Leveraging big data to improve care for people with Parkinson's disease

Amir H. Talebi

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This thesis made possible by the Proactive and Integrated Management and Empowerment in Prakinson's disease (PRIME) project. PRIME Parkinson project was funded by the Gatsby Foundation (GAT3676) as well as by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences and Health to stimulate public-private partnerships.

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Radboud Dissertations Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben
Cover: Proefschrift AIO | Guntra Laivacuma
Printing: DPN Rikken/Pumbo

ISBN: 9789465150291
DOI: 10.54195/9789465150291
Free download at: https://doi.org/10.54195/9789465150291

RADBOUD
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Leveraging big data to improve care for people with Parkinson's disease

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

maandag 26 mei 2025
om 14.30 uur precies

door

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geboren op 14 juni 1992
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Dissertation to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. J.M. Sanders,
according to the decision of the Doctorate Board
to be defended in public on

Monday, May 26, 2025
at 2.30 pm

by

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Chapter 1

Introduction

Parkinson's disease (PD) is one of the fastest growing neurodegenerative disorders around the globe (box 1). Factors such as greater disease awareness, aging and increased life expectancy, and more industrialization-related environmental exposures led to a doubling in the number of people with PD worldwide between the years 1990 to 2016 (1). Experts initially anticipated another doubling in PD prevalence from 6.1 million in 2016 to over 12 million individuals by 2040 (2), but the latest findings suggest that the number of affected individuals has now risen to 11.8 million in 2021 (3). Due to an increased PD life expectancy after the introduction of levodopa and distinguishing PD from other atypical parkinsonism forms (4, 5), more individuals will develop more advanced forms of the disease. Because of an extensive list of motor and non-motor symptoms, which is due to the involvement of extensive damage to the central nervous system as well as multiple other body systems, PD diminishes the person's capabilities of performing activities of daily living. Consequently, the disease burden increases among individuals with PD and their caregivers, which ultimately affects their quality of life (6).

Currently, healthcare providers are not optimally equipped to make decisions about the use of allied health and drug treatments for people with PD due to two important limitations in the current state of knowledge. First, when making decisions, healthcare providers primarily have scientific evidence from small, selective populations with limited follow-up duration at their disposal. However, these populations provide only a fragmented picture of a complex and long-lasting disease such as PD. Indeed, many patients from everyday clinical practice are excluded from clinical trials due to strict inclusion and exclusion criteria. Second, scientific findings made in groups are difficult to apply to the specific individual context of a patient. This is because PD is a highly heterogenous disease, meaning that symptoms in people with PD vary considerably from person to person. Even within an individual, symptoms typically vary from day to day, and within any given day. Therefore, treatment goals also vary among individuals and this highlights the need to develop a personalized care approach in PD. Such personalized care could be delivered through the development of a system that supports the decisions of the clinician involved in the care of person with PD. One of the challenges regarding the development of such a much needed decision support system is the lack of evidence, whether quantitative or qualitative, with regard to the current treatment modalities and medications. For instance, there is a lack of quantitative evidence on the timing of the initiation of pharmacological treatments such as levodopa; similarly, evidence is missing with regards to the effectiveness of non-pharmacological treatments (e.g., physiotherapy, occupational therapy, and speech & language therapy). Such evidence is required as input before such a decision support system can be developed. Importantly, support

systems should have a multidisciplinary focus, because management of a complex disease such as PD requires the involvement of multiple professional disciplines. And even more crucially, any decision support should also consider the patient as the center of this multidisciplinary approach.

Box 1: Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterized by various motor and non-motor manifestations (7). The current criteria for clinical diagnosis of PD include the presence of bradykinesia accompanying either rest tremor, rigidity, or both (8). PD presents its features in various forms, but more common motor and non-motor symptoms are as follows (9): motor symptoms include bradykinesia, rigidity, rest tremor, and postural instability; non-motor symptoms include hyposmia, sleep disorders, autonomic dysfunction, psychological disorders, cognitive impairments, fatigue, speech and swallowing deficits. The wide variety of these symptoms leads to the development of different complications such as depression, anxiety, constipation, urinary tract infections, sexual dysfunction, falls, and aspiration pneumonia. Among these PD-related complications, the most common reasons for hospitalization are falls, aspiration pneumonia, urinary tract infections, reduced mobility, and psychological disorders, with pneumonia as the most frequent cause of death in advanced stages of PD (10). PD progression rates vary relative to factors such as age at diagnosis, dominancy of specific symptoms at presentation, and response to medications (9, 11).

Treatment guidelines are currently mainly focused on the more prominently observed PD-related symptoms and complications. However, commonly observed PD symptoms are only the tip of the iceberg (12) and the management of such a multifaceted disease requires the involvement of multiple professional disciplines. PD management includes non-pharmacological interventions, pharmacological interventions (including pump therapies) and neurosurgical interventions (deep brain surgery) for well-selected individuals. Some well-known non-pharmacological interventions are physiotherapy, speech & language therapy, occupational therapy, psychological therapy, and social work. These allied health therapies can address important motor and non-motor symptoms that are only marginally addressed by other treatments. For instance, there is evidence regarding the beneficial effects of physiotherapy on the reduction of falls and pneumonia in PD (13). However, throughout the existing literature and guidelines, there is still insufficient evidence to support the contribution of

other allied disciplines in PD management (14, 15). PD is mainly characterized by a degeneration of dopamine-producing neurons in the substantia nigra, which leads to a deficiency of dopamine in the brain. Therefore, dopamine replacement therapies are considered the primary pharmacological treatment for managing the motor symptoms of PD. Among all dopamine replacing agents, levodopa, also known as L-dopa, is the most widely used medication in many countries. Motor complications such as motor fluctuations and dyskinesias start to occur in most persons with PD several years after initiation of the pharmacological treatment with dopaminergic medication (16). Although evidence suggests that the development of motor complications might not be attributed directly to the pharmacotherapy itself, but rather to progression of the underlying disease pathology (17), there is still an ongoing debate among clinicians and patients on when to initiate levodopa treatment (18-21).

A promising novel avenue to overcome these limitations is to leverage *big data*. Big data means high volumes of data that are highly variable and have a high rate of production (velocity). One example of big data in the healthcare arena is electronic healthcare records (including medical claims data). In medical claims databases, each transaction in the healthcare system continuously produces more data in a short amount of time. In order to transform big data information into value, we can use methods beyond the usual statistical methods, such as machine learning, deep learning, network analysis, etc. (22, 23).

Leveraging claims data in healthcare research has the potential to revolutionize the field by providing valuable clinical insights on a population level, improving person-related outcomes, and enhancing the efficiency of healthcare systems. The benefits of leveraging claims data are already being seen for many chronic diseases, like cancer (24). Also, for Alzheimer's disease, several studies could predict (25, 26) or ascertain (27) Alzheimer's onset, estimate the prevalence of specific symptoms in Alzheimer's (28), or evaluate the association of COVID-19 and dementia (29), by leveraging claims data.

The benefits of leveraging claims data can also be applied to PD research. To date, several scientific research studies from all around the world have used claims data in the PD field. As an illustration, one study aimed to predict PD (30), while others examined the risk of fractures and their impact on people with PD (31-34). Furthermore, using claims data from health insurance companies, a higher mortality among people with parkinsonism was seen in Canada compared to healthy controls (35).

Analyzing claims data presents a potential solution to the limitations of traditional clinical trials, offering the advantage of including large and diverse patient populations that have been observed over extended periods, without attrition that typically plagues clinical trials. Although traditional clinical trials remain the main approach for drawing causal interpretations in PD research, analyses of claims data offer a useful complementary approach, that comes with numerous advantages. This includes the better reflection of real-world clinical practice and the option to link the data with clinical outcome registries, allowing for evaluations of the comparative cost-effectiveness of multiple interventions. Finally, analyzing an existing dataset comes with significantly lower cost than clinical trials (36). Below, I will illustrate how claims data can be used for PD care in two distinct ways.

Non-pharmacological treatment of PD

I already emphasized that PD management requires a multidisciplinary team approach, including involvement of multiple different allied health disciplines (examples include physical, occupational, and speech & language therapy, but many others can also be involved). These allied health therapies can alleviate motor and non-motor manifestations that can only partially be addressed by pharmacological or surgical approaches (37). Despite all the advancements brought forth by previous studies in the field of allied health therapies, there are still key gaps in knowledge regarding this relatively young topic (15). These include the long-term effectiveness and impact of allied health disciplines on disease progression, a lack of studies that compared the effectiveness of different allied health disciplines, and insufficient evidence on the effectiveness of integrated care approaches (i.e. whether the combination of different allied health disciplines in PD leads to greater health benefits than the sum of the isolated therapies). These key knowledge gaps are important reasons for taking a deeper look into the effectiveness of allied health therapies in different subgroups with different characteristics.

The highly heterogenous nature of PD, as well as the complexity of various targeted dimensions of allied health therapies, make it challenging to address these gaps using traditional clinical trials.

In **chapter 2**, I review the current state of knowledge on what constitutes specialized allied health care for PD and which domains are targeted. I also describe the effects of the three most commonly deployed allied health care disciplines in PD (physiotherapy, occupational therapy, and speech & language therapy) on clinical outcomes and costs of PD care. I also identify important research topics for future studies.

In **chapter 3**, I use national administrative healthcare claims data in the Netherlands, owned by Vektis, which contains the diagnostic and treatment information of more than 99% of the Dutch population collected from all national insurance companies (38). The Vektis claims database also includes the demographic and clinical characteristics of people with PD. I specifically use these data to go in-depth into non-pharmacological treatment to longitudinally assess how the level of expertise (specialized vs. generic) of physiotherapy, occupational therapy, and speech & language therapy, is associated with the incidence rate of PD-related complications. I also investigate whether there is a synergistic effect among multiple specialized disciplines and whether each allied health discipline prevents specific complications.

Pharmacological treatment of PD

The best time of levodopa initiation for the management of motor symptoms is still an unresolved question in PD pharmacological management even though previous evidence rejects the levodopa withholding approach (39). Delaying the initiation of levodopa until later stages of the disease is still considered an option by some clinicians and patients. For persons with PD with relatively mild symptoms that do not affect daily functioning, the initiation of levodopa might be postponed. On the other hand, some people with PD might postpone levodopa treatment because they fear possible side effects, and in particular the development of response fluctuations.

Determining the most appropriate starting time based on disease proxies, age, and other patient-specific factors would optimize treatment outcomes. There are also some debates as to whether levodopa might have disease modifying effects.

I dedicate **chapter 4** to address this debate in newly diagnosed people with PD. I approach this discussion by leveraging healthcare claims data (Vektis database) to evaluate the long-term effects of levodopa. To address the challenges of using claims data, I use advanced analytical and statistical methods to draw a reasonable causal conclusion. I specifically examine whether early levodopa initiation postpones mortality as primary objective. One of the challenges for deducting causal interpretation using claims data is the problem with randomization and the problem of the possible effect of current prescription of a treatment on the next prescription (namely time-varying confounding). Therefore, to overcome this particular challenge I use the inverse probability weighting method (40). Another drawback of using claims data is the lack of direct information on disease-specific patient characteristics, which makes the process of defining factors related to the disease

stage and the progression of the disease impossible. To overcome this drawback, I use the incidence of PD-related complications or receiving advanced treatment as secondary objectives to examine the effect of early levodopa on disease progression.

The decision-making process of clinicians in PD management while having access to insufficient and lower quality of evidence could really be challenging. The insight provided from my thesis will equip clinicians and patients with useful tools for making more optimized decisions in PD care. This decision-making optimization from using the evidence from these chapters and from relying on a big data approach can provide directions for clinical practice on both non-pharmacological and pharmacological interventions for people with PD.

The overall objective of my thesis is to explore whether the care for people with PD could be improved by scrutinizing healthcare claims using a big data approach. Specifically, I will investigate non-pharmacological and pharmacological interventions for PD. As for the former, I will evaluate whether specialized allied health therapies may contribute to the prevention of PD-related complications. To this end, I will propose a definition and criteria of specialized allied health therapies for PD. As for the latter, I will investigate whether early levodopa initiation can delay mortality, the use of device-aided therapies and reduce PD-related complications.

Chapter 2

Specialized Allied Health Care for Parkinson's Disease: State of the Art and Future Directions

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Abstract

People with Parkinson's disease (PD) experience a range of progressive motor and non-motor symptoms, that negatively affect their daily functioning, social participation and quality of life. Pharmacological and neurosurgical treatments are effective at alleviating some motor symptoms of PD, but have limited effect on other symptoms such as balance, cognitive and swallowing deficits. Over the past two decades, specialized allied health therapies have emerged as a complementary treatment approach to alleviate these symptoms. In this article, we review the current state of knowledge on what constitutes specialized allied health care for PD and which domains are targeted. We also describe the effects on clinical outcomes and costs of PD care. We focus on the three most common allied health care disciplines in PD (physical therapy, occupational therapy and speech-language therapy), and on an integrative approach through interdisciplinary allied health interventions. We also highlight important remaining knowledge gaps that are likely to be the focus of future studies.

Keywords: Parkinson Disease, Allied Health Personnel, Rehabilitation, Patient Care Team, Physical Therapy Specialty, Speech Therapy, Occupational Therapy, Health-related Quality of Life, Activities of Daily Living

Introduction

People with Parkinson's Disease (PD) experience progressive motor and non-motor symptoms, that negatively impact on their daily activities, social participation and quality of life (41, 42). There is considerable inter-individual variation in the motor and non-motor symptoms experienced by people with PD, and the individual presentation of symptoms also varies considerably, even on a day-to-day basis. In addition, the impact of these symptoms on daily life varies from person to person, depending on the personal context and values of the person with PD (8). This calls for personalized and multi- or interdisciplinary interventions, that are organized and delivered to meet the specific needs of people with PD.

Within multidisciplinary care, pharmacological and neurosurgical treatments are well established and effective in alleviating symptoms such as bradykinesia, rigidity and tremor (8). However, these interventions have limited effect on other symptoms, such as impaired balance, cognition and swallowing. These symptoms negatively impact daily life functioning and can put patients at increased risk for potentially serious complications, such as hip fractures or aspiration pneumonia (37, 43). Over the past two decades, allied health care interventions have emerged as a promising complementary treatment approach in the multidisciplinary care of people with PD to alleviate the impact of PD on daily functioning and to prevent medical complications. The three allied health disciplines that are traditionally best known and most involved in the care of people with PD are physical therapy, speech and language therapy and occupational therapy. More recently, the role of other allied health disciplines such as social workers and dieticians is emerging (44).

Because of the complexity of PD, there is a growing awareness that personalized and interdisciplinary interventions require specific knowledge and expertise. In this article, we describe what constitutes specialized allied health care for PD and we describe the evidence for its effectiveness in terms of both clinical outcomes and health care costs. We also focus globally on accessibility and the remaining knowledge gaps that are likely to be the focus of future studies.

What constitutes 'specialized' allied health care

As far as we are aware, there is no consensus statement on specific criteria for distinguishing between "specialized" and "generic" allied health care in PD. In interdisciplinary care in other areas (e.g. motor neuron disease (45)), specialized care generally refers to high-quality integrated care that is designed and tailored for a specific disease or patient population and delivered by professionals with a special

interest and competence in that area. In PD, this would mean that specialized allied health care is tailored to the specific care needs of people with PD and is provided by allied health professionals with specific expertise in PD.

There are different ways to operationalize specialized care, and different initiatives have been explored around the world. While a comprehensive overview of these initiatives is beyond the scope of this review, we highlight a few examples. PD-specific training courses and resources for allied health professionals are provided by specialist health professional organizations such as the International Parkinson and Movement Disorder Society, or by Parkinson's disease associations, such as Parkinson's UK. Specialized treatment approaches are offered through courses that include certification, such as SPEAK OUT (46), LSVT LOUD® (47) for speech and language therapists and LSVT BIG® (48) for physical and occupational therapists. A step further is the provision of PD-specific training and certification as part of an infrastructure for specialized multidisciplinary network care, such as the ParkinsonNet model (49). This model was initiated in the Netherlands and has since been adopted in other countries as well (50-52). Within ParkinsonNet, an initial criterion for expertise is the completion of a dedicated training program to understand the causes, presentation and impact of PD symptoms, as well as the specific intervention options per problem or need, according to the latest scientific evidence. Certified therapists can be found through a public Parkinson Care Finder. To maintain the 'specialized' predicate, it is required that professionals sustain a substantial caseload of people with PD, regularly engage in courses and attend multidisciplinary meetings. The rationale is that professionals who fulfil these criteria develop expert skills. They are also more likely to integrate guidelines for PD management in their clinical practice, and are well aware what other disciplines contribute to care, thereby facilitating tailored and integrated service delivery.

Trials that evaluate allied health interventions often provide a rationale for why the intervention is tailored to the needs of people with PD, but only few clearly state the level of expertise of the professionals delivering the intervention.

Domains and interventions of specialized allied health care

While a comprehensive description of specialized care across all allied health disciplines involved in PD is beyond the scope of this paper, we summarize key components of specialized care in the three most studied disciplines: physical therapy, occupational therapy, and speech-language therapy.

Physical therapy

People with PD experience many movement-related challenges that have a huge impact on activities of daily living, thus affecting participation and quality of life. Physical therapy aims to improve movement-related limitations in functions, activities and participation. Core areas of physical therapy include physical capacity, transfers, manual activities, balance, gait and posture. These functions are essential for performing activities and to participating in daily life (i.e. for self-care, shopping, performing hobbies etc). Physical therapy also plays an important role in preventing falls. Falls are very common in PD and can have serious consequences such as fractures, leading to reduced mobility, quality of life and even mortality (53). Early referral to physical therapy is recommended (53). In the early stages when there is limited disability, a physical therapist can provide specific advice on staying physically active and preventing complications by providing tailored exercise advice. Later on, the focus shifts to treating and training reduced functions and improving activities and participation. However, staying physically active remains important throughout the disease.

Physical therapists have many treatment modalities at their disposal. The first and probably best known strategy is exercise. Exercise is used for general health benefits as well as for specific motor symptoms (see clinical effects section) and even non-motor symptoms. Exercise includes aerobic exercise, strength training, flexibility, balance, agility and multitasking (54). Physical therapists perform a comprehensive personal assessment from which an individualized exercise prescription can be made. This is particularly important to 1) ensure appropriate dosing of the intervention, 2) ensure safety in terms of potential fall risk and cardiovascular risk, and to facilitate long-term adherence. A second important treatment modality is practice. Practice relates to motor learning aimed at improving motor skills and functional performance. Practice is most often applied in the context in which the person with PD uses the motor skill, and the physical therapist has several options to either challenge or facilitate the skill: i.e., using cues, dual tasks, or action observation. Thirdly, physical therapists use movement strategy training in which complex motor sequences (such as transfers), that are no longer performed automatically, are broken down into smaller components and are consciously trained and performed. Cues can also be used to induce compensatory mechanisms. Last, but not least, physical therapists use education and coaching to enable people with PD to integrate what they have learned into their daily lives and to engage in a physically active lifestyle.

Occupational therapy

Occupational therapy aims to maximize people's participation in meaningful activities and roles at home, work and in the community (55-57). This may be relevant

at all stages of the disease. The nature of goals may include maintaining or improving the efficiency, independence, safety, self-efficacy and satisfaction in performing prioritized activities of daily living. For many people with PD, daily functioning is compromised by a mismatch between the demands of activities or the environment and the abilities and needs of the person with PD. This can be caused by many factors. Important disease-related factors include changes in functional mobility, manual dexterity, functional cognition, and fatigue. The presentation of symptoms and disability can vary depending on the time of day, the psychosocial state of mind at the time, the effects of medication, the complexity and duration of the task, and the complexity of the environment. For example, a person may have difficulty cooking a family meal due to difficulty in planning and organizing the task, difficulty in maneuvering around in a small kitchen due to freezing of gait and difficulty chopping vegetables due to reduced arm/hand dexterity. Difficulties are exacerbated by time pressure and distractions of family members present. Occupational therapists with PD expertise are competent to analyze and address the complexity of factors involved. To do this, specialized occupational therapy is best delivered in the context of the person's activity performance, meaning at home, at work or in the community.

