1= Unilateral involvement only, 2= Bilateral involvement without impairment of balance, 3= Mild to moderate bilateral disease; some postural instability; physically independent, 4= Severe disability; still able to walk or stand unassisted, 5= Wheelchair bound or bedridden unless aided.
	The mean sum of scores is used (sum / number of questions answered), ranging from 0 to 5, in which a higher score indicates a higher COVID-19 burden.

Supplementary table S2. Mode of data collection.

Mode of data collection	PRIME (n = 414)	Usual care (n = 570)
Online: n (%)	222 (54)	447 (78)
Paper: n (%)	187 (45)	119 (21)
Telephone: n (%)	5 (1.2)	4 (0.7)

Supplementary table S3. Reasons for dropping out of the study.

Reason: n (%)	PRIME (n = 33)	Usual care (n = 20)	Total (n = 53)
Personal choice	27 (82)	14 (70)	41 (77)
– Disease progression	14 (42)	7 (35)	21 (40)
– Too intensive	5 (15)	1 (5)	6 (11)
– Too confrontational	2 (6)	3 (15)	5 (9)
– Questions do not match disease	1 (3)	1 (5)	2 (4)
– Other / unknown	5 (15)	2 (10)	7 (13)
Other diagnosis	1 (3)	0 (0)	1 (2)
Lives abroad	0 (0)	2 (10)	2 (4)
Participant can no longer be reached	5 (15)	4 (20)	9 (17)