Clinical guidelines for occupational therapy in PD include many treatment modalities, often used in combination (55-57). First, tailored education and coaching to promote insight, self-management, and motivation for behavior change related to activity performance and participation. Second, the practice of skills and activities, preferably in the context of daily life. Often, compensatory movement strategies (e.g., cues, strategies for complex movement sequences) or functional cognitive strategies (e.g., attention and planning strategies) are incorporated to improve activity performance. When these compensatory strategies are not (fully) sufficient, an additional treatment modality is to adapt activity demands and patterns or to modify the environment. An example of activity adaptation is the use of simple recipes and pre-cut vegetables when cooking or receiving assistance for some steps of the activity. Adapting activity patterns may involve balancing rest and activity, considering on/off times when planning the day and week, or changing activity repertoire. Adapting the environment may include rearranging the furniture/work space, adjusting the lighting or using assistive devices or adaptive equipment. Occupational therapists can also advise caregivers on how and when to assist and supervise the person with PD in activities of daily living and how to prevent or reduce caregiver burden.

Speech-language therapy

The characteristic features of PD are also manifested in oral motor functioning and verbal communication. Therefore, speech-language therapists focus on improving

three main domains in PD: problems with speech, swallowing and saliva control (58). Hypokinetic dysarthria is characterized by increasingly soft mumbled speech, that limits intelligibility and social interaction. In addition, cognitive decline may reduce word finding and conversational skills further limiting communicative participation (59). Severe dysarthria is not an early sign of PD, but the majority of people with PD may struggle with intelligible speech during the course of their disease (60). Swallowing disorders (dysphagia) are prevalent in more than one-third of the PD population, depending on the diagnostic technique (61). Dysphagia in PD is usually associated with older age and longer disease duration, but mild symptoms may also occur in early stages of disease (62). It is characterized by slow chewing and eating, aspiration of liquids, or food getting stuck in the throat, especially when distracted during dual tasks such as conversation. While a normal protective response to aspiration of liquid, saliva or food is to cough hard, the coughing response may decrease as the disease progresses (dystussia) (63). This means that severe dysphagia combined with severe dystussia may increase the risk of aspiration pneumonia if left untreated. Drooling is a debilitating multifactorial problem that is generally not caused by dysphagia, but is predicted by hypomimia, which causes an unwanted and unnoticed open mouth, combined with both a stooped posture and saliva accumulation due to reduced swallowing frequency (64).

Treatment options for speech-language therapists are tailored education, generally followed by exercise training or personalized compensations; manuals and guidelines are available (58, 65). Education is needed for example to better understand why speaking in itself is a dual task by combining motor speech with comprehensible messages. This knowledge is also needed to be able to improve speech intelligibility through exercise training. Exercises with precise feedback to speak louder need to be intensive enough (several times a week) to overcome hypokinetic speech, not only by improving a strong voice, but also aiming to regain the ability to intentionally speak well. Another therapeutic approach is to use compensatory techniques, such as avoiding aspiration when drinking.

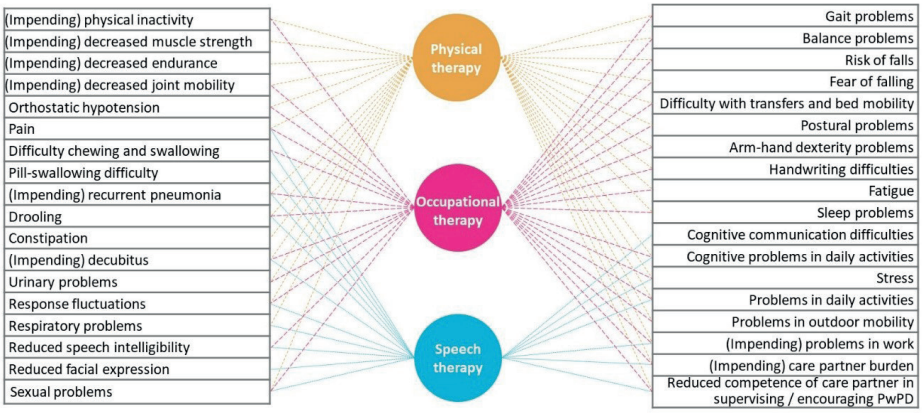
Caregivers are usually involved as well, because they benefit from understanding the consequences of PD on speech and swallowing. In addition, they may have a role in supporting the person with PD in using compensations or by being a challenging conversational partner.

Interdisciplinary specialized allied health care

Persons with PD often have multiple problems that require the expertise of different health care disciplines, both within and outside the scope of allied health

professions. In fact, some symptoms or areas of activity or participation may require treatment by several allied health disciplines simultaneously (Figure 1). In the case of interdisciplinary overlap, the contribution of each allied health professional will often be different, depending on the discipline-specific perspective and the availability of appropriate interventions (66). An example is the management of a person with PD who has difficulty eating due to dysphagia and postural problems. For a speech and language therapist, upright posture is a prerequisite for good swallowing. A physical therapist may provide an exercise program to train the muscles involved in postural control, or sensory cues or visual feedback strategies to improve sitting posture. At the same time, an occupational therapist may integrate the use of these strategies into home mealtime activities, and also provide advice on meal timing, adjust positioning at the table, or provide more external postural support while sitting. This example - albeit one of the many - illustrates how interdisciplinary care can have synergistic effects. In fact, there is currently widespread interest in developing training and guidelines for interdisciplinary care in PD to integrate knowledge and methods from different disciplines. In the Netherlands, an online integrated allied health guideline with embedded decision support has just been developed to support interdisciplinary care (67). An important prerequisite for integrated specialized allied health care in PD is regular communication and coordination between different health professionals involved in the care of a person with PD. This could be facilitated by digital health technologies such as free and secure messaging apps for health professionals (e.g. Siilo).

Figure 1. Overview of interdisciplinary overlap between specialized Allied Health Professionals for Parkinson's disease



Legend: Possible problem areas of people with PD that are relevant to physical therapy, occupational therapy and/or speech and language therapy are listed in this figure. The lines between the problem area and the disciplines indicate which discipline may be involved (to a greater or lesser extent) in providing interventions.

Evidence for (cost-)effectiveness of specialized allied health care

Over the past two decades, several randomized controlled trials and longitudinal observational studies have examined the effects of specialized allied health care in PD on clinical outcomes. There have also been a few studies that have examined the effects of specialized allied health care on health care costs and mortality. In general, the control arm in these trials consisted of usual care (with or without a waiting list design) or generic therapy within the same discipline. Most of the early studies of specialized allied health care focused on physical therapy, but over the past decade other disciplines have increasingly become the focus of trials and prospective studies. In the following sections, we summarize the current state of evidence for the three most studied disciplines: physical therapy, occupational therapy, and speech-language therapy.

Physical therapy

There is a large and growing body of evidence on the effects of physical therapy. Most attention has been paid to the modality of exercise, and many reviews and meta-analyses have been published, showing overall positive effects on motor symptoms and quality of life (68). There are also studies suggesting non-motor benefits, such as improvements in mood and sleep (68). Aerobic exercise has been studied extensively, and in addition to an effect on motor symptoms (68-72), high-intensity aerobic exercise has been hypothesized to slow disease progression. These hypotheses are based on converging evidence from observational cohort studies (73, 74), animal studies (75), and early human clinical trials (76). While definitive studies are still needed, these findings are extremely exciting because there are currently no disease-modifying treatments for Parkinson's disease (PD), and specialized physical therapy may be extremely important for people with PD.

In addition to exercise, physical therapy as a discipline using various treatment modalities has been extensively studied. A comprehensive meta-analysis showed a positive effect on motor symptoms, fear of falling and gait freezing based on the pooled effects of 45 studies (77). Detailed observations in registry data have further confirmed that specialized physical therapy is more effective (i.e. fewer complications) and efficient (lower costs) than regular physical therapy (13).

There are also important gaps in the current evidence. For example, safety and side effects have not been well studied, nor have people with advanced PD. In addition, we still have limited knowledge about the underlying mechanisms of exercise and the comparative effectiveness of different treatment modalities. Future studies should focus on elucidating these fundamental questions (71, 78).

Occupational therapy

Research on the effectiveness of occupational therapy for people with PD is still limited. Some recent systematic reviews have mainly included interventions 'within the scope of' occupational therapy, i.e. all interventions that focus on improving activities and participation (79-81). The pitfall is that other allied health disciplines also aim to improve activity performance and participation (82). Therefore, these reviews also include interventions delivered by other professionals and do not provide insight into the unique contribution of occupational therapy. Recent systematic reviews that only included studies where the intervention was (mainly) delivered by occupational therapists, can only be cautious in their conclusions due to the limited number of studies included, the heterogeneity of interventions, outcomes and study design (83, 84).

Three randomized controlled trials were conducted that examined occupational therapy as a single intervention. These include a trial of individualized, goal-directed home-based occupational therapy (85), a dexterity-focused home-based exercise program (86), and a multicomponent occupational therapy program focused on motor limitations in activities of daily living (87). Overall, the results suggest an improvements in (perceived) activity performance (85, 87) and short-term improvements in dexterity-related ADL (86). For quality of life, these studies did not show a significant effect for patients, but in the individualized, goal-directed home-based occupational therapy trial, quality of life improved for caregivers (85). This study also assessed cost-effectiveness from a societal perspective. It showed that the specialist occupational therapy intervention had no significant impact on total costs compared with care without occupational therapy over a 6-month period. However, there was a significant and substantial saving in institutional care in the intervention group (88).

The evidence base for occupational therapy in PD is likely to grow, as more feasibility studies have been conducted or planned in recent years on occupational therapy programs for specific problems that affect daily life and participation such as functional cognition (89, 90), fatigue (91), anxiety (92), or studies focused on specific domains of activity, such as work (93). Finally, there are studies that compare occupational therapy interventions, such as the addition of a task-oriented LSVT-BIG® program to general occupational therapy (94).

Given the large gap between the role of occupational therapy in PD care and the limited evidence base, there is an urgent need for more research in the area of occupational therapy interventions in PD. Research on the effects and working

mechanism of occupational therapy interventions that address specific problems, such as impaired functional cognition, fatigue, dexterity problems, postural problems etc. In addition, research on the effects of occupational therapy interventions that focus on prevention. In the early stages of the disease, this may focus on job retention or prevention of other participation limitations; in the later stages, it may focus on prevention of falls and medical complications such as pressure ulcers.

Occupational therapists have a unique focus and approach, but occupational therapy in PD is rarely delivered in isolation; it is naturally part of multidisciplinary programs. In order to assess the specific value of occupational therapy, it is important that research projects properly describe and monitor the occupational therapy intervention used and always include outcome measures at the level of participation in activities of daily living.

Speech-language therapy

There is a growing body of evidence supporting the benefits of specialized speech-language therapy for Parkinson's disease. The first studies of speech therapy evaluated the Lee Silverman Voice Treatment (LSVT LOUD) three decades ago (95). A recent meta-analysis confirms the efficacy of this approach in improving voice loudness and functional communication (47). However, the success of such programs depends on their high intensity for a short period of time (3 to 4 times per week for 4 weeks), which is reflected in the inclusion of participants with mild to moderate PD (47). Meanwhile, large randomized controlled trials of personalized approaches are underway, including people with severe PD (96). Importantly, tele-rehabilitation has been shown to be non-inferior to face-to-face treatment sessions, facilitating the delivery of intensive speech-language therapy in the home(97). In addition, the non-motor aspect of verbal communication (communicative efficacy) has recently attracted scientific interest. Studies suggest that approaches such as Communication Partner Training (CPT) may also be valuable for caregivers of people with PD (98), but there is a clear need for more research on this topic.

Treatment of dysphagia in PD depends on timely compensation to prevent aspiration or to facilitate swallowing (58). Exercise training may also be helpful, either direct swallowing exercises [[62] or indirect exercises such as expiratory muscle strength training (EMST) (99). Expiratory strength training may also improve coughing as a protective response to aspiration of liquids or food, but intensive skills training to improve cough efficiency seems to be more effective (100). There is now convincing evidence that specialized speech-language therapy reduces the rate of pneumonia in PD(101).

Behavioral treatment of drooling in PD is mainly based on education and finding the right cues to improve swallowing frequency. However, since saliva is swallowed throughout the day, wearable devices are being studied (102), but results are still awaited.

The costs of specialized speech-language therapy compared with usual care have not been well studied. An exploratory economic evaluation along the pilot study of the PD COMM trial compared the costs and outcomes of LSVT LOUD, standard SLT care, and no treatment. There were no differences in outcomes at 12 months, but the full study is awaited for a more definitive assessment of the cost-effectiveness of speech and language therapy for people with voice and communication problems due to PD (103).

Interdisciplinary allied health interventions

There is converging evidence that the concurrent provision of specialized allied health therapy across multiple disciplines (e.g., specialized physical therapy and specialized occupational therapy) may have synergistic protective effects in people with PD. A recent large observational study in the Netherlands found that the putative protective effects of specialized occupational therapy in the prevention of PD-related complications was most distinct in individuals who also received specialized physiotherapy, suggesting that specialized occupational therapy and specialized physiotherapy may have synergistic protective effects(101).

Studies on specific multidisciplinary programs with a focus on specialized allied health care, are limited. In Italy, a specific multidisciplinary inpatient program, called Motor-cognitive and Intensive Rehabilitation Treatment (MIRT), has been evaluated in several studies. These studies evaluated the efficacy and effectiveness of MIRT on several domains in people with PD and showed improvements in mobility (104), sleep (105), motor performance (106), balance and gait (107), and quality of life (108, 109).

A randomized clinical trial in China showed an improvement in health-related quality of life in people with idiopathic PD while evaluating the effect of an outpatient personal rehabilitation program with specialized allied health professionals (110).

In a three-arm randomized clinical trial in the United States, people with PD significantly improved their health-related quality of life, particularly in the areas of mobility and communication, as a result of 6 weeks outpatient group rehabilitation focused on self-management. Benefits were greater in the group that received additional home-based training to transfer strategies to the home environment (111). A three-arm randomized clinical trial in the United Kingdom compared the effect of

a 6-week specialized multidisciplinary rehabilitation in the home with and without ongoing support from a trained care assistant, with usual care. The results showed that the multidisciplinary intervention significantly reduced anxiety in people with PD and improved psychological well-being in their informal caregivers. The benefits, although not significant, were better maintained in the group that received ongoing support (112).

Gaps and future perspectives

Although there is a growing body of evidence for specialized allied health care in Parkinson's there is still a great need for more and more focused research to address specific gaps. In Table 1, we list general recommendations for future research on specialized health care for PD. Here, we discuss the most important recommendations.

In future studies, more attention needs to be paid to investigating the effects of specialized allied health care in both the early and advanced stages of the disease, as these groups are underrepresented in current research. Evidence of efficacy across disease stages, may help to better understand what are the effective mechanisms of treatment approaches and how to adapt them according to personal and disease characteristics. This should also include the use of technology, which can further support more personalized care. In longitudinal studies, outcome measures that indirectly address the effect of allied health therapy, including composite endpoints such as PD-related complications or mortality and hospitalization could be used.

In addition, the investigation of the cost-effectiveness of each and combinations of different specialized allied health disciplines or studies of cost- effectiveness of community-based care versus institutionalized care are of high importance for health policy that could be included in future research.

Another important area of research is how to improve access to specialized allied health care in different regions of the world and in different settings and subgroups within the countries. Although, allied health care is available in most countries around the world, access to allied health care, let alone specialized allied health care for PD, is still limited (113, 114). Future studies should examine facilitators and barriers of access to specialty care by country, region, setting, stage of disease, gender, socioeconomic status or racial and ethnic group (113-117). Potential barriers may include both person-level and system-level barriers (115). Examples of person-level barriers that merit further study include limited health care literacy, an individual's ability to navigate the health care system effectively, their ability to actively participate in health care plans, or financial constraints. Examples of financial constraints that merit further study include the (in)availability of specialized service provision. System-level

barriers are more related to the health care infrastructures and their availability. Infrastructures such as medical professionals, diagnostic tools, medications, and availability of allied health professionals who have access to PD-specific training and receive sufficient referrals to increase their caseload and expertise. Due to the growing number of people living with PD worldwide (118), the demand for access to specialized PD-related allied health care is likely to increase in the coming years, highlighting the need for studies that address these gaps.

Table 1. Overarching recommendations for future research on specialized health care for Parkinson's disease

Research area	Content	Detail
Effectiveness/ efficacy	Attention for early and advanced stages of disease	Evaluate the effectiveness of specialized allied health care in early PD to prevent disability and reduced participation. Evaluate the effectiveness of specialized allied health care in late PD to maintain well-being and prevent complications.
	Effectiveness for specific subgroups	Evaluate the required tailoring and subsequent intervention effects in subgroups of people with fatigue or cognitive problems.
	Integration of technology	Explore the utility and benefits of integrating telemedicine and novel technology (i.e., wearable devices) into personalized and efficient health care provision.
	Working mechanism	Include process evaluations and other research designs to elucidate the mechanisms by which interventions work.
	Appropriate outcome selection	Selected outcomes in allied health care effectiveness research should include activity performance and/or participation. Preferably, a combination of individualized patient-reported outcome measures and objective performance-based outcome measures. Indirect outcomes can include PD-related complications, mortality, and hospitalization.
	Different models of care	Comparing the effects of integrated care in the community versus in secondary/tertiary care settings
	Cost-effectiveness	Include evaluation of costs and cost-effectiveness in trials, to allow comparison of specific interventions and models and settings of care. (i.e., community care versus secondary of tertiary care)
Access	Geographical access	Access to and utility of specialized care in low-resource countries.
	Subgroups within countries	Access to and utility of specialized care for people with PD from different cultural or socioeconomic backgrounds.

Conclusion

Overall, the available evidence underscores the potential benefits of specialized allied health care and its strategies for people with PD, including improvements in motor and non-motor symptoms, quality of life, and overall well-being. We also conclude that this evidence supports the wider implementation of specialized allied health care in the multidisciplinary care for people with PD.

Acknowledgments
The authors have no acknowledgments to report.

Funding
The authors have no funding to report.

Conflict of Interest
Ingrid Sturkenboom has received research grants from The Netherlands Organisation for Health Research and Development.

Amir Talebi has no conflict of interest to report.

Nienke de Vries has received research grants from The Netherlands Organisation for Health Research and Development, the Michael J Fox Foundation and Verily Life Sciences. She serves as an associate editor of the Journal of Parkinson's disease

Sirwan Darweesh has received funding from the Parkinson's Foundation (PF-FBS-2026), ZonMW (09150162010183), ParkinsonNL (P2022-07 and P2021-14), Michael J Fox Foundation (MJFF-022767) and Edmond J Safra Foundation.

Johanna Kalf has received research grants from the Michael J Fox Foundation, The Netherlands Organisation for Health Research and Development and the Dutch Association for Speech and Language Therapy.

Chapter 3

Specialized Versus Generic Allied Health Therapy and the Risk of Parkinson's Disease Complications

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Financial Disclosure/Conflict of Interest concerning the research related to the manuscript

There are no conflicts of interests related to the research in this report.

Funding sources of study

This research is part of the PRIME project, which was funded by the Gatsby Foundation [GAT3676] as well as by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships. The Center of Expertise for Parkinson & Movement Disorders was supported by a center of excellence grant by the Parkinson Foundation.

Abstract

Background

Specialized versus generic physiotherapy (PT) reduces Parkinson's Disease (PD)-related complications. It is unclear whether (i) other specialized allied heath disciplines, including occupational therapy (OT) and speech & language therapy (S&LT), also reduce complications; (ii) there is a synergistic effect among multiple specialized disciplines; and (iii) whether each allied health discipline prevents specific complications.

Methods

We longitudinally assessed if the level of expertise (specialized versus generic training) of PT, OT and S&LT was associated with the incidence rate of PD-related complications, using claims data of all insured persons with PD in the Netherlands between January 1, 2010 and December 31, 2018. ParkinsonNet-trained therapists were classified as specialized, other therapists as generic. We used mixed-effects Poisson regression models to estimate rate ratios adjusting for sociodemographic and clinical characteristics.

Results

The population of 51,464 persons with PD (mean age 72.4 years, standard deviation 9.8) sustained 10,525 PD-related complications during follow-up (median 3.3 years). Specialized PT was associated with fewer complications (incidence rate ratio (IRR) of specialized versus generic=0.79, 95% confidence interval [0.74-0.83], p-value <0.0001), as was specialized OT (IRR=0.88[0.77-0.99], p-value=0.03). We found a trend of an association between specialized S&LT and a lower rate of PD-related complications (IRR=0.88[0.74-1.04], p-value=0.18). The inverse association of specialized OT persisted in the stratum who also received specialized PT (IRR=0.62[0.42-0.90], p-value=0.001). The strongest inverse association of PT was seen with orthopedic injuries (IRR=0.78[0.73-0.82], p-value<0.0001), and of S&LT with pneumonia (IRR=0.70[0.53-0.93], p-value=0.03).

Conclusions

These findings support a wider introduction of specialized allied health therapy expertise in PD care, and conceivably for other medical conditions.

Keywords: Parkinson's disease, specialized care, allied health therapy, medical claims data, longitudinal study

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterized by various motor and non-motor manifestations (123). Because of these manifestations, persons with PD (PwP) are at increased risk of complications such as orthopedic injuries and pneumonia (124). Pharmacological and neurosurgical treatments have limited effects on the prevention of certain complications, such as orthopedic injuries or pneumonia, because they only marginally relieve symptoms related to these complications such as balance and swallowing deficits. Therefore, there is a need for complimentary treatments that are applicable to a broad spectrum of PwP.

There is growing evidence to support the merits of specialized allied health therapies (AHT) such as physiotherapy (PT), occupational therapy (OT), and speech & language therapy (S&LT), yielding improvements in daily life functioning and quality of life in PwP (77, 78, 125-127). Specialization through a dedicated PD-specific training program appears to be important in mediating such beneficial effects. A recent study in the Netherlands found that treatment by specialized physiotherapists who attracted a high caseload was associated with fewer PD-related complications and with lower costs of care, as compared to treatment by generically trained therapists who managed only few PwP (125). The same study also found that specialized physiotherapists were more efficient, as they required fewer treatment sessions to achieve their good outcomes (125).

However, it is unclear whether these results can be translated to other allied health disciplines, whether the beneficial effects are sustainable over longer time periods, and whether there is a synergistic effect among specialized disciplines combinations. Here, we aim to address these issues by investigating the protective effect of three specialized allied health disciplines on PD-related complications. We specifically examine if these protective effects are greater for specialized therapists versus generically trained therapists. We also study whether each specific allied health discipline is associated with an overall reduction in PD-related complications, or only with prevention of specifically targeted complications. Finally, we investigate whether the effects apply to all PwP or only to specific subgroups (by stratifying PwP by clinical and demographic factors) and whether any observed beneficial effects are sustained over longer periods.

Methods

Overview

We used a national administrative claims database, held by Vektis, which contains the diagnostic and treatment data of more than 99% of the Netherlands population (128) from January 1st, 2010, to December 31st, 2018 to create a retrospective cohort study. PwP were identified by the Diagnosis Related Group code of 501 using records of all neurological departments in the Netherlands. We extracted data from all PwP who had received AHT at any time post-diagnosis. Follow-up time started on the first date on which an individual had a Diagnosis Related Group of PD and received AHT, irrespective of which came first. Follow-up time ended at the first of the following events: death, December 31st, 2018, or 30 days after the last AHT session. We added the 30 days lag to account for the censoring of the individuals' follow-up time, assuming that PD-related complications that happened during 30 days after the last treatment session are related to the last AHT level. We also investigated any longer term residual effect by increasing the lag period in sensitivity analyses. Note that individuals who received AHT both before and after PD diagnosis were eligible for inclusion, but that follow-up time for these individuals started after PD diagnosis. Individuals who only received AHT before (not after) their PD diagnosis did not contribute any person-time (figure 1).

In analyses comparing outcomes by AHT level of expertise (explained in the next section), we calculated separate starting dates for follow-up with generic AHT or with specialized AHT. We also performed discipline specific analyses, by calculating separate starting dates for follow-up time with PT, OT or S&LT. In analyses on any discipline (any combination specialized vs. generic PT, OT and or S&LT in the same month) of AHT, we used the first of these dates.

Specialized AHT

AHT was classified specialized if the practitioner was registered with the Dutch national ParkinsonNet. This specialized network approach has been described in detail in articles elsewhere (129, 130). Briefly, all ParkinsonNet therapists have received a baseline 3-days training program to enhance their PD-specific expertise, according to evidence-based guidelines, and subsequently receive annual follow-up training courses. Participating therapists complete annual standardized questionnaires on their quality of care. They are also required to treat minimally five PwP annually.

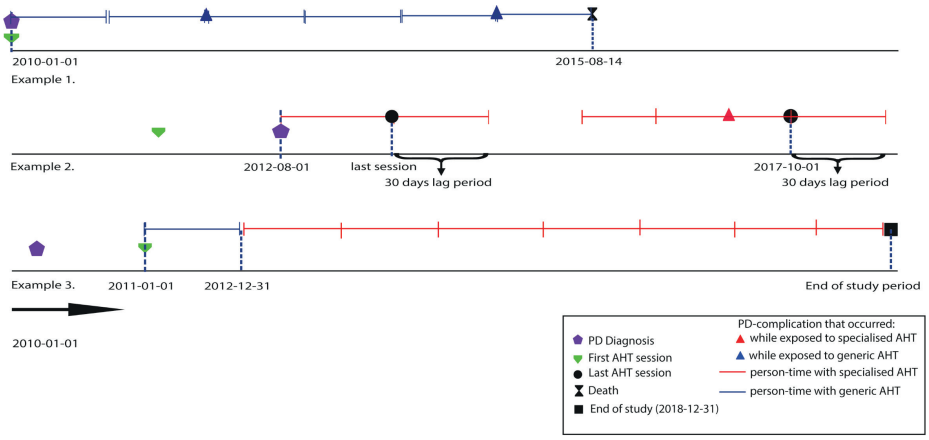

Figure 1. Follow-up time illustration. AHT: Allied Health Therapy. PD: Parkinson's Disease. Example 1) A person received only generic AHT throughout the entire follow-up period starting by the diagnosis date. Example 2) A person starts amass person time by first AHT session after (and not before) the diagnosis. Example 3) A person could amass person time in both strata of level of expertise, for instance if they were diagnosed with PD in 2010-01-01, received generic AHT between January 1st, 2011 and December 31st, 2012 (person time with generic AHT: 2 person years) and specialised AHT between January 1st, 2013 and December 31st, 2018 (person time with specialised AHT: 6 person years).

Complications

We used Diagnosis Related Group codes to identify PD-related complications (supplementary table 1), which comprised any orthopedic injury (including fractures) or pneumonia. We selected these outcomes as we believed a priori that they may be prevented by higher quality AHT and because they are relatively common in PwP.

Covariates

To minimize the potential risk of biases while using medical claims-data we used a set of clinical and demographic variables that could predict complications as covariates. These were (a) modified Charlson comorbidity score, PD-specific medications, and risk of prior complications in the year prior to enrolment; (b) sociodemographic characteristics as age, sex, and an ecological marker of socioeconomic status (SES). We used a combination of Pharmaceutical Cost Group and healthcare product specific codes, which are assigned to different services delivered to patients, to build a modified Charlson Comorbidity Index. Pharmaceutical Cost Group codes are special codes in the Netherlands healthcare claims-data system which assign to multiple chronic conditions for the ease of prediction of future healthcare costs and to facilitate the future research for demonstration of disease severity (131). We defined a binary variable of having or not having a PD-specific medication using the data of medication codes. We classified SES ecologically based on area characteristics

of level of income, education, and employment status of people in each neighborhood (postal code area) that is used in the Netherlands (132).

Statistical analysis

We calculated mean and standard deviation values of baseline characteristics, stratified first by having received AHT (yes/no) and separately -in those who did receive AHT- by the predominant level of expertise of AHT received. For the baseline characteristics (table 1), people who received >50% of their sessions from a specialized therapist were classified as having predominantly received specialized AHT, while people who received >50% of their sessions from a generic therapist were classified as having received predominantly generic AHT.

Table 1. Population Characteristics

	Predominant level of expertise of allied health therapy received		
	Total	**Specialized**	**Generic**
N	51464	16070	35394
Female (%)	21607 (42%)	5937 (37%)	15670 (44%)
Age (SD)	72.4 (9.8)	71.5 (9.5)	72.8 (9.9)
Socioeconomic status* (SD)	-0.12 (1.1)	-0.10 (1.1)	-0.13 (1.1)
Participants with >1 PD-specific medication (%)	44288 (86%)	14526 (90%)	29762 (84%)
Participants with >1 complication† during year prior to enrolment (%)	2363 (4.6)	550 (3.4)	1830 (5.1)
CCI score‡ (SD)	3.96	3.76	4.04

Columns indicate level of expertise of any discipline of allied health therapy predominantly received. For this analysis, people who received >50% of their sessions from a specialized therapist were classified as having predominantly received specialized AHT, otherwise classified as generic AHT. CCI, Charlson Comorbidity Index. Continuous characteristics presented with mean (standard deviation); Categorical characteristics presented with number (percentage). * Standardized socioeconomic status derived from characteristics such as education, income, and employment status of people in each neighborhood. † Complications defined as any fracture or orthopedic injury and pneumonia. ‡ Weighted scores for each comorbid disorder calculated based on CCI. Mean propensity score for both groups: 0.37, standard deviation: 0.06.

We compared the effectiveness of specialized versus generic AHT on the rate of any recurrent PD-related complication. For this analysis, we used Poisson regression models in which the individuals' unique identifier was entered as a random effect to account for correlation of recurrent complications within a single individual (e.g., the occurrence of a complication might influence the occurrence of a next complication).

In each model, the level of expertise of AHT received was the exposure. We computed level of expertise of AHT care as a time-dependent variable (figure 1, example 3) so that the person-years of risk is allocated to the type of specialized AHT if an individual receives more than one type of AHT. The primary outcome across analyses was a composite of all PD-related complications, though further analyses looked at the cause of complication.

In the main analyses, we assessed the effect of any-discipline AHT or discipline-specific AHT (PT, OT or S&LT) on a composite of PD-related complications, with adjustment for age, sex, having at least one PD-specific medication, SES and comorbidity (modified CCI). We performed several further analyses to explore the robustness of the main results and if there was evidence of effect modification. A detailed description of these further analyses is provided in Supplementary methods 2.

Data sharing statement

Data are available on request, within the constraints of medical claims data privacy laws in the Netherlands. Interested researchers can contact the corresponding author of this study.

Results

Baseline characteristics

We observed 59,313 individuals with a diagnosis of PD between January 1st, 2010 and December 31st, 2018, of whom 51,464 received any-discipline AHT. Those who received AHT were 4 years older, were more often women, and were more likely to use PD-medication, with higher comorbidity and complications in the year prior to enrolment (Supplementary table 2). As shown in supplementary figure 1, most PwP who received care by any discipline of AHT, also received PT by either one of the specialized or generically trained therapists. Specifically, 49,948 (97% of the 51,464 with any-discipline AHT) received PT (only PT or in combination with OT and or S&LT), 23,716 (46%) received OT (only OT or in combination with PT and or S&LT) and 14,113 (27%) received S&LT (only S&LT or in combination with PT and or OT).

Within the population who received AHT, PwP who received specialized AHT were slightly younger, more likely to be men and more likely to receive PD medication, with a lower comorbidity score and fewer prior complications but very similar SES (table 1). The distribution of the propensity score for receiving specialized AHT or generic AHT was identical in both groups.

Table 2. Level of Allied Health Therapy and the Risk of Parkinson's Disease-related Complications

	Any discipline			Physiotherapy		
	Total	**Specialized**	**Generic**	**Total**	**Specialized**	**Generic**
Person-years at risk of any complication	131362	48649	82713	127004	45234	81769
Total N complications	10527	3698	6829	10164	3383	6781
Rate of any complication	0.08	0.076	0.082	0.08	0.075	0.083
Incidence Rate Ratio(IRR)(95% CI)	0.80(0.76-0.84)*			0.79(0.74-0.83)*		
p-value	< 0.0001			< 0.0001		

N, number. CI, confidence interval. IRR, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, and PD-specific medication. P-value demonstrates the p-value of the estimated IRR.

Effect of specialized AHT on PD-related complications

During follow-up, 51,464 PwP contributed 131,363 person-years which varied among different disciplines (table 2). Specialized PT was associated with a reduced rate of PD-related complications (incidence rate ratio (IRR) of specialized versus generic=0.79, 95% confidence interval (CI) [0.74-0.83], p-value <0.0001) as was specialized OT (IRR=0.88 [0.77-0.99], p-value =0.03). We found a trend of an association between specialized S&LT and a lower rate of PD-related complications (IRR=0.88[0.74-1.04], p=0.18) (table 2). After stratification by exposure to PT, the inverse association of specialized OT and PD-related complications persisted in those who received specialized PT but not in others (table 3).

Complication-specific analyses (table 4) showed that the strongest inverse association of specialized PT was seen with orthopedic injuries, and of specialized S&LT with pneumonia.

We observed no significant subgroup differences in the analyses (Supplementary figure 2).

The inverse associations of specialized any-discipline AHT and PT sustained over longer treatment exposure days (>365 treatment exposure days), albeit with a less pronounced IRR for any-discipline AHT and PT (Supplementary table 3). Specialized OT was inversely associated with the rate of complications only in those with less than 365 treatment exposure days (Supplementary table 3).

Speech & Language Therapy			Occupational Therapy		
Total	**Specialized**	**Generic**	**Total**	**Specialized**	**Generic**
9743	5861	3882	10447	6028	4420
973	575	398	1316	746	570
0.1	0.098	0.102	0.126	0.124	0.129
0.88(0.74-1.04)			0.88(0.77-0.99)*		
0.18			0.03		

Table 3. Level of Speech & Language Therapy and Occupational Therapy and the Risk of Parkinson's Disease-related Complications Stratified by Exposure to Physiotherapy

Speech & Language Therapy	**Specialized Physiotherapy**	**Generic Physiotherapy**	**No Physiotherapy**
N	1447	2995	301
Incidence Rate Ratio (IRR) for any complication(95% CI)	1.04(0.44-2.45)	0.88(0.58-1.32)	0.35(0.07-1.65)
P value (SE)	0.9 (0.5)		
Occupational Therapy			
N	4052	9572	667
Incidence Rate Ratio (IRR) for any complication(95% CI)	0.62(0.42-0.90)*	0.98(0.78-1.24)	1.42(0.55-3.65)
P value (SE)	0.01 (0.2)		

Columns show stratification of PwP based on receiving S&LT or OT and specialized PT (>50% sessions from specialized physiotherapist); generic PT (>50% sessions from generic physiotherapist); or No PT. N, number of persons with Parkinson. CI, confidence interval. IRR, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, and PD-specific medication. P value, p for interaction between the level of each discipline with specialized physiotherapy in a separate model. SE, standard error.

Table 4. Level of Allied Health Therapy and the Risk of Each Parkinson's Disease-related Complication

	Any discipline				Physiotherapy			
	P-T	**N Comp**	**Comp Prp**	**IRR(95% CI)**	**P-T**	**N Comp**	**Comp Prp**	**IRR(95% CI)**
Pneumonia (overall)	131362	2920	4.30%		127004	2777	4.30%	
Specialized	48649	1042	2.50%	0.98(0.88-1.08)	45234	941	2.60%	0.98(0.88-1.11)
Generic	82713	1878	3.30%		81769	1836	3.40%	
Orthopedic injuries (overall)	131362	7663	9.90%		127004	7438	10.00%	
Specialized	48649	2677	5.80%	0.78(0.73-0.82)*	45234	2456	6.30%	0.76(0.71-0.81)*
Generic	82713	4986	7.90%		81769	4982	8.10%	

CI, confidence interval. P-T, person time. N Comp, number of PD-related complications. Comp prp, percentage of individuals with at least one PD-related complication over their follow-up period. IRR, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, and PD-specific medication.

Further adjustment for the propensity score did not have a considerable effect on the results of specialized PT (IRR=0.76, 95% CI [0.73-0.80], p-value<0.0001).

After cessation of treatment, the reduced relative rate of complications between PwP who had received specialized or generic any-discipline AHT and PT slowly declined with increasing lag periods, though there was evidence of some modest persisting benefits (Supplementary table 4.1). Analysis of the sustainability of the specific effects after cessation of two specialized disciplines of PT and S&LT showed that the inverse association between specialized PT and the rate of orthopedic injuries and specialized S&LT and the rate of pneumonia slowly declined with increasing lag periods after treatment cessation, though there was evidence of modest persisting benefits specifically until another 90 days (Supplementary table 4.2). We examined if individuals who received specialized versus generic AHT, at a later moment, already had a lower rate of complications in the period from diagnosis to onset of AHT treatment (median time from diagnosis to onset of specialized and generic any-discipline AHT was 0.6 and 0.7 years respectively) to determine possible selection of participants into specialized or generic therapy (Supplementary table 5). This analysis showed that PwP receiving any of the specialized therapies did have lower rate ratios for PD-related complications prior to receipt of therapy although the benefits of OT (median time to onset of specialized and generic OT: 2.8 and

Speech & Language Therapy				Occupational Therapy			
P-T	**N Comp**	**Comp Prp**	**IRR (95% CI)**	**P-T**	**N Comp**	**Comp Prp**	**IRR(95% CI)**
9743	376	2.30%		10447	432	1.70%	
5861	202	1.80%	0.70(0.53-0.93)*	6028	238	1.40%	0.84(0.67-1.05)
3882	174	2.10%		4420	194	1.30%	
9743	604	3.60%		10447	897	3.30%	
5861	377	3.20%	1.01(0.82-1.26)	6028	516	2.90%	0.89(0.76-1.05)
3882	227	2.80%		4420	381	2.60%	

2.0 years respectively) and S&LT (median time to onset of specialized and generic S&LT: 2.6 and 2.0 years respectively) were markedly attenuated after adjustment for prior PT. We observed that 8.3% of PwP treated by a specialized and 8.8% treated by a generically trained allied health therapist received care at a university medical center (Supplementary table 6). Additional adjustment of the main analysis for hospital type, did not change the incidence rate ratio of specialized AHT for the rate of complications (Supplementary table 6). People who received *any-level vs. no* allied health therapy generally had higher disease severity indicators, and we observed no significant association between *any-level vs. no* allied health therapy with the rate of complications (Supplementary table 2).

Discussion

We found that any type of AHT as a combined group but specifically specialized PT was associated with a lower incidence of PD-related complications. The inverse association of specialized AHT with complications was largely consistent across different subgroups of people with PD. In analyses of all three specialized disciplines, we observed inverse associations of PT and OT but for S&LT the association was consistent with chance. OT was inversely associated with complications after

restriction to individuals who already received specialized PT, suggesting that specialized OT may have incremental benefits (synergistic effect) beyond specialized PT. We found that different disciplines of specialized AHT may prevent specific complications as we observed the strongest inverse association of PT with orthopedic injuries and of S&LT with pneumonia.

Causality of the observed associations

We cannot conclude on a clear causal relationship because of the observational nature of our study. Here, we present key arguments for and against a possible causality of our findings (133, 134). Supporting arguments are as follows. First, the inverse association of specialized PT was restricted to the risk of developing orthopedic injuries, while the inverse association of S&LT was restricted to the risk of developing pneumonia. These associations provide mechanistic plausibility for a causal protective effect of specialized AHT on the prevention of complications in PD. Similarly, observing no association between S&LT and the rate of orthopedic injuries strengthens the causality of our findings, because this specific allied health intervention should not have an effect on this unrelated outcome (135). Second, we found that after the last session of AHT, the inverse associations of specialized AHT (any discipline) or of PT alone with PD-related complications gradually diminished over time. This finding suggests that the protective effects of specialized AHT are reversible, which would be clinically plausible. Third, by implementing methods (i.e., propensity score adjustment) that tries to mimic randomization, we observed a similar predicted probability to receive specialized AHT, based on known determinants of PD-related complications, in individuals who received specialized or generic AHT, which is in favor of the causality. Fourth, for specialized PT we found a consistency in our findings, i.e., over multiple subgroups and over different sensitivity scenarios, which is in line with a causal pathway. Fifth, it is possible that there was preferred referral to ParkinsonNet therapists by movement disorders specialists. This may have introduced some confounding bias if a larger proportion of PwP in the specialized AHT group were treated by a movement disorders specialist. It is unlikely that this had a major effect on the results, since adjustment for the hospital type in which PwP received care (university medical center vs. other) did not alter the results.

However, there are also counter-arguments against the causal nature of these associations. As these data are observational and allocation to specialized therapy is not random, it is possible that patients with milder disease, less comorbidity or other beneficial demographics were more likely to receive specialized AHT. In this scenario, their lower risk of complications would reflect their better health status rather than

the therapy itself. There was some weak evidence in support of this hypothesis (lower CCI score and probability complications in the year prior to enrolment). However, the benefits of specialized AHT persisted despite our use of multivariable models and propensity score adjustment to account for any differences. We also demonstrated that PwP who went on to get specialized AHT had a lower risk of complications prior to the onset of any-discipline AHT. This would further support confounding by prior health status. However, we noted that PwP who went on to receive specialized AHT had a shorter gap in time between diagnosis and initiation of therapy. This could also explain our observation, as the generic therapy group were left untreated for longer and hence would be more likely to have a PD complication event, making the specialized AHT group appear artefactually better. This may reflect an important difference between specialized and generic management as timely referral is part of the treatment guidelines and an approach to care within the specialized Dutch ParkinsonNet network. In the main analyses, we classified the study entry date as either the date of diagnosis or first AHT session date, depending on which was later, to correct for potential selection bias as much as possible.

Physiotherapy

Previous studies on the effectiveness of specialized AHT have primarily focused on PT. Specialized PT professionals using interventions such as treadmill training, stationary bicycle training or multimodal exercise can decrease the risk of PD-related complications (124, 136-138). Recent work showed that PT delivered by specialized therapists led to fewer PD-related complications and lower costs than PT delivered by generic therapists (125). These good outcomes were reached by the specialized therapists with fewer treatment sessions. Our current study builds on that study in several ways. First, we had a considerably longer follow-up period (maximum 9 years vs maximum 3 years in the previous study) and a much larger population (n=51,464 vs n=4,381). These two factors allowed us to investigate the effects of specialized AHT in subgroups and to assess whether the effects changed over time. Second, we also evaluated the effects of specialized AHT in other disciplines than PT, namely OT and S&LT. This is very valuable because in everyday clinical practice, increasingly many PwP are already being treated by these allied health disciplines, either as a monodisciplinary approach or as part of a multidisciplinary team approach. This practice is now supported by better evidence, offering further incentives to extend this type of care to other PwP as well.

Occupational therapy

Specialized OT professionals employ assessments of safety in the home and work environment of PwP. They also provide PwP with internal and external cueing

techniques to improve postural stability and mobility (139). These improve their ability to self-manage and maintain functional independence in domestic tasks of PwP, which leads to improved motor functions, activities of daily living, and quality of life (77, 78, 139). Our study is the first to evaluate the effects of specialized OT on PD-related complications in real life. We found that specialized OT is associated with a lower rate of PD-related complications when combined with specialized PT, suggesting a potential synergistic effect between these two disciplines (140).

Speech & language therapy

Speech and swallowing disorders are commonly seen in PwP and can lead to complications such as aspiration pneumonia (141). Importantly, dysarthria and dysphagia typically do not respond well to pharmacotherapy (127), but might be responsive to specialized S&LT interventions including dedicated voice and swallowing training (88, 127, 142). In our study, we found convincing evidence for the effectiveness of specialized S&LT on lowering the rate of pneumonia, which is stated as a therapeutic goal in guidelines (88).

Strengths and limitations

There are several strengths to our study. (i) Our analyses are based on a large sample size based on a nationwide medical claims data of more than 99% of the Dutch population. (ii) We have a long follow-up of up to 9 years (median 3.3 years per person). It would have been very time-consuming, costly and probably unrealistic to undertake a clinical trial with such a long follow-up period. (iii) We could compare the effects of specialized AHT to the effects of generic AHT, because no preferred therapist referral guidelines for clinicians were in place during the study period, thereby mimicking a randomized controlled trial. We successfully used this approach in a prior analysis of specialized physiotherapy (125). This approach also reduces the likelihood of confounding-by-indication, which would have been a concern if we had compared the effects of specialized AHT to no AHT (as AHT would then appear to be deleterious). However, we note that in the main analysis, we deliberately focused on the comparison of referral to a specialized or generic therapist, since this choice is predominantly influenced by awareness of ParkinsonNet by the patient or their treating clinician in The Netherlands. By contrast, the comparison of *any-level vs. no* allied health therapy is considerably affected by confounding-by-indication, as referral to *any* allied health therapist almost completely depends on the severity of clinical symptoms of a person with PD. We could not verify whether the complications that we studied were always related to PD. In addition, we did not measure the actual proficiency of the therapists but assumed that those ascribed to be specialized were better. Moreover, in the Netherlands, the majority of AHT

sessions are reimbursed by healthcare insurers, and >99% of the population receives healthcare insurance. This explains the high number of AHT treatment sessions in our study, which may somewhat limit the generalizability of our findings to countries with different healthcare systems. We also acknowledge that the exact nature and components of the interventions provided by each discipline were not known, and that these ingredients may differ considerably between individuals. Finally, despite our best efforts, we could not fully exclude residual confounding, patient's health status rather than the type of therapy, as an explanation for our findings.

Implications for future research

First, our findings support a more widespread introduction of specialized AHT for a wide population of PwP. Our observations were made in the Netherlands, a high income country, and it is now important to further investigate the effectiveness of specialized AHT in low or middle income countries, where the resources for pharmacological treatment are more limited. Second, future research should also examine potential benefits of specialized AHT -in particular specialized OT- on functional outcome measures, such as institutionalization or utilization of nonmedical aids given that this could reveal additional protective effects on complications that are more responsive to OT interventions. Third, we did not distinguish between intermittent or continuous AHT in our study. A recent randomized trial compared high-frequent sessions of physiotherapy over a shorter period vs. low-frequent sessions over a longer period (143). This complementary approach would be a promising topic for future studies in order to determine short- and longer-term effects of specialized AHT on complications. Fourth, we had considerably fewer cases in the specialized PT plus specialized S&LT stratum in the analysis of combination disciplines effects and likely an insufficient statistical power for this analysis. This would be a valuable topic for future studies with even longer follow-up to build upon this. Fifth, we have examined the effectiveness of each therapy in isolation (monotherapy). It would be valuable to investigate specialized AHT that is delivered in parallel by more than one discipline (in one multidisciplinary package), with greater integration across therapists, e.g. by providing joint clinics. On-going evaluations using new integrated care models, such as the PRIME-NL or PRIME-UK care interventions and the evaluation of the lifetime effects of such care models, should provide further evidence on this (144, 145).

Ethical approval and informed consent

Based on Central Committee on Research involving Human Subjects (CCMO), our study does not need an approval of ethics committee. As part of health insurance policy all persons agreed on using their data anonymously for study purposes.

List of abbreviations

PD	Parkinson's Disease
PwP	Persons with Parkinson's disease
AHT	Allied Health Therapy
PT	Physiotherapy
S&LT	Speech & Language Therapy
OT	Occupational Therapy
CCI	Charlson Comorbidity Index

Acknowledgments

The Centre of Expertise for Parkinson and Movement Disorders was supported by a grant from the Parkinson Foundation. The contributions by BRB, SKLD, JHLY, and MM are part of the collaborative Proactive and Integrated Management and Empowerment in Parkinson's Disease (PRIME) project, which is financed by the Gatsby Foundation [GAT3676] and Dutch Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public–private partnerships. The Gatsby Foundation and the Top Sector Life Sciences & Health have a seat in de advisory board of the PRIME Parkinson project, but played no role in the design of the study, analysis, and interpretation of data and in writing of the manuscript. YBS is a recipient of a Radboud Excellence award. The authors thank Vektis for providing access to the healthcare claims data and their continuing collaboration with our research group.

Author contributions

All authors played a substantial role in interpretation of data and reviewing manuscript. The study concept was conceptualized by AHT, JHLY, SKLD, and BRB. AHT, JHLY, and SKLD were responsible for data acquisition. AHT, JHLY, SKLD, TH, and YBS were responsible for statistical analysis and validation. AHT, JHLY, and SKLD drafted the manuscript and all other authors were responsible for reviewing manuscript and providing critical intellectual input.

Financial Disclosures

BRB currently serves as Editor in Chief for the *Journal of Parkinson's disease*, serves on the editorial board of *Practical Neurology* and *Digital Biomarkers*, has received honoraria from serving on the scientific advisory board for Abbvie, Biogen and UCB, has received fees for speaking at conferences from AbbVie, Zambon, Roche,

GE Healthcare and Bial, and has received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, UCB, Abbvie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, the Gatsby Foundation and the Parkinson Vereniging.

YBS has received research support from the UK Medical Research Council, Wellxome Trust, NIHR, Parkinson's UK, Versus Arthritis, Gatsby Foundation, Dunhill Trust.

SKLD was supported in part by a Parkinson's Foundation- Postdoctoral Fellowship (PF-FBS-2026) and a ZonMW Veni Award (09150162010183).

Chapter 4

Effect of Early Levodopa Treatment on Mortality in People with Parkinson's Disease

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Abstract

Background
The ideal timing for initiating levodopa in newly diagnosed people with Parkinson's disease (PD) is uncertain due to limited data on the long-term effects of levodopa.

Objectives
To investigate whether early levodopa initiation postpones mortality (primary outcome), the requirement of device-aided therapies and the incidence of PD-related complications, such as fall-induced injuries.

Methods
Using nationwide claims data from Dutch hospitals (2012-2020), we grouped newly diagnosed PD individuals as 'early initiators' (initiating levodopa within two years of diagnosis) or ' non-early initiators.' We used the national death registry to assess mortality and healthcare claims to assess PD-related complications and device-aided therapies. We used marginal structural models to compare mortality and device-aided therapy rates between groups, and a Poisson regression model to compare PD-related complication rates.

Results
Among 29,943 newly diagnosed PD individuals (mean age at diagnosis 71.6; 38.5% female), there were 24,847 early and 5,096 non-early levodopa initiators. Over a median 4.25 years, 8,109 (27.1%) died. The causal risk ratio for mortality was 1.04 (95%Confidence Interval[CI] 0.92-1.19) for early vs. non-early initiators. The risk ratio of receiving any device-aided therapy was 3.19 (95%CI 2.56-5.80). No association was observed with PD-related complications incidence (incidence rate ratio 1.00, 95%CI 0.96-1.05).

Conclusions
Early levodopa initiation in PD does neither postpone nor accelerate mortality or PD-related complications, nor does it precipitate earlier occurrence of PD-related complications or mortality. However, we cannot exclude that the results were influenced by residual confounding due to unmeasured risk factors of mortality.

Keywords: Parkinson Disease, antiparkinsonian agents, Levodopa, deep brain stimulation, claims analysis

Levodopa has been the main drug treatment for people with Parkinson's Disease (PwP) for more than 50 years (146, 147), due to its effectiveness in reducing symptoms. However, there is still uncertainty what the optimal timing is for levodopa initiation for newly diagnosed PwP (148). In particular, it remains unclear whether symptomatic improvements due to early initiation of levodopa may help prevent complications such as fall-related injuries, which could in turn delay death. Also, it remains unclear whether early initiation of levodopa may exert long-term disease-modifying effects, which would postpone the need for one of the advanced treatment strategies (DBS or pump therapies).

Previous studies on this topic yielded conflicting findings (20, 147, 149-151). One clinical trial found that initiating treatment with levodopa was more effective on quality of life than treatment initiation with other anti-parkinsonian medications (150). A recent observational study found small improvements in motor functioning when treatment with levodopa was initiated early (within two years of diagnosis), suggesting short-term benefits of levodopa on mobility assessments in earlier stages of PD (152). A recent large clinical trial with a study period of 80 weeks found a beneficial symptomatic effect of levodopa during the first 40 weeks but no disease modifying effect of levodopa at the end of trial (149). Historically, there was a notion that the incidence of motor fluctuations and dyskinesia later in the clinical course would occur more frequently in early initiators of levodopa (16). However, there is now robust evidence that the development of these late motor complications is not caused by levodopa initiation, but is rather due to progression of the disease itself, i.e., confounding-by-indication (17). Indeed, this was confirmed very recently in a recent long-term follow-up (5 years) of the LEAP trial (which was a delayed start levodopa study in people with early stage PD), and which showed that there was no difference in prevalence of motor complications between early versus late starters with levodopa over the subsequent 5 years (153).

Another important gap in knowledge that remains concerns the long-term effects of early levodopa initiation on relevant clinical milestones. Examples of such long-term milestones include the incidence of PD-related complications, such as orthopedic injuries or aspiration pneumonia, or the time to deployment of device-aided therapies (deep brain stimulation (DBS) or pump therapies to reach more continuous dopaminergic stimulation). Thus far, no population-based studies have examined the long-term effects of early levodopa initiation on the incidence of these clinical milestones or an mortality.

To address this gap, we used a large healthcare claims dataset comprising all insured PwP in the Netherlands to emulate a target trial. Specifically, we assessed the effect of early levodopa initiation on mortality (primary outcome). We also assessed the effect of early levodopa initiation on the time to receiving an advanced treatment strategy and on the incidence of PD-related complications (secondary outcomes). These latter outcomes were used as proxies to evaluate the long-term effect of early levodopa initiation on disease progression.

Methods

Population

We used a national claims database held by Vektis, which contains the diagnostic and treatment data of more than 99% of the population of the Netherlands. We previously leveraged this database to study the association between specialized allied health therapy and PD-related complications (154, 155). The inclusion and exclusion criteria are explained in table 1. We defined individuals as a newly diagnosed person with PD if they fulfilled both of the following criteria: (I) there was no 30-501 diagnostic identifier, which is the Diagnosis Related Group (DRG) code of PD in the claims based data (156), observed during the two years prior to the diagnosis; and (II) they did not use levodopa during the two years prior to diagnosis. We excluded those PwP who did not fulfill either of these criteria. We considered database entries from January 1st, 2012, until and excluding January 1st, 2021.

Table 1. Study Population Inclusion.

Number	Criteria & Rationale	Status
31349	Newly diagnosed PwP.	Enrolled
1397	PwP whose diagnosis changed from PD to any atypical parkinsonism at the final visit they had in the hospital records.	Excluded
9	PwP for whom we do not have any data records of their SES throughout the entire available dataset.	Excluded
29943	Final population in analysis.	Included

This table shows the Population with newly diagnosed Parkinson's Disease (PwP) between years 2012-2020. PD, Parkinson's Disease; SES, Socio-Economic Status.

Levodopa treatment

Since the prescription of levodopa without a decarboxylase inhibitor is rare due to its intolerability, we defined levodopa treatment as either of the following combinations: a) levodopa and a decarboxylase inhibitor (as indicated by the ATC code N04BA02),

b) levodopa, a decarboxylase-inhibitor, and a COMT-inhibitor (as indicated by the ATC code N04BA03). We defined early levodopa initiation as receiving levodopa within two years after PD diagnosis. We classified all other PwP, including those who initiated levodopa at a later time point and those who never used levodopa during follow-up, as non-early initiators.

Outcome ascertainment

We used the national Dutch death registry to determine mortality as our primary outcome. We report the primary outcome as the average mortality ratio, that would be the (estimated) average probability of death in the early initiators divided by the (estimated) average probability of death in the non-early initiators. Our secondary analysis aimed to address the longer-term associations between early levodopa initiation and disease progression. Since we did not have any specific measurement as a proxy for disease progression in the claims data, we used two secondary outcomes, namely time to receiving one of the device-aided therapies and the incidence rate ratio of PD-related complications. Device-aided therapies was defined as one of the three following treatments: DBS; levodopa-carbidopa intestinal gel pump therapy; and continuous subcutaneous apomorphine pump therapy. In this secondary analysis we followed the individuals until the first receipt of any device-aided therapy, death, or Jan 1st, 2021 (study end date). We used a similar method to estimate the likelihood of receiving device-aided therapies as average mortality ratio. Therefore, we similarly report the average causal risk ratio of receiving any device-aided therapies, by dividing the (estimated) average probability of receiving any device-aided therapy in the early initiators by the (estimated) average probability of receiving any device-aided therapy in the non-early initiators. PD-related complications were defined as a composite endpoint of pneumonia or orthopedic injuries, similar to two prior studies in our group (13, 154).

Follow-up time

Follow-up started from the PD diagnosis and ended with the first of the following events: death or January 1st, 2021 (study end date). We restricted the population to those PwP who had complete data of at least two years, unless they had shorter follow-up due to death.

Covariates

We selected a set of relevant covariates based on our scientific and clinical knowledge to minimize the potential risks of bias and time-varying confounding.

We used time-invariant baseline demographics, namely age at diagnosis, sex, receiving other anti-parkinsonian drugs during the first two years post diagnosis, and the most frequently visited healthcare setting. The healthcare setting is a categorical variable corresponding to different care levels: *university hospital*, which includes care covered by special medical operations in university medical centers; *top clinic*, which also includes care covered by special medical operations, but not in university medical centers; *general clinic*, which only covers basic care needs; or *other types clinic* (157).

We also used a number of time-varying covariates, including PD-related complications, weighted Charlson Comorbidity Index score (*see supplementary methods - A Practical Note on Modified Charlson Comorbidity Index Score*), and Socioeconomic status (SES), the last of which varied based on individualized annually updated data. SES in the Netherlands builds upon characteristics such as the level of income, education, and the employment status of people living in each neighborhood (132).

Statistical analysis

In the primary analysis, we assessed the average causal effect of early initiation of levodopa on mortality. To address the problem of time-varying confounding in an observational design we computed inverse probability (IP) weights to correct for covariate imbalance in the two groups *(see supplementary methods – Inverse Probability Weights)*. Both time-invariant and time-variant covariates were incorporated into the IP weights equation *(see supplementary methods – Equation 1)*. We then used the IP weights to fit Marginal Structural Models (MSM) (158). In our analysis, we handled those PwP who had less than two years of follow-up due to death the same as those with incomplete treatment history (*see supplementary methods - People with Incomplete Treatment History)*. The methodology used to compute the IP weights and to fit outcome MSMs is explained in detail in the supplementary methods. We used the bootstrap statistical method by fitting the models on multiple random resamples (by re-sampling with replacement from the main data 1000 times) to calculate the 95% bootstrap confidence interval (95% CI).

Sensitivity analysis

We conducted a sensitivity analysis to ascertain the robustness of our findings. Since we were not completely certain about identifying the newly diagnosed PwP from the data we had available, we changed our identification criteria by shifting the period of not observing 30-0501 during the previous two years to not observing 30-0501 during the previous i) three years and ii) one year before diagnosis.

We conducted all analyses in the R statistical software package, version 3.4.3.

Results

Baseline characteristics

From a total of 31,349 newly diagnosed PwP, 29,943 (mean age 71.6, SD 10.0) had the defined criteria to enroll in the analysis (*table 1*). Out of these, 24,847 were early levodopa initiators (83% of the study population) and 5,096 were non-early initiators (17% of the study population) (*table 2*). Early levodopa initiators were older, were less often female, had PD-related complications less frequently, used other anti-parkinsonian drugs during the first two years post diagnosis more often, and had slightly fewer comorbid disorders (*table 2*). The mean (SD) peak daily dosage of levodopa within first two years after diagnosis was 90.1 (52.8) mg among the early levodopa initiators. 24847 (83%) initiated levodopa in the first two years after diagnosis, 1523 (5%) initiated levodopa after the first two years after diagnosis, and 3573 (12%) never initiated levodopa during follow-up. The non-early levodopa initiators comprise both late and never initiators, who have an average disease duration of 5.53 (2.20) and 4.10 (2.38) respectively.

Table 2. Baseline Characteristics.

Characteristic	Total	Early Levodopa Initiators	non-Early Levodopa Initiators
N	29943	24847 (83%)	5096 (17%)
Age (SD)	71.6(10.0)	72.0 (9.6)	69.5 (11.4)
Sex (female)	11519 (38.5%)	9521 (38.3%)	1998 (39.2%)
SES [a] (SD)	-0.1 (1.1)	-0.1 (1.1)	-0.1 (1.2)
PwP with at least one PD-related complication [b]	717 (2.4%)	581 (2.3%)	136 (2.7%)
CCI score [c] (SD)	3.8 (1.7)	3.9 (1.6)	3.7 (1.8)
Other anti-parkinsonian medications (e.g., Dopamine agonists) during the first two years after diagnosis, N (%)	5348 (17.9%)	4479 (18.0%)	869 (17.1%)
Hospital setting			
General, N (%)	12861 (43.0%)	10679 (43.0%)	2182 (42.8%)
Other, N (%)	151 (0.5%)	111 (0.4%)	40 (0.8%)
Top clinical center, N (%)	14874 (49.7%)	12404 (49.9%)	2470 (48.5%)
UMC, N (%)	2057 (6.9%)	1653 (6.7%)	404 (7.9%)

Early, levodopa initiated within the first two years post-diagnosis; non-Early, levodopa has not been initiated within the first two years or ever post-diagnosis; UMC, University Medical Center.

[a] Standardized socioeconomic status is derived from characteristics such as education, income, and employment status of people in each neighborhood.

[b] Complications are defined as any fracture or orthopedic injury or pneumonia.

[c] Weighted scores for each comorbid disorder were calculated based on Charlson Comorbidity Index.

Continuous variables are expressed as mean (Standard Deviation), Categorical variables are expressed as number of people (percentage)

Primary analysis

The total numbers of person-years at risk of mortality was 107,946.8 for early initiators and 23,491.25 for non-early initiators (*table 3*). After a median of 4.25 years of follow-up, 8,109 (27.1%) PwP died, out of whom 6,711 had been early levodopa initiators and 1,398 had been non-early initiators (*table 3*). The estimated average mortality ratio of early levodopa initiation using a weighted MSM, was 1.04 (95% Confidence Interval [95%CI] 0.92-1.19) (*table 3*). The mortality ratios obtained in our sensitivity analyses were consistent with our main result. The estimated mortality causal risk ratio of early levodopa initiation, when we changed the criteria of newly diagnosed PwP to not having the 30-0501 PD diagnostic code during the previous three years before diagnosis was 1.04 (95%CI 0.93-1.19) and when we changed the criteria to not having diagnostic code during the previous one year before diagnosis was 1.03 (95%CI 0.90-1.16) (*supplementary tables 1 & 2*).

Table 3. The Time of Levodopa Initiation and the Mortality Rate Ratio.

	Total	**Early**	**non-Early**
Number deaths (%)	8109 (27.1%)	6711 (27.0%)	1398 (27.4%)
Person-years at risk for mortality	131438	107946.8	23491.25
Death rate	0.062	0.062	0.060
Crude death ratio*		0.98	
Mortality risk ratio (95 % CI)**		1.04 (0.92-1.19)	

Early, levodopa treatment initiated within the first two years post-diagnosis; non-Early, levodopa treatment has not been initiated within the first two years or ever post-diagnosis.
*Represents the division of percentage number of deaths in early vs. non-early group
**represents the value computed by the model adjusted with IPW

Secondary analysis

Early levodopa initiation and device-aided therapies

The total numbers of person-years at risk of receiving any device-aided therapy was 107,823.8 for early initiators and 23,488 for non-early initiators (*table 4*). During follow-up, 558 (1.9%) PwP received device-aided therapies, out of whom 485 had been early and 73 had been non-early initiators (*table 4*). The average causal risk ratio of receiving any device-aided therapy, computed using a weighted MSM, was 3.19 (95%CI 2.56-5.80) for early vs. non-early levodopa initiators. The total numbers of person-years at risk of receiving only DBS was 107,932.2 for early initiators and 23,496.5 for non-early initiators (*table 4*). At the end of follow-up, 295 (1.9%) PwP received DBS, out of whom 260 had been early and 35 had been non-early initiators (*table 4*). The average causal risk ratio of receiving DBS, was 4.58 (95%CI 3.11-9.62)

Table 4. The Time of Levodopa Initiation and the Risk Ratio of Receiving Advanced Device-Aided Therapies.

	any Device-Aided Therapy			**DBS**			**Infusion Pump Therapies**		
	Total	**Early**	**non-Early**	**Total**	**Early**	**non-Early**	**Total**	**Early**	**non-Early**
N	29902	24809	5093	29940	24844	5096	29904	24811	5093
N used device-aided therapies	558(1.9%)	485(2%)	73(1.4%)	295(1.0%)	260(1.0%)	35(0.7%)	272(0.9%)	234(0.9%)	38(0.7%)
Person-years	131311.8	107823.8	23488	131428.8	107932.2	23496.5	131315.8	107833	23482.75
Rate of using device-aided therapies	0.0042	0.0045	0.0031	0.002	0.002	0.001	0.002	0.002	0.002
Risk ratio (95 % CI)		3.19 (2.56-5.80)			4.58 (3.11-9.62)			3.32 (2.09-8.43)	

Early, levodopa treatment initiated within the first two years post-diagnosis; non-Early, levodopa treatment has not been initiated within the first two years or ever post-diagnosis; DBS, Deep Brain Stimulation.

In the group who had device-aided therapies, follow-up ends at the date they received device-aided therapy and in the group that did not receive any device-aided therapy, the follow-up ends at either death or censoring (administrative end of follow-up which is 2021-01-01).

for early vs. non-early levodopa initiators. The total numbers of person-years at risk of receiving only levodopa-carbidopa pump form was 107,833 for early initiators and 23,482.75 for non-early initiators (*table 4*). At the end of follow-up, 272 (0.9%) PwP received levodopa-carbidopa pump form, out of whom 234 had been early and 38 had been non-early initiators (*table 4*). The average causal risk ratio of receiving levodopa-carbidopa pump form was 3.32 (95%CI 2.09-8.43) for early vs. non-early levodopa initiators (*table 4*).

Effect of early levodopa initiation on PD-related complications

Early levodopa initiation was associated with an increased rate of PD-related complications (Incidence Rate Ratio [IRR] of early vs. non-early initiators = 1.19, 95%CI 1.11–1.27) (*see Table 5*). However, after adjustment via the inverse probability treatment weights in the model, there was no association left between early levodopa initiation and the rate of PD-related complications (Incidence Rate Ratio [IRR] of early vs. non-early initiators = 1.00, 95%CI 0.96-1.05).

Table 5. The Time of Levodopa Initiation and the Risk of each PD-Related Complication

	N comp	**Time to comp (person-years)**	**Rate**	**IRR (95% CI)**	**IRR (95% CI)** **
Complications (Overall)	7258	1520490	0.005		
Early	6064	1226542.8	0.005	1.19* (1.11-1.27)	1.00 (0.96-1.05)
non-Early	1194	293947.5	0.004		

Early, levodopa treatment initiated within the first two years post-diagnosis; non-Early, levodopa treatment has not been initiated within the first two years or ever post-diagnosis; N Comp, number of PD-related complications; IRR, incidence rate ratio of early vs. non-Early (reference) levodopa initiators, adjusted for age, sex, SES, CCI weighted score, and hospital setting at baseline; CI, confidence interval.
*Statistically significant
**After adjusting for inverse probability treatment weights

Discussion

Levodopa is the most commonly prescribed medication for treating PD in most countries around the globe. Although introduced over 50 years ago, the timing of levodopa treatment initiation in PwP remains debated among clinicians and PwP. Some studies suggest that early levodopa initiation may lead to better short-term outcomes (slower rate of symptom progression, and better motor functioning) (149, 152). However, some PwP prefer to hold off on initiating levodopa for several years (20). Insights into long-term effects would help in making an informed decision about

treatment initiation, and the present data offer such insights. Specifically, we present the first population-based study to evaluate the effect of early levodopa initiation on both mortality and late clinical milestones. We observed no evidence to support the notion that early levodopa initiation has a beneficial effect on long-term clinical outcomes in PwP, but we neither observed any detrimental effects.

Limitations

Before interpreting these findings we first note several limitations. First, given the observational nature of this study, PwP were not randomized to either early or non-early initiation of levodopa. This means that the clinical decision to (not) initiate early on may have been influenced by the severity of the clinical PD presentation, i.e. confounding-by-indication. We accounted for this as much as possible by adjusting for potential confounders which we could measure by means of an advanced analytical approach (IP weighting), but we cannot rule out that residual confounding-by-indication by other unmeasured characteristics occurred. The attenuation of the positive association between early levodopa initiation and incidence of PD-related complications after adjustment for covariables may support the notion that there was confounding-by-indication, although we did not observe a similar attenuation in other analyses. Residual confounding could also be due to the lack of data on orthostatic hypotension, rapid eye movement sleep behavior disorder, PD subtype or genetic status, which are all relevant predictors of survival.

Second, a limitation of this study is that it relied on a diagnostic code of PD for which no specific validation study has previously been conducted. We believe that it is conceivable that this led to under-detection of PD cases (i.e. false-negative cases), but that it is unlikely that there was substantial erroneous classification of individuals as having PD (i.e. false-positive cases), because of three reasons. The first is that diagnostic codes for other diseases have previously been demonstrated to have very high (>99%) specificity in this national claims database (159), albeit with lower estimates of sensitivity, suggesting that not all cases with a disease are registered. The second is that these diagnoses were made by neurologist (mostly a generically trained one, although a smaller proportion of the patients will have been seen by a movement disorders expert), according to accepted international diagnostic criteria which are part of the national guideline for the diagnosis and management of PD (160). As such, this database is much more reliable than e.g. mortality registries or registries based on use of dopaminergic medication. But we do acknowledge that there is a proportion of misclassification in the hands of generically trained neurologists, in particular concerning the differential diagnosis of PD versus atypical parkinsonism (note that the database contains separate codes for PD vs. atypical parkinsonism, as

a prerequisite for reimbursement). The third is that we have previously replicated various associations between established risk factors of PD in this database (13, 154).

Strengths compared to previous research

A recent observational study, which was conducted on data from the Parkinson Progression Marker Initiative (PPMI) study (161), showed that early initiation of levodopa did not worsen motor outcomes in PwP and possibly offered small improvements (152). Our current study builds on that study in several ways. We had a considerably longer follow-up (maximum of nine years vs. maximum of four years in the previous study) and a much larger population (n=29,943 vs. n=423). While in our study we did not directly measure the cumulative duration of levodopa use and its impact on survival, it represents an important factor in the existing literature on the association between levodopa treatment and mortality in PD. Previous population-based studies suggested a reduction in the risk of mortality following levodopa initiation, regardless of pre-levodopa duration of illness (162, 163). In another population-based study with over 20 years of follow-up, researchers investigated the impact of levodopa initiation timing on the survival of people with PD, revealing that early levodopa treatment was associated with higher life expectancy compared to delayed treatment, highlighting the detrimental effect of delaying levodopa to more advanced stages of the disease (164). In a previous multicenter study of 359 individuals with PD, early initiation of dopa treatment was linked to a reduced mortality risk; however, the study did not clearly specify the type of anti-parkinsonian drug considered as dopa treatment (165). Discrepancies in the impact of levodopa initiation on mortality are raised in another study, where researchers analyzed data from 474 people with parkinsonism, employing covariates such as age at onset, initial symptom manifestation, and levodopa treatment to investigate survival factors. They observed that initiating levodopa treatment at any point in time was associated with higher mortality risk, although disentangling its effect from other treatment-related factors proved challenging (166). However, it is worth noting that all these studies utilized conventional "associational" statistical methods, which contrasts with our approach.

Our findings

Concluding on a definite causal relationship is challenging due to the observational nature of this study. We addressed this challenge in two ways. By implementing statistical methods for causal inference (i.e., MSM estimated with IPW) we addressed time-varying confounding. Also, our findings were found to be consistent over two different sensitivity scenarios.

We observed that PwP who initiated levodopa treatment early had similar levels of mortality compared to those who never initiated or initiated their levodopa later than two years post-diagnosis. These findings are in line with a previous study that found an equal survival among early and late levodopa initiators by employing a more generic analytical method (167). However, we employed a more advanced analytical method, and we also studied a larger population with much longer follow-up.

Our secondary analysis suggests that PwP who initiated levodopa early had a higher chance of receiving any device-aided therapy than those in the non-early initiation group. We conducted this specific analysis with the goal of using these advanced treatment strategies as a proxy variable of disease progression in PwP.

We observed a higher chance for receiving any separate device-aided therapy in PwP who initiated levodopa early. This finding suggests that individuals who require early initiation of levodopa already have greater disability (possibly because of more profound depletion of endogenous nigrostriatal dopamine production). It is conceivable that early initiators -compared to non-early initiators- also develop more severe motor fluctuations within fewer years, necessitating the initiation of advanced (continuous) dopaminergic treatment. Alternatively, we cannot rule out that our results reflect a harmful effect of early levodopa initiation on disease progression, although we are unaware of evidence for a plausible mechanism that would explain such a harmful effect. Furthermore, we adjusted all our analyses for age to account for a residual difference in age between two groups.

Finally, we observed that non-early initiators, who were younger than early initiators, had a lower incidence rate of PD-related complications. However, this difference in incidence rate of PD-related complications between both groups disappeared after we adjusted this effect using IP weights, supporting the presence of confounding-by-indication. Early levodopa initiation in PD does not postpone mortality or PD-related complications, nor does it lead to earlier occurrence of PD-related complications or death. This finding is also supported in previous literature (21, 149, 152, 153). This is particularly important given the reluctance of some people with PD to commence levodopa therapy due to unsubstantiated concerns that this would lead to motor fluctuations such as dyskinesia (18, 20, 168).

Implications for future research

Several suggestions could be made for future studies on the effects of early levodopa initiation. First, there is a need for studying the effect of early levodopa initiation in lower-income countries. Second, use of patient-centered outcomes, including wearable sensor technologies and mobile health apps, could help capture the perspectives of patients and caregivers regarding the impact of early levodopa initiation on daily activities, quality of life, disease progression, and overall well-being. Third, exploring the long-term effects of early initiation of common anti-parkinsonian drugs, such as dopamine agonists, on the development of response fluctuations should be examined in future studies. Additionally, given the association of these anti-parkinsonian drugs with an increased risk of neuropsychiatric complications in older individuals with PD, future research could investigate whether delaying levodopa initiation is linked to higher neuropsychiatric burdens in older PD populations who initially receive dopaminergic treatment with drugs other than levodopa. Fourth, future observational studies should explore factors such as orthostatic hypotension and rapid eye movement sleep behavior disorders as additional factors to account for residual confounding. The same applies to testing for genetic forms.

Acknowledgments

The authors thank Vektis for providing access to the healthcare claims data and their continuing collaboration with our research group.

Author Roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

A.H.T.: 1A, 1B, 1C, 2B, 3A
S.K.L.D.: 1A, 1B, 2A, 2C, 3A, 3B
B.R.B.: 1A, 2C, 3B
I.G.B.: 1A, 1B, 2A, 2C, 3A, 3B
T.H.: 1A, 1B, 2A, 2C, 3B

Disclosures

Funding Sources and Conflict of Interest
This research is part of the Proactive and Integrated Management and Empowerment in Parkinson's Disease (PRIME Parkinson) project, which is a healthcare innovation project in selected areas of the United Kingdom and the Netherlands. The PRIME Parkinson project was funded by the Gatsby Foundation [GAT3676] as well as by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships. The Center of Expertise for Parkinson & Movement Disorders was supported by a center of excellence grant by the Parkinson Foundation.

There are no conflicts of interests related to the research in this report.

Financial Disclosures for the previous 12 months
A.H.T. and I.G.B. have no financial disclosures to report. B.R.B. currently serves as Editor in Chief for *Journal of Parkinson's disease;* serves on the editorial board of *Practical Neurology* and *Digital Biomarkers;* has received honoraria from serving on the scientific advisory board for AbbVie, Biogen, and UCB; has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare, and Bial; and has received research support from the Netherlands Organization for Scientific Research, The Michael J. Fox Foundation, UCB, AbbVie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, the Gatsby Foundation, and the Parkinson Vereniging. T.H. has no financial disclosures to report. S.K.L.D. has received funding from the Parkinson's Foundation (PF-FBS-2026), ZonMW (09150162010183), ParkinsonNL (P2022-07 and P2021-14), Michael J Fox Foundation (MJFF-022767) and Edmond J Safra Foundation.

Ethical Compliance Statement
Based on Central Committee on Research involving Human Subjects (CCMO), the authors confirm that patient consent was not required for this work and our study does not need an approval of ethics committee. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. As part of health insurance policy, all persons agreed on using their data anonymously for study purposes.

Data Sharing Statement

Data are available on request, within the constraints of medical claims data privacy laws in the Netherlands. Interested researchers can contact the corresponding author of this study.

Supporting Information

Supporting information may be found in the online version of this article.

Supplementary methods. Explanation of the Inverse Probability Weights, Outcome Model: Weighted Marginal Structural Model, People with Incomplete Treatment History, A Practical Note on Modified Charlson Comorbidity Index Score, Handling of Missing Data,

Sensitivity Table 1. Flowchart of eligible study population *(population with Parkinson's disease between years 2012-2020)* – Selected by not having the PD diagnostic code during the previous recent three years.

Sensitivity Table 2. Flowchart of eligible study population *(population with Parkinson's disease between years 2012-2020)* – Selected by not having the PD diagnostic code during the previous recent one year.

4

Chapter 5

Summary

Summary (English)

Leveraging claims-data to improve care for people with Parkinson's disease

In **chapter 1**, I introduce the key components of optimal clinical care for people with Parkinson's disease (PD) and briefly discuss several knowledge gaps in the current treatment of PD, including both non-pharmacological and pharmacological interventions. The overall aim of my thesis is to determine whether the care for people with PD can be improved by leveraging medical claims data. I specifically focus on the clinical effects of a key set of non-pharmacological therapies, namely specialized allied health interventions, and of the most commonly used pharmacological therapy in PD, namely levodopa.

Specialized care for people with Parkinson's disease: an appraisal of the literature

In **chapter 2**, I conduct a review of the literature on specialized allied healthcare for persons with PD. I critically appraise the literature on what constitutes *specialized* care in this context, what various allied health therapies can offer, what domains of daily life they tackle, and what their (cost-)effectiveness is in PD. I also give directions for future research on specialized allied healthcare for PD. My main conclusions are as follows:

- Specialized physiotherapy, particularly through aerobic exercise and various treatment modalities such as movement strategy training, demonstrates promising positive effects on motor and non-motor symptoms, and on quality of life in PD. The supporting scientific evidence for this professional allied health discipline is highest, compared to the other allied health interventions.
- Evidence from clinical trials indicates the effectiveness of specialized occupational therapy in PD on daily life activities and performance in dexterity-related activities.
- Specialized speech & language therapy improves voice loudness, functional communication and also shows effectiveness in the management of dysphagia (which reduces pneumonia risk) and drooling.

Specialized allied health therapies for people with Parkinson's disease: a claims-data approach

In **Chapter 3**, I utilize claims data from individuals with PD in the Netherlands, investigating the effects of the three most commonly deployed of allied health disciplines (namely physiotherapy, occupational therapy, and speech & language therapy). I conduct rigorous analyses, adjusting for demographic and clinical

variables and employing a composite endpoint of orthopedic injuries or pneumonia to compare the effectiveness of specialized care (namely allied health therapies delivered by ParkinsonNet-educated therapists) versus a generic form of care (the same allied health interventions, but delivered by generically trained therapist). My main findings are as follows:

- Specialized allied health therapies, when delivered by professionals trained specifically in the management of persons with PD, are associated with a lower incidence of PD-related complications.
- Discipline-specific analyses reveal that specialized physiotherapy and occupational therapy are linked to a reduced rate of PD-related complications.
- The putative beneficial effects of specialized occupational therapy are more pronounced in patients who are also treated by a specialized physiotherapist. This suggests that these two allied health disciplines have a synergistic effect
- Specific allied health disciplines show specific effectiveness, with specialized physiotherapy linked to fewer orthopedic injuries and specialized speech & language therapy associated with lower pneumonia rates.
- Sustainability analyses post-treatment cessation indicate a gradual decline in the benefits, with evidence of persisting effects for up to three months for specialized physiotherapy.

Early levodopa treatment for people with Parkinson's disease: a claims-data approach

The optimal timing of levodopa initiation in people newly diagnosed with PD remains a matter of debate because data on the long-term effects of levodopa are scarce. In **chapter 4**, I address this gap by examining whether early levodopa initiation postpones mortality (primary objective), delays the time to the need for initiation of advanced treatment or delays the incidence of PD-related complications (secondary objectives). My main findings are as follows:

- Early levodopa initiation does not impact mortality.
- Early levodopa initiation is associated with a higher likelihood of receiving advanced dopaminergic treatments such as Deep Brain Stimulation or levodopa-carbidopa pump therapy.
- Early levodopa initiation is not associated with a different rate of PD-related complications, as compared to late levodopa initiation.

A holistic view of key findings

In **chapter 6**, I discuss the key findings of this thesis as well as key methodological considerations in interpreting these findings. I outline remaining key gaps in knowledge regarding specialized care and early levodopa treatment and provide directions for future research on these topics.

Chapter 6

General discussion

General discussion

The overall aim of my thesis was to determine whether the care for people with PD could be improved by leveraging a big data approach, using a large medical claims database as source. Specifically, I focused on a set of common non-pharmacological and pharmacological interventions of PD. From the broad spectrum of non-pharmacological interventions in PD, I focused on three specific allied health therapies (physical therapy, occupational therapy, and speech & language therapy), because these are commonly deployed, and because they address motor and non-motor symptoms that are not alleviated adequately by pharmacological or surgical treatments. For pharmacological therapy, I focused on the most widely prescribed drug for persons with PD, namely levodopa.

I first reviewed the literature to investigate which non-pharmacological therapies are more frequent in PD care, what their impact is, and how they might interact. Then, I used a big data approach, using a large medical claims database as source, to study their effectiveness. Regarding pharmacological interventions, I investigated the long-term effects of levodopa, because some patients and clinicians have historically been afraid to initiate levodopa in an early disease phase because of fear of potential levodopa toxicity, or the risk of developing response fluctuations. Specifically, I investigated whether initiating levodopa early in the disease course had a beneficial effect on long-term clinical milestones in PD. For all of these studies in this thesis, my intended outcome was to provide novel insights to inform clinical decision-making.

Below, I describe the main findings of my thesis in a broad context and discuss the implications of my work for clinical practice and research. First, I delve into non-pharmacological interventions, then into pharmacological interventions, followed by discussing some limitations and directions for future research.

Non-pharmacological interventions of Parkinson's disease

Convergence in Parkinson's disease specialized allied health therapies: Evaluating treatment components across multiple disciplines

In **chapter 2**, I reviewed the literature on allied health therapies for people with PD. I focused specifically on specialized physiotherapy, occupational therapy, and speech & language therapy, as these are the most widely deployed and also the most widely studied allied health disciplines in the field of PD. My main observation was that specialized physiotherapy was the most extensively studied professional discipline,

and this included multiple Randomized Clinical Trials (RCT) (169-177). Taken together, I identified robust evidence for positive effects on motor functioning, quality of life and the prevention of PD-related complications (68). My review also revealed that there are still limitations in our current knowledge on the cost-effectiveness of specialized physiotherapy. Also, in many RCTs to date, it was not exactly clear what constituted 'specialized' therapy (which I would define as treatment delivered by therapists who have received some dedicated extra training to become optimally equipped for the management of persons with PD). This means that some of the prior results may in part reflect what can be achieved when the treatment is delivered by a generically trained therapist who may not have received such extra dedicated training in the field of PD. The fact that the level of expertise was often not specified in prior publications might be due to the lack of uniform criteria that can differentiate generic from specialized physiotherapy for PD. Consequently, it is currently difficult to determine whether PD patients, or at least specific subgroups among them, would benefit from referral to a specialized physiotherapist.

Some RCTs examined the efficacy of occupational therapy in PD, and the results suggested improvements in activity performance (78, 80), as well as short-term improvements in dexterity-related activities of daily living (178). The limited available evidence regarding occupational therapy underscores an urgent requirement for further research. Specifically, there is a scarcity of research on the effectiveness of specialized occupational therapy as a standalone discipline in preventing complications, such as falls in people with PD. For specialized speech & language therapy, most current knowledge is based on observational studies. These studies showed the effectiveness of therapies like the Lee Silverman Voice Treatment (LSVT) in enhancing voice loudness and functional communication in people with PD (179). To date, a limited number of RCTs as shown the efficacy of specialized speech & language therapy strategies, ranging from direct swallowing exercises to indirect methods like expiratory muscle strength training (EMST) in the management of dysphagia in PD (98). Moreover, an RCT showed the efficacy of intensive skills training for effective coughing and lowering the risks of aspiration (99). The costs of specialized speech & language therapy compared to usual care have not been studied robustly.

These three specialized allied health therapies complement each other, but also share some overlapping goals to enhance the quality of life in people with PD. However, there is a gap in evidence regarding potential synergistic effects across multiple disciplines of specialized care (**chapter 2**). Analyzing the claims data of specialized allied health disciplines in **chapter 3**, I observed not only that specialized

physiotherapy is associated with a lower rate of PD-related complications, but also that specialized occupational therapy has a protective effect on these complications. Specialized speech & language therapy was also associated with a lower rate of complications, although this finding was not statistically significant. I also found that a combination of specialized allied health therapies is associated with a further reduction in the incidence of PD-related complications, suggesting a synergistic [or perhaps additive] effect. My analysis revealed that most of the study population received specialized physiotherapy as part of their treatment plan. I observed that the inverse association between the level of professional expertise (specialized vs. generic) and the incidence rate of PD-related complications (among people who received specialized occupational therapy and any level of physiotherapy) only persisted in those individuals who received both specialized occupational therapy and specialized physiotherapy. Furthermore, different specialized allied health therapies may prevent different complications. Specifically, my analysis showed that the beneficial effect of specialized (vs. generic) any-discipline allied health therapy (i.e., therapies combination) and physiotherapy on reducing the rate of complications slowly declines as a function of time post-treatment cessation.

Although my findings offer valuable targets for further PD care improvement, several important questions remain. The finding that the effect of specialized care wanes post-treatment raises questions about the optimal treatment regimens, such as intensity and frequency of specialized care, and also the duration of treatment. This raises important questions, because if a lifelong maintenance therapy is advisable, then this would certainly be associated with a marked increase in healthcare costs, which may preclude other critical treatments. These questions have been highlighted in a recent RCT (180). This RCT, delivering a total of 12 physiotherapy sessions, randomized participants into a burst approach (two sessions weekly for 6 weeks) and a spaced approach (one session every 2 weeks for 6 months). The RCT findings unveiled the ability of the spaced approach to sustain improvements in Timed Up and Go (TUG) scores among participants over the 6-month follow-up post-treatment cessation. In contrast, the conventional burst approach showed a significant worsening of the physical functioning throughout the six-month period after therapy cessation. Future treatment guidelines for specialized care should be influenced by the insights from these findings. Furthermore, not every newly diagnosed person will benefit equally from specialized (physio-)therapy, and this will depend for example on their clinical profile and personal priorities. This is while the European guideline of physiotherapy for PD clearly recommends referring every patient early to physiotherapy, for physical activity advice (181). Optimal allocation of specialized therapists in resource-limited settings requires prioritizing based on individual

needs and utilizing screening algorithms to identify high-risk cases for targeted care. This applies to the selection of people with PD for all specialized therapies that are commonly used in PD care. For instance, screening for swallowing deficits is a good example of identifying optimal candidates for targeted care by speech & language therapists. Notably, another question is whether other allied health therapies, beyond those currently considered in the present thesis, are also effective in PD care. Examples of other professional disciplines include psychiatrist, pharmacologist, dietician, clinical geriatrician, sexologist, neuropsychologist, and social worker. This will have to be studied for each professional discipline specifically, with a specific focus on the outcomes that are targeted by this type of intervention. On a related note, it is important to consider whether the outcomes typically measured in studies on the effectiveness of specialized allied health therapies, including those used in **chapter 3**, are the pertinent metrics for assessing all dimensions of PD, or whether factors such as institutionalization or mortality would better indicate the impact. These latter two could better capture the disabilities caused by PD and demonstrate the impact on reducing the burden of the disease.

Pharmacological interventions of Parkinson's disease

Decoding Levodopa: Unravelling the timing and duration in Parkinson's disease pharmacotherapy

In **chapter 4,** I analyzed a maximum of nine years follow-up healthcare claims data of all the people with PD in the Netherlands who were newly diagnosed (de novo cases). I found that mortality in people with PD who initiated levodopa treatment early, versus those who delayed or never initiated it, was similar. My finding on the mortality outcome could not confirm the benefit of earlier initiation of levodopa in PD, and at least from this one perspective, no recommendation can be made regarding the optimal time to start levodopa (20, 149). There is still a feeling among some clinicians and certainly also among patients that the initiation of levodopa should be postponed until motor symptoms become more pronounced, so that treatment can be postponed, the main motivation being fears about potential levodopa toxicity (182) or concerns about the development of treatment response complications, like dyskinesias (16). There are still uncertainties whether or not levodopa treatment itself is the main reason for the appearance of dyskinesias several years after treatment. Recent evidence suggests that response fluctuations following levodopa initiation are more associated with dose adjustments or disease duration rather than the timing of this treatment following the diagnosis (17), suggesting that these fluctuations that occur within the earlier years post treatment do not have a significant negative effect

on quality of life for most patients. Other studies have in the meantime offered a clear reason to consider early levodopa initiation, showing that an early start of levodopa is associated with greater symptomatic relief, better motor functioning and a better quality of life (149, 152). Although I did not find a beneficial long-term effect of early levodopa treatment on postponing mortality, I neither found arguments that would justify delaying the initiation of this medication, since I observed similar mortality rates between early starters and late starters.

My analyses also indicate that early levodopa initiators have a higher likelihood of receiving device-aided therapies. This possibly indicates a more advanced disease stage that may stem from a more profound depletion of endogenous dopamine production in early initiators, leading to severe motor fluctuations and the need for advanced device-aided therapies. The observed results might also reflect a greater disease severity in early initiators, prompting both early levodopa initiation and the eventual need for advanced medications. Current efforts are underway to explore the use of imaging biomarkers, like dopaminergic scans (DAT-scans), to facilitate an earlier diagnosis of PD and to enable ongoing monitoring of PD progression. Combining DAT-scans with early PD symptoms such as rapid eye movement (REM) sleep behavior disorder can unveil dopaminergic deficits (183, 184). Considering my finding that early initiators of levodopa are more likely to receive advanced device-aided therapies, suggesting a more advanced disease stage at diagnosis, and the promising role of biomarkers in detecting dopaminergic deficits, I believe that future RCTs on the long-term effects of levodopa should incorporate biomarkers as additional outcome measures. Finally, my analysis indicated that there was no difference in the rate of PD-related complications between early levodopa initiators and non-early levodopa initiators. Non-early levodopa initiators showed a lower rate of PD-related complications initially, but no significant difference remained after adjusting for covariates via inverse probability weights. Interestingly, this apparent null finding may point to a balance between the positive and negative impacts of initiating levodopa early. On one hand, levodopa could alleviate bradykinetic gait, potentially reducing complications related to falls. On the flip side, it might also trigger autonomic dysfunction, such as orthostatic hypotension, potentially contributing to an increased risk of falls.

The outcome measures I used in this chapter also demonstrate another significant knowledge gap, namely the long-term effect of levodopa initiation timing in different subtypes of PD, with various progression rates for each. The difference arises mainly because PD progression rates vary relative to factors such as age at diagnosis, dominancy of specific symptoms at presentation, and response to medications (19).

A well-known approach classifies PD into three different subtypes including mild motor-predominant, intermediate, and diffuse malignant. This classification is based on several factors like a motor summary score, but also cognitive impairment, REM sleep behavior disorder and dysautonomia as non-motor features (185). In a recent study (186), these different subtypes displayed distinct profiles in terms of both time to significant milestones (such as repetitive falls, becoming wheelchair-bound, onset of dementia, or institutionalization) and post-diagnosis survival. The diffuse malignant subtype exhibited a shorter duration to milestones and a shorter average lifespan. The intermediate subtype showed intermediate values for both, while the mild motor-predominant form demonstrated longer periods for both milestones and survival. Such a significant difference in progression and survival among different subtypes makes it challenging to study the long-term effects of early levodopa for the various subtypes of PD. Hypothetically, specific detrimental effects of levodopa (such as orthostatic hypotension) could be more pronounced in the diffuse malignant subtype because PD patients with this subtype manifest greater autonomic dysfunction.

Methodological considerations

Electronic healthcare records data

This thesis started during the COVID-19 pandemic, at a time when conducting clinical trials was faced with a significant challenging situation. Using the medical claims database allowed me to perform my research and I could answer my research questions without problem of patient physical availability. However, even if there had been no COVID-19 pandemic, conducting a clinical trial simultaneously evaluating the effectiveness of physiotherapy, occupational therapy, and speech & language therapy in a single study with almost nine years follow up with inclusion of more than 51 thousand people with PD would be impossible. By leveraging already available data in **Chapter 3**, I could efficiently answer important questions that would otherwise have taken years and incurred significant costs in a trial. Additionally, big medical claims database offer a comprehensive view of healthcare in real-life clinical settings while capturing a representative population from all ages, disease severities, and co-morbid conditions. Moreover, utilizing medical claims databases proves to be a cost-efficient alternative to conducting clinical trials because data collection is part of routine healthcare practices and therefore this approach significantly reduces expenses (187).

Although access to this type of data had clear advantages, it also carried its own challenges along the way. One of the challenges of using big claims databases is the advanced statistical models that are used to make assumptions about possible causality in the findings. For example, drawing causal conclusions using advanced statistical models depends on how representative the data sample is, meaning, to what extent the data sample represents and how adequately replicates the characteristics of the larger real population. These advanced models, when applied on a dataset, remain valid only under specific assumptions that might therefore reduce the applicability of the findings to different circumstances. Furthermore, there might be some degrees of inaccuracy in the measurement of study variables (i.e., measurement error) in these types of datasets due to several reasons, such as human error or inconsistent measurement methods (187, 188). Another challenge working with big claims databases incurs technical challenges during the pre-processing and cleaning of raw data before obtaining information from them. These technical challenges may lead to inadvertent coding errors that could, irrespective of how small they are, possibly alter the results in the end.

Causality in observational studies

In both chapters 3 and 4 I used an observational study method and therefore my findings reflect causality only under specific assumptions. In **chapter 3** specifically, key supporting arguments in favor of causality of my findings were as follows: distinct inverse associations between specialized physiotherapy and orthopedic injuries, as well as speech & language therapy and pneumonia, provided mechanistic plausibility (135). Additionally, the gradual diminishment of protective effects post-treatment suggested that the protective effects of specialized allied health therapies were reversible, which would be clinically plausible.

The main challenge in both **chapters 3 and 4** was the lack of randomization between study groups. Randomization boosts the chances of intervention and control groups sharing similar baseline characteristics. In this process, any remaining difference between groups will be due to chance (189). In **chapter 3**, I used covariate adjustment with propensity scores as one additional sensitivity analysis to deal with the lack of randomization, which did not alter my findings compared to the unadjusted estimates. In **chapter 4**, I delved deeper into the observational study methodology, employing the novel inverse probability weighting method (40) to address randomization challenges. This approach effectively handled baseline characteristic imbalances between early versus non-early levodopa initiation subgroups. Additionally, it tackled time-varying confounding in a longitudinal setting where the confounders of the treatment-outcome relationship could be affected by prior

medication use and could also predict the probability of receiving the next medication prescription (190, 191). Despite these efforts, residual confounding-by-indication from unmeasured characteristics remains a potential consideration against the accuracy of my findings.

Future directions for the research

The findings of my thesis pave the way for numerous future research avenues. **Chapter 2** hints at the potential of using modern technology to measure outcomes and utilize big data that is generated by wearable device outputs as additional measures. I anticipate that this will be further investigated in the next years, for instance in an ongoing UK study which employs wearable cueing assistive devices for managing drooling in PD (101). Further investigations should explore the impact of specialized occupational therapy on specific facets like functional cognition and fatigue, emphasizing its role in preventive strategies. This could be achieved by leveraging the specific claims database of using cognition-related drugs or other types of healthcare services used for cognitive well-being, which highlights another potential of big claims databases. Furthermore, exploring the potential of claims databases in PD research, particularly due to the presence of information on medical expenses within these datasets, offers a promising avenue in assessing cost-effectiveness of various treatment plans post-implementation including the economic evaluations of specialized speech & language therapy compared to standard care, which currently warrants attention. **Chapter 3**, by leveraging big data, encourages examining the benefits of specialized allied health therapies in diverse populations and settings, including low- or middle-income countries, and delving into integrated care models involving multiple disciplines. Future research should also focus on the effects of specialized care across different PD stages, incorporating outcome measures such as institutionalization and mortality that could be found in big medical claims databases. Looking ahead, the focus is on embracing patient-centered outcomes through wearable sensors and mobile health apps. This shift aims to uncover the impact of specific treatment choices on daily life, quality of life, disease progression, and overall well-being. The inclusion of both patient and caregiver perspectives in how to optimally leverage big data, while carefully handling privacy concerns, will be pivotal for shaping the future of PD care.

Chapter 7

Dutch summary | Nederlandse samenvatting

Samenvatting (Nederlands)

Zorgverzekeringsgegevens gebruiken om de zorg voor mensen met de ziekte van Parkinson te verbeteren

In **hoofdstuk 1** introduceer ik de belangrijkste onderdelen van de klinische zorg voor mensen met de ziekte van Parkinson en geef ik een kort overzicht van hiaten in de kennis over de huidige behandeling van Parkinson, waaronder zowel niet-farmacologische als farmacologische interventies. Het algemene doel van mijn proefschrift is om te onderzoeken of de zorg voor mensen met Parkinson kan worden verbeterd door gebruik te maken van zorgverzekeringsgegevens. Ik richt me specifiek op de klinische effecten van een belangrijke groep niet-farmacologische therapieën, namelijk gespecialiseerde paramedische interventies, en van de meest gebruikte farmacologische therapie bij Parkinson, namelijk levodopa.

Gespecialiseerde zorg voor mensen met de ziekte van Parkinson: een literatuuroverzicht

In **hoofdstuk 2** geef ik een overzicht van de literatuur over gespecialiseerde zorg voor mensen met de ziekte van Parkinson. Ik evalueer kritisch de literatuur over wat gespecialiseerde zorg in deze context inhoudt, waar verschillende disciplines van gespecialiseerde zorg zich op richten, op welke domeinen van het dagelijks leven ze ingrijpen, en wat hun (kosten)effectiviteit is bij mensen met Parkinson. Ik geef ook aanwijzingen voor toekomstig onderzoek naar gespecialiseerde zorg voor Parkinson. Mijn belangrijkste conclusies zijn als volgt:

- Gespecialiseerde fysiotherapie, met name door middel van aerobe oefeningen en gerichte behandelmodaliteiten zoals beweegstrategietraining, laat veelbelovende positieve effecten zien op motorische en niet-motorische symptomen, en op de kwaliteit van leven bij mensen met Parkinson.
- Uit klinisch onderzoek blijkt dat gespecialiseerde ergotherapie bij Parkinson effectief is in het verbeteren van het dagelijks functioneren en van activiteiten die met de motoriek te maken hebben.
- Gespecialiseerde logopedie verbetert de luidheid van de stem en functionele communicatie bij mensen met Parkinson, en is ook effectief bij de behandeling van slikproblemen en kwijlen, wat het risico op een longontsteking vermindert.

Gespecialiseerde paramedische zorg voor mensen met de ziekte van Parkinson: een benadering op basis van zorgverzekeringsgegevens

In **hoofdstuk 3** maak ik gebruik van zorgverzekeringsgegevens van mensen met Parkinson in Nederland en onderzoek ik de effecten van de drie meest voorkomende

disciplines van gespecialiseerde paramedische zorg (namelijk fysiotherapie, ergotherapie en logopedie). Ik gebruik hiervoor rigoureuze analysetechnieken, waarbij ik corrigeer voor demografische en klinische variabelen. Ik maak gebruik van een samengesteld eindpunt van botbreuken (en andere letsels van het bewegingsapparaat) of longontstekingen om de effectiviteit te vergelijken van zorg die geleverd wordt door gespecialiseerde Parkinson-therapeuten ten opzichte van niet-gespecialiseerde therapeuten. Mijn belangrijkste bevindingen zijn als volgt:

- Gespecialiseerde paramedische behandelingen door getrainde professionals zijn geassocieerd met een lagere incidentie van Parkinson-gerelateerde complicaties.
- Discipline-specifieke analyses laten zien dat gespecialiseerde fysiotherapie en ergotherapie samenhangen met een lagere incidentie van Parkinson-gerelateerde complicaties.
- De beschermende effecten van gespecialiseerde ergotherapie zijn meer uitgesproken bij patiënten die ook behandeld worden door een gespecialiseerde fysiotherapeut.
- Er zijn discipline-specifieke effecten, namelijk dat gespecialiseerde fysiotherapie geassocieerd is met minder botbreuken (en andere letsels van het bewegingsapparaat) en gespecialiseerde logopedie geassocieerd is met minder longontstekingen.
- Na beëindiging van de behandeling treedt een geleidelijke afname op van de gunstige effecten van gespecialiseerde zorg, waarbij de effecten van gespecialiseerde fysiotherapie tot drie maanden na het staken waarneembaar zijn.

Vroege behandeling met levodopa bij mensen met de ziekte van Parkinson: een benadering op basis van zorgverzekeringsgegevens

De optimale timing van het starten met levodopa bij mensen die gediagnosticeerd zijn met de ziekte van Parkinson is momenteel onduidelijk, omdat gegevens over de langetermijneffecten van levodopa schaars zijn. In **hoofdstuk 4** adresseer ik deze kennislacune door te onderzoeken of vroege levodopa-initiatie de mortaliteit (primaire doelstelling), de noodzaak tot het inzetten van geavanceerde behandelingen en/of de incidentie van Parkinson-gerelateerde complicaties (secundaire doelstellingen) uitstelt. Mijn belangrijkste bevindingen zijn als volgt:

- Vroege start van de behandeling met levodopa heeft geen invloed op mortaliteit bij mensen met Parkinson.
- Vroege start van de behandeling met levodopa is geassocieerd met een grotere kans op het ontvangen van geavanceerde dopaminerge behandelingen, zoals diepe hersenstimulatie of levodopa-carbidopa pompvormen, later in het ziektebeloop.
- Vroege start van de behandeling met levodopa heeft geen invloed op het optreden van Parkinson-gerelateerde complicaties.

Een holistische kijk op de belangrijkste bevindingen

In **hoofdstuk 6** bespreek ik de belangrijkste bevindingen van dit proefschrift en de belangrijkste methodologische overwegingen bij het interpreteren van deze bevindingen. Ik schets de belangrijkste kennishiaten over gespecialiseerde paramedische zorg en vroege levodopa behandeling en geef aanwijzingen voor toekomstig onderzoek over deze onderwerpen.

Chapter 8

Appendices

A1. Research data management

Data management plan

Ethics and privacy

No ethical approval or informed consent was needed for the studies in this thesis due to the observational nature of chapters 1 and 2, which were based on a claims database (Vektis). As part of the standard health insurance policy in the Netherlands, all patients included in the claims database had agreed to their data being used anonymously for research purposes. At Vektis the application for data is screened by compliance officers of all health insurers in the Netherlands and approved by the BCVU (Bestuurscommisie Verzekeringen en Uitvoering) consisting of health insurers directors. The original submitted medical claims data is critical and sensitive. The dataset provided by Vektis is anonymized and all factors that enable identification of an individual and competition-sensitive or confidential elements are removed before the data is made available for research. No ethical approval or informed consent was needed for chapter 3, which was based on a literature review.

Data collection and storage

For chapters 1 and 2 I used patient data from the Vektis health insurance company. Medical claims data were submitted by health care providers to health insurers to be eligible for reimbursement, and storing such data is a natural process of the insurance company. The dataset was accessed from Radboud University Medical Center, through a secure connection with the Vektis environment. Therefore, all analyses were performed in the Vektis environment. The output of the analyses (i.e., results) were stored both in the Vektis environment and at the Radboudumc server. Additionally, all the software scripts developed for analysis purposes were extracted and saved in Radboudumc server for future replications. The data of patients were anonymized by Vektis. Other data and outputs, such as manuscript data have been stored on the secured servers of Radboudumc.

Data sharing

The Radboudumc will be the rightsholder of the data, except for data that is delivered and processed and analyzed from Vektis. However, the raw database will only be made available to the research team. For long-term data storage purposes, all medical claims data since 2006 is stored at Vektis. All other data will be stored in the Data Archiving and Network Services (DANS) repository: https://dans.knaw.nl/en . DANS is frequently used as a repository for clinical scientific research at Radboudumc. Data will be stored in accordance with Radboud University's data management

policy: 10 years as a minimum retention period for achieving data. For giving access to medical claims data, Vektis policies do not allow to share data with others, though an official application can be made to Vektis for accessing the dataset for reuse. Data were made reproducible by adding sufficient documentation (research methodology, online supplementary material, codebook, and a readme file for scripts). Regarding the publications, all studies are published open access.

A2. Publications

List of publications and manuscripts

Articles published in this thesis

Talebi AH, Ypinga JHL, deVries NM, Nonnekes J, Munneke M, Bloem BR, Heskes T, Ben-Shlomo Y, Darweesh SKL. Specialized Versus Generic Allied Health Therapy and the Risk of Parkinson's Disease Complications. Movement Disorders, 2023. 38(2): 223-231.

Sturkenboom IHWM, Talebi AH, deVries NM, Darweesh SKL, Kalf JG. Specialized Allied Health Care for Parkinson's Disease: State of the Art and Future Directions. Submitted.

Talebi AH, Darweesh SKL, Bloem BR, Bucur IG, Heskes T. Effect of Early Levodopa Treatment on Mortality in People with Parkinson's Disease. Submitted

Other articles

Gelissen LMY, vdBergh R, Talebi AH, Geerlings AD, Maas BR, Burgler M, Kroeze Y, Meinders MJ, Smink A, Bloem BR, Munneke M, Ben-Shlomo Y, Darweesh SKL. PRIME-NL: Assessing the validity of a Parkinson's care innovation study. Submitted.

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A3. Acknowledgements

Acknowledgements

To my beloved wife, Mahshid,
You are the unwavering pillar of strength in my life, and I am endlessly grateful for your steadfast support throughout not only the intricate journey of my Ph.D. but also the arduous moments of medical school. Your resilience and love have been my guiding light, especially during the challenging moments I encountered. Your unwavering belief in me propelled me forward, and your wholehearted support accompanied me at every step of my Ph.D. thesis. Thank you for being my anchor, my confidante, and my greatest source of inspiration.

To my dear parents,
Your love and support have been the bedrock of my journey, and I am profoundly grateful for the unwavering foundation you provided. From the earliest stages of my life to the challenges of academia, you stood by me with unwavering devotion. Your sacrifices, guidance, and boundless love have shaped me into the person I am today. I am truly blessed to have been raised and nurtured by two incredible individuals who always offered their best. Your constant support, both emotionally and otherwise, has been a source of strength that fueled my pursuit of knowledge. I love you both immensely and thank you for being my unwavering pillars of support.

To my dear sister and brother,
Mohadeseh, from the earliest days of my childhood, your emotional support has been a constant source of comfort. Your guidance and encouragement have been my refuge, and I am deeply grateful for the unwavering bond we share.

Amirreza, you are not just family; you are my best friend. Your companionship, loyalty, and shared laughter have made every challenge more manageable and every success more joyful. I am fortunate to have you by my side, not just as a sibling, but as a cherished confidant.

Thank you both for being integral parts of my journey, offering support, love, and friendship that made the path to my Ph.D. all the more meaningful.

To my beloved extended family,
Grandma Tooba, Grandma Sakineh, Grandpa Hashem, and Grandpa Zolfaqar, your love and wisdom have been the roots of our family tree. Your presence in my life has been a constant source of strength, and I am grateful for the values and traditions you have instilled in me. The unfortunate event of CVA that happened to Grandpa Hashem served as the root inspiration for me to pursue my career goal in medicine, specifically focusing on movement disorders. This inspiration became the driving force behind the research and exploration that culminated in the completion of this thesis.

Aunts Bibi, Zohreh, Banoo, Fereshteh, Fariba, Masoom, Narges, and Parisa, your warmth and care have created a tapestry of love around me. Your encouragement and support have been a guiding light, and I appreciate the love you have showered on me throughout my academic journey.

Uncle Kevan, you have been more than an uncle; you have been my role model since high school. Your mentorship has shaped my aspirations, and I am inspired by the person you are. Your all time support has meant the world to me. Thank you for being not just an uncle but a guiding force in my life.

To my esteemed supervisors,
Bas, you are more than an academic mentor; you are like an academic father to me. Your caring and nurturing approach have shaped not only my professional journey but also my perspective on life. Your unwavering belief in me has been a constant source of inspiration, and I am grateful for the trust and guidance you have provided throughout my Ph.D. journey.

Sirwan, meeting you was a turning point that led to a remarkable opportunity for my Ph.D. Your role as not just a daily supervisor but also an older brother has been invaluable. Your support during my personal life challenges made a significant impact on my well-being, and I always felt your presence as a comforting force during my work.

Tom, from our first meeting, I sensed the wisdom that would inspire me throughout my Ph.D. journey. Your insights and guidance have been instrumental, and I hold great respect for the perspective you have shared.

Gabriel, witnessing your work with computers left an indelible mark on me. Your genius in the field has been a wellspring of inspiration, and your wise guidance along the way of my Ph.D. has been truly transformative.

Thank you all for being not just supervisors but mentors who have shaped my academic and personal growth.

To my dear cousins,
Mohammad, your presence in my life since childhood has been invaluable. From teaching me important life lessons to guiding me through the preparation for the university entrance exam, your support has been unwavering, and I am grateful for the bond we share.

Saeed and Ahmad, you are more than cousins; you are my brothers. We have grown up together, facing life's challenges side by side. Your companionship has been a constant source of joy and strength, and I cherish the memories we have created together.

Amin, your academic achievements have been a beacon of inspiration for me. As an older cousin, your accomplishments have set a high standard, motivating me to strive for excellence in my own academic pursuits. Your success has been a guiding light, and I am grateful for the inspiration you have provided.

To my cherished friends,
From Iran:
Dr. Hamed Asghari and Dr. Arash Mardani, my classmates and friends since kindergarten, have been constants in my life, accompanying me through the challenges of medical school and beyond. Our shared journey holds a special place in my heart, as we grew and learned together.

Dr. Mohammadsobhan Sheikh Andalibi, your guidance in research has been invaluable, and your emotional support has been a pillar during challenging times.

Dr. Ali Khabazzade, meeting you during my obligatory military service turned a challenging period into one of the happiest times in my life. Your friendship was a true blessing.

Dr. Ramin Hassani, Dr. Mehrad Naseri, Dr. Navid Ebrahimipour, and Dr. Mostafa Jami, the fun moments and lovely times we shared are treasured memories that have added joy to my journey.

Dr. Yahya Sajedifar, Dr. Mohammadhossein Hassani, and Dr. Amir Nik, hiking the highest summit of Iran with you during our medical school years stands as one of my greatest sportive achievements. Our shared adventure created bonds that transcend the ordinary.

From the Netherlands:
Iman, Yadollah, Farzaneh, Pouyan, and Jan, your support during my personal life challenges was a testament to the strength of our friendship. Your encouragement and understanding were instrumental in overcoming those difficult moments.

To all my friends, both near and far, thank you for being the pillars of support, the companions in joy, and the shoulders to lean on throughout my academic and personal endeavors.

To my wonderful officemates and colleagues,
Robin and Jules, our weekly update meetings for our Ph.D. thesis were more than just a professional ritual—they were a true source of motivation, marking a memorable journey of accomplishment in my mind.

Bauke, our daily morning coffee and chat sessions were the perfect start to my workday. Your kindness in lending your race bike for cycling in the hills with you and Luc added an extra layer of joy to my time at work.

Luc, thank you for being the patient listener to all my imaginary futuristic ideas during our late-night work sessions. Your patience is admirable, and I will forever be grateful for your lifesaving assistance during the Bike for Parkinson event.

Stacha, Janna, Amber, and Bart, thank you for the delightful conversations that made the work environment lively and enjoyable. Janna, a special thanks for always lending a hand in writing in Dutch for the Parkinson blog.

To all of you, thank you for being the supportive and friendly faces in my work life, contributing to the positive atmosphere that made the challenging task of a Ph.D. all the more manageable.

In closing, I would like to express my heartfelt thanks to all those whose names may have inadvertently missed from this section. This small thank-you note captures just a glimpse of the many individuals who have profoundly impacted my life and academic journey. Countless friends, family members, colleagues, and mentors

have contributed to the person I am today, and I am sincerely grateful for each and every one of them. Though their names may not be explicitly mentioned here, their influence is woven into the fabric of my journey, and I carry their support, encouragement, and kindness with me. Your collective presence has shaped my path in ways beyond measure, and I extend my appreciation to all those who have played a role, no matter how subtle, in the tapestry of my life.

Amir Hossein Talebi
Nijmegen, December 2023

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A4. Curriculum Vitae

Curriculum Vitae

Name: Amir Hossein Talebi, MD

Contact: Amir.talebi.iran.23@gmail.com, Amirhossein.talebi@radboudumc.nl

Current position: PhD Candidate, Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands.

Thesis title: "Leveraging big data to improve care for people with Parkinson's disease"

Summary: "*Medical Doctor and Scientific Researcher in Movement Disorders. With a strong foundation in clinical practice and research, currently wrapping up a Ph.D. adventure. Focused on leveraging health claims data, my research in Parkinson's disease employs advanced analytical methods in causal inference to uncover valuable insights. In addition to my professional endeavors, I have also achieved personal milestones. I successfully summited the highest volcano in Asia, Mount Damavand. I have participated in athletic events to raise awareness for Parkinson such as taking part in the Bike for Parkinson event in 2022. I also completed the Rotterdam Marathon in April 2023.*"

A. ACADEMIC HISTORY

Education:

Jun 2021 – Present Ph.D. Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands. Thesis: "Leveraging Big Data to Improve Care for People with Parkinson's Disease"

Feb 2011 – Apr 2018 M.D. Mashhad University of Medical Sciences

B. EMPLOYMENT HISTORY

Jun 2021 – Present PhD Candidate, Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands

May 2018 – Aug 2018 General Practitioner, Jondi Shapour University of Medical Sciences, Gotvand, Khouzestan, Iran

Aug 2018 – Sep 2019 General Practitioner, Mashhad, Iran

Oct 2019 – Aug 2020 Emergency Physician, North Khorasan University of Medical Sciences, Shirvan, Iran

Sep 2020 – Jun 2021 Funded Research Assistant Position, Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands

C. WORK & RESEARCH SKILLS

Healthcare emergency section management
Programming (**R**)
Microsoft office
Longitudinal and observational study methodology
Medical statistics
Claims-data
Scientific writing
Problem solving
Flexibility
Creativity
Critical thinking

D. GRANTS AND AWARDS

2023 Nominated for the jaarprijs Bewegingsstoornissen
(EN: annual prize movement disorders)

During my PhD program I was partly supported by the PRIME Parkinson project, which is financed by the Gatsby Foundation (grant code: **GAT3676**) (UK) and co-funded by the PPP Allowance made available by **Health~Holland** (https://www.health-holland.com/funding-opportunities/tki-match), Top Sector Life Sciences & Health, to stimulate public-private partnerships.

2011 Accepted in fully funded General Doctorate in Medicine in the National University Entrance Exam out of about 409.000 applicants

E. PUBLICATIONS *(Peer-Reviewed)*

Talebi, A. H., Ypinga, J. H. L., De Vries, N. M., Nonnekes, J., Munneke, M., Bloem, B. R., Heskes, T., Ben-Shlomo, Y., & Darweesh, S. K. L. (**2023**). Specialized Versus Generic Allied Health Therapy and the Risk of Parkinson's Disease Complications.

Movement disorders: official journal of the Movement Disorder Society, 38(2), 223–231. (**IF: 8.6**)

Gelissen, L. M. Y., van den Bergh, R., **Talebi, A. H.**, Geerlings, A. D., Maas, B. R., Burgler, M. M., Kroeze, Y., Smink, A., Bloem, B. R., Munneke, M., Ben-Shlomo, Y., & Darweesh, S. K. L. (**2024**). Assessing the validity of a Parkinson's care evaluation: the PRIME-NL study. European journal of epidemiology, 10.1007/s10654-024-01123-7. Advance online publication. (**IF: 13.6**)

Sturkenboom I., **Talebi, A.H.**, deVries, N.M., Darweesh, S.K.L., Kalf, J.G. REVIEW: Specialized Allied Health Care for Parkinson's Disease: State of the Art and Future Directions Journal of Parkinson's Disease. Journal of Parkinson's Disease. (**IF: 5.2**)

Talebi, A.H., Darweesh, S.K.L., Bloem, B.R., Bucur, I.G., Heskes, T. Effect of Early Levodopa Treatment on Mortality in People with Parkinson's Disease. Movement Disorders Clinical Practice. (**IF: 4.0**)

Sheikh Andalibi, M. S., Rezaei Ardani, A., Amiri, A., Morovatdar, N., **Talebi, A.**, Azarpazhooh, M. R., & Mokhber, N. (**2021**). The Association between Substance Use Disorders and Long-Term Outcome of Stroke: Results from a Population-Based Study of Stroke among 450,229 Urban Citizens. Neuroepidemiology, 55(3), 171–179. (**IF: 5.7**)

Anvari, M., Seddigh, A., Shafei, M. N., Rakhshandeh, H., **Talebi, A. H.**, Tahani, M. R., Saeedjalali, S. M., & Hosseini, M. (**2012**). Nigella sativa extract affects conditioned place preference induced by morphine in rats. Ancient science of life, 32(2), 82–88.

F. CONTRIBUTION AS AN EDITORIAL BOARD OR INVITED PEER-REVIEWER

2022 Neurology **(IF: 10.0)**

2021 European Journal of Neurology (IF: **5.1**)

G. ABSTRACTS & PRESENTATIONS AT INTERNATIONAL CONFERENCES

Talebi, A. H., Ypinga, J., Munneke, M., Bloem, B., & Darweesh, S. (2022, May). Unraveling the Potential of Specialized Allied Health Therapy in Parkinsons Disease. In NEUROLOGY (Vol. 98, No. 18). TWO COMMERCE SQ, 2001 MARKET ST, PHILADELPHIA, PA 19103 USA: LIPPINCOTT WILLIAMS & WILKINS. The 74th AAN Annual Meeting took place in Seattle April 2-7, 2022. **(IF: 10.0)**

AH. Talebi, JHL. Ypinga, M. Munneke, B. Bloem, SKL. Darweesh. Unraveling the Potential of Specialized Allied Health Therapy in Parkinson's Disease [abstract]. Mov Disord. 2022; 37 (suppl 2). The MDS International Congress of Parkinson's Disease and Movement Disorders took place in Madrid, Spain 2022. (**IF: 8.6**)

H. MEMBERSHIP IN PROFESSIONAL ASSOCIATIONS
2023 Movement Disorders Society (MDS)

2022 American Academy of Neurology (AAN)

2018 Iran Medical Council

I. PUBLIC SERVICE & CHARITY
Aug 2018 – Sep 2019 General Practitioner, Doctors Without Borders (MSF), Mashhad, Iran

J. INTERESTS
Sportive Activities and Accomplishments:
2023 Completed 42 kilometers NN marathon, Rotterdam, the Netherlands.

2022 ZEVENHEUVELENLOOP, completed 15 kilometers running event, Nijmegen, the Netherlands.

2022 BIKEVOORPARKINSON, completed 100 kilometers cycling route, "Bike for Parkinson" is the annual unique cycling event where people with Parkinson(ism), loved ones, caregivers and everyone who cares for these people come together to have a cycling day together in the hills of South Limburg and to raise money for a nice Parkinson's project, Limburg, the Netherlands.

2022 – 2023 Player of Radboud university student rugby team, Nijmegen, the Netherlands.

2019 Damavand summit, the highest volcano in Asia, Iran.

K. LANGUAGES
Persian: Native
English: Native or Bilingual proficiency
Khorasani Turkish: Native
Dutch: Limited working proficiency

L. CONTACT REFERENCES

Bas Bloem Radboudumc, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Center of Expertise for Parkinson and Movement Disorders, Netherlands. Full professor

Tom Heskes Institute for Computing and Information Sciences, Radboud University, Netherlands. Full professor

Sirwan Darweesh Radboudumc, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Center of Expertise for Parkinson and Movement Disorders, Netherlands. Neurologist and clinical epidemiologist

Gabriel Bucur Institute for Computing and Information Sciences, Radboud University, Netherlands. Assistant professor

Yoav Ben-Shlomo Population Health Sciences, Bristol Medical School, University of Bristol, UK. Full professor

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A5. Dissertations of the Disorders of Movement research group, Nijmegen

Dissertations of the Disorders of Movement research group, Nijmegen Center of Expertise for Parkinson & Movement Disorders

Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, June 17th 2008.
Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, May 27th 2009.

W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, October 7th 2009.

Samyra H.J. Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, April 29th 2010.

Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, November 29th 2010.

Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, November 29th 2010.

Rick C.G. Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, May 24th 2011.

Ilona B. Bruinsma. Amyloidogenic proteins in Alzheimer's and Parkinson's disease. Interaction with chaperones and inflammation. Radboud University Nijmegen, September21st 2011.

Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, December 6th 2011.

Johanna G. Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, December 22nd 2011.

Anke H. Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen, June 4th 2012.

Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, November 22nd 2012.

Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, February 13th 2013.

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Arlène D. Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, March 6th 2013.

Tjitske Boonstra. The contribution of each leg to bipedal balance control. University Twente, June 6th 2013.

Marjolein A van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, January 20th 2014.

Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, May 21st 2014.

Marjolein B. Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, June 27th 2014. 578030-L-bw-Lennaerts

Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, February 13th 2015.

Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, June 23th 2015.

Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, September 25th 2015.

Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, December 1st 2015.

Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, February 11th 2016.

Merel M. van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, April 13th 2016.

Arno M. Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, June 2nd 2016.

Annette Plouvier. De ziekte van Parkinson, een gezamenlijke reis van huisarts en patiënt. Radboud University Nijmegen, juni 15th 2017.

Nico Weerkamp. Parkinson's disease in long-term-care facilities. Radboud University Nijmegen, September 1st 2017.

Digna de Kam. Postural instability in people with chronic stroke and Parkinson's disease: dynamic perspectives Radboud University Nijmegen, October 4th 2017.

Freek Nieuwhof. The complexity of walking: Cognitive control of gait in aging and Parkinson's disease Radboud University Nijmegen, October 27th 2017.

Koen Klemann. A molecular window into Parkinson's disease. Radboud University Nijmegen, November 3th 2017.

Jeroen Venhovens. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. Radboud University Nijmegen, March 20st, 2018.

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Esther Bekkers. Freezing and postural control in Parkinson's disease. Defense at KU Leuven, May 15th 2018.

Erik te Woerd. Feeling the beat: The neurophysiology of cueing in Parkinson's disease. Radboud University Nijmegen, January 18th 2019.

Ana L. Silva de Lima. Quantifying Parkinson's disease: the use of technology for objective assessment of motor symptoms. Radboud University Nijmegen, March 26th 2019.

Monique Timmer. Neurocognitive mechanisms underlying depression in Parkinson's disease. Radboud University Nijmegen, April 16th, 2019.

Sabine Janssen. Virtual visual cues: vice or virtue? University of Twente, March 11th, 2020.

Anna Santaella Tortós-Sala. Tackling Parkinson's disease: a proteomic approach to biomarkers and regenerative therapy. Radboud University Nijmegen, October 22nd 2020.

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Michiel Dirks. Neural mechanisms of Parkinson's tremor. Radboud University Nijmegen, November 22nd, 2020.

Sjors van de Weijer. Digital technology-enabled home health care: Gamification in online cognitive therapies for Parkinson's disease. Maastricht University, September 1st 2021.

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Danny Hommel. Impairment and disability in late-stage parkinsonism. Radboud University Nijmegen, September 27th, 2021.

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Tamine Capato. Clinical assessment and Management of Balance Impairments in Parkinson's disease. Radboud University Nijmegen, June 29th, 2022.

Herma Lennaerts. Palliative care for people with Parkinson's disease and their family caregivers. Radboud University Nijmegen, July 6th, 2022.

Carlijn Borm. Vision in Parkinson's disease: more than meets the eye. Radboud University Nijmegen, February 22th, 2023.

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Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, April 5th 2012.

Susanne T. de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, December 20th 2013.

Catherine C.S. Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, January 7th 2014.

Ella M.R. Fonteyn. Falls, physiotherapy, and training in patients with degenerative ataxias. Radboud University Nijmegen, June 29th 2016.

Britt Sofie Hoffland. Investigating the role of the cerebellum in idiopathic focal dystonia. Radboud University Nijmegen, March 22nd 2018.

Ilse Eidhof. Common biological denominators and mechanisms underlying ataxialike motor dysfunction: from human to fly, 2 April 2020.

Bas van Lith. Balance and gait problems in people with in hereditary spastic paraplegia, 16 November 2020.

Nienke van Os. Ataxia telangiectasia - disease course and management, 19 March 2021.

8

A6. 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 700 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:

http://www.ru.nl/donders/graduate-school/phd/

A7. Online Supplementary Material

Online Supplementary Material Chapter 2

Supplementary material A. Search strategy

The following search string was entered in PubMed at 2024/01/10:

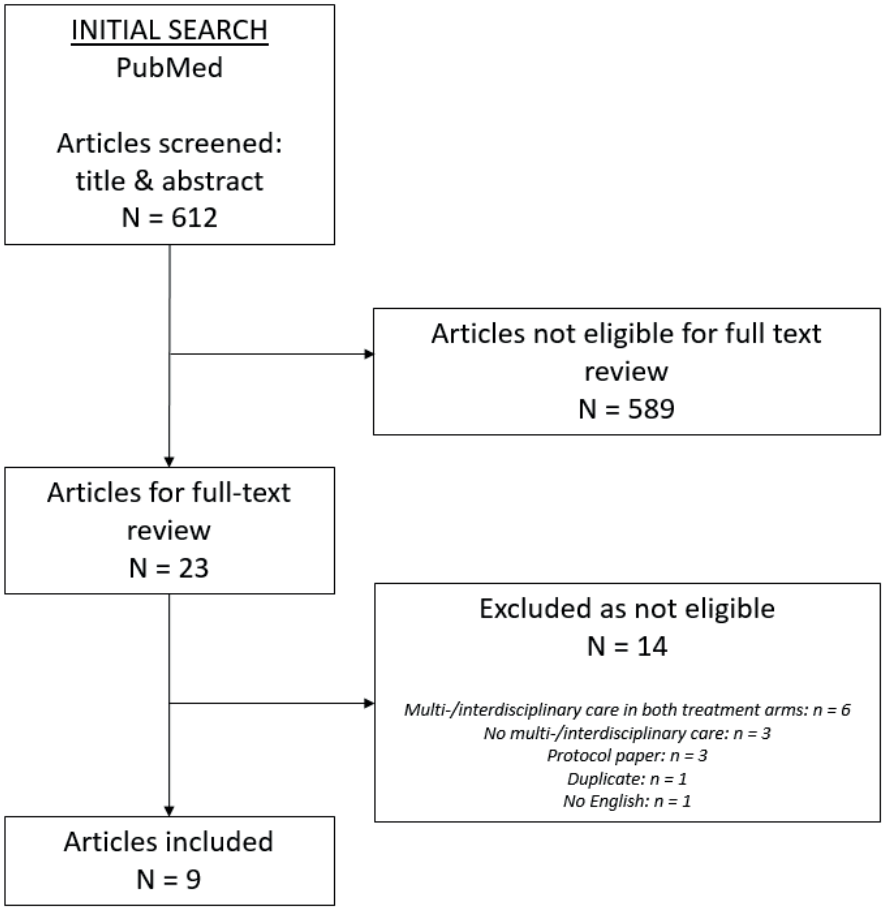
("**rehabilitation**"[All Fields]) OR ("**allied health**"[All Fields]) OR ("**multidisciplinary**" [All Fields]) OR ("**interdisciplinary**") OR ("**physiotherapy**"[All Fields]) OR ("**occupational**" [All Fields])) OR (("**speech**" [All Fields]) OR ("**language**" [All Fields]) AND ("**therapy**" [All Fields])) AND ("**Parkinson s disease**"[All Fields])

The box 'randomized controlled trial' was checked in PubMed

Inclusion criteria:

- Randomized controlled trial
- Intervention group received care from a combination of two or more allied health disciplines
- Control group did not receive care from multiple allied health disciplines

Supplementary material B. Flowchart literature search



Supplementary file C. Detailed assessment of meeting criteria for specialized allied health care

Author (date)	PD trained AHPs	Personalized intervention	PD-specific intervention
Clarke et al. (2016)(103)	Not reported	Yes Therapy was tailored to an individual patient's requirements using a patient-centered joint goal-setting approach	Uncertain A framework for therapy content was developed and agreed on by expert therapist groups based on previous work on standards of NHS PT and OT and European guidelinesHowever, logs showed few use PD-specific exercise, strategies or task related practice.
Frazzitta et al. (2012)(104)	Not reported	Not fully reported Intervention protocolized, tailoring not reported	Not fully reported Designed for Parkinson. PT focused on exercise programs. Exercise was augmented with cues, but no strategy training reported for functional mobility. OT focused on autonomy in transfers, dressing and arm-hand function. Not described how.
Frazzitta et al. (2015)(105)	Not reported	Not fully reported Intervention protocolized, tailoring partly reported (max heart rate)	Not fully reported Designed for Parkinson. PT focused on exercise programs. Exercise was augmented with cues, but no strategy training reported. OT focused on autonomy in transfers, dressing and arm-hand function. Not described how.
Ferrazzoli et al. (2018a)(106)	Not reported	Not fully reported Intervention protocolized, "goal-based", tailoring partly reported	Partly PT: Focused only on capacity (exercise). OT: yes. Dexterity, writing and ADLS with PD-specific strategies. No reference to guidelines/evidence for this. ST: Does not seem to include evidence-based interventions for speech.

	Appropriate treatment context	Appropriate intervention dose	Appropriate multidisciplinary care
	Yes In community: home-based (mostly OT) and outpatient clinic (mostly PT).	No Median number of therapy sessions was 4 (range, 1-21) over 8 weeks for OT and PT together.	Yes PT and OT appropriate for focus on daily activities. Joint goal setting approach
	Partly For exercise appropriate, for training of autonomy in activities questionable. Patients were given (unsupervised) exercise program for use at home	Yes Focus on motor exercise and skill training- high intensity. Repeated after a year. Not too burdensome?	Yes PT and OT appropriate to target motor functioning and ADL. However, collaboration not described.
	Partly For exercise appropriate, for training of autonomy in activities questionable Patients were given (unsupervised) exercise program for use at home	Yes Focus on motor exercise and skill training- high intensity. Repeated after a year. Not too burdensome?	Yes PT and OT appropriate to target motor functioning and ADL. However, collaboration not described.
	Partly For exercise appropriate. For training of autonomy in activities questionable, but people were early stage. Patients were given (unsupervised) exercise program for use at home	Yes Focus on motor exercise and skill training- high intensity: 21 sessions per week for 4 weeks. Not too burdensome?	Yes PT and OT appropriate to target motor functioning and ADL. However, collaboration not described.

Supplementary file C. Continued

Author (date)	PD trained AHPs	Personalized intervention	PD-specific intervention
Ferrazzoli et al. (2018b)(107)	not reported	Yes Therapy was tailored to an individual patient by team	Partly PT: focused only on capacity (exercise). No strategies or functional mobility OT, yes. Dexterity, writing and ADLS with strategies. No reference to guidelines/evidence ST: Does not seem to include evidence-based interventions for speech.
Tickle-Degnen et al. (2010)(108)	Yes AHPs trained and supervised for consistency in the standardized, manualized, and interdisciplinary intervention.	Yes Focus on own valued domains and self-management.	Yes Following evidence based guidelines, exercise and strategies and self-management.
Wade et al. (2003)(109)	Uncertain A 'specialist team', but not specified	Yes Individual treatment plan	Not reported
Stożek et al. (2016)(110)	Not reported	Not fully reported Only described that number of repetition depended on individual capacity	Not fully reported For functional mobility: yes; for speech no mention of evidence based guidelines
Monticone et al. (2015)(111)	Not fully reported 'equally experienced'	Not fully reported Not clearly reported. Treatment was individually delivered.	Yes PT: combination of task oriented training of functional mobility, also using PD-specific strategies and training physical capacity; OT: functional practice and adaptation, focus on home.

Abbreviations: PD, Parkinson's disease; AHPs, allied health professionals; OT, Occupational therapy; PT, physical therapy; ST, speech-language therapy; ADL, Activities of Daily Living

	Appropriate treatment context	Appropriate intervention dose	Appropriate multidisciplinary care
	Partly For exercise appropriate, for training of autonomy in activities questionable. For ST? Patients were given (unsupervised) exercise program for use at home.	Yes Focus on motor exercise and skill training- high intensity. 21 sessions per week for 4 weeks. Repeated after a year. Too burdensome?	Yes OT, PT and ST appropriate to target motor functioning, ADL and speech. However, collaboration not described.
	IG1: Partly IG2: Yes IG2 was combination of outpatient and home-based therapy.	IG1: Uncertain IG2: Yes Either a total of 18 hrs. (2 times a week) or 27 hrs. (3 times a week) over 6 weeks. Focus on self- management. Uncertain whether people practiced at home.	Yes Combination of OT, PT and ST, worked interdisciplinary
	No Outpatient rehab program; no mention of working towards transfer to home context	No Once a week x 6: insufficient for training skills	Yes Combination of individual treatment and group intervention within a multidisciplinary team
	No Outpatient rehab program; no mention of working towards transfer to home context	Yes 4 weeks, 28 sessions	Uncertain Involvement of PT, but not clear what discipline provided speech therapy. No mention of a speech therapist.
	Partly Inpatient program, but attention for home. Exercise program was given for after discharge.	Partly 8 weeks, PT: daily 90 min, adequate; OT 1x a week 30 min, insufficient for skills practice	Yes Combination of PT and OT appropriate for improving daily functioning

Online Supplementary Material Chapter 3

Supplementary methods 1

Web-based referrals support physicians to specifically refer their PwP to a qualified therapist. Referral to a specialized (i.e., ParkinsonNet-affiliated) therapist is based on choices by either PwP, their treating clinician, or both, but is influenced to very limited extent by geographical proximity to specialized therapists. Specifically, patients and clinicians can find specialized therapists who work geographically close to the patient through a web-based healthcare finder (www.ParkinsonZorgzoeker.nl). There is nationwide coverage of specialized therapists (192). Importantly, this network approach reached full nationwide coverage in the Netherlands by 2010, so that access to both specialized ParkinsonNet care and generic AHT was available throughout the country for the timeframe that we analyzed. Any clinician can refer PwP to ParkinsonNet therapists, regardless of whether or not this clinician is himself or herself associated with ParkinsonNet. It is possible that there was preferred referral to ParkinsonNet therapists by movement disorders specialists. This may have introduced some confounding bias if a larger proportion of PwP in the specialized AHT group were treated by a movement disorders specialist. It is unlikely that this had a major effect on the results, since adjustment for the hospital type in which PwP received care (university medical center vs. other) did not alter the results.

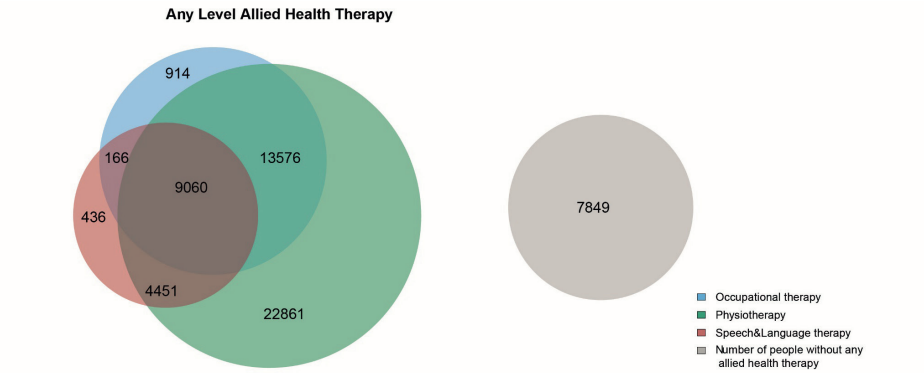
Supplementary methods 2

Detailed description of further analyses

We performed several further analyses to explore the robustness of the main results and if there was evidence of effect modification. (i) We repeated the main OT and S&LT analyses with additional adjustment for exposure to PT (no PT, generic PT, specialized PT) and after stratification for level of exposure to PT. (ii) We repeated the main models for complication-specific outcomes (i.e., pneumonia or orthopedic injuries). (iii) We repeated the main models in strata defined by age, SES, CCI score, PD-specific medication or sex. For stratification of continuous variables, we used the median value as cut-off, except for disease duration which we dichotomized at 5 years, because that is a commonly used milestone in clinical practice. Since we had no information about the date of diagnosis before January 1st, 2009, we could not use the complete dataset for this analysis; instead, the follow-up time in this analysis started on January 1st, 2015, so that, individuals diagnosed with PD in or before 2009 could be classified as having had clinical PD for >5 years. (iv) To determine whether the effect of specialized AHT versus generic AHT varied by different numbers of treatment exposure period, we compared the main models on strata that included

only treatments in the first year (individuals with ≤365 treatment exposure days), in the second year (individuals with >365 treatment exposure days and <730 treatment exposure days), or beyond two years (individuals with ≥730 treatment exposure days) after PD diagnosis. (v) We assessed sustainability of the effects after cessation of specialized AHT by extending the lag period of exposure to 60, 90, 365, 730, 1460, or 1825 days. As an addition, in another sensitivity analysis we assessed the sustainability of the specific effects after cessation of two specialized disciplines of PT and S&LT by using complication-specific outcomes. Specifically, we used orthopedic injuries as the main outcome for PT and pneumonia for S&LT and extended the lag period of exposure to 60, 90, 365, 730, 1460, or 1825 days. (vi) To determine whether residual confounding may have affected the main analyses, we assessed whether there was an association between the rate of complications with future exposure to specialized AHT versus. generic AHT. In a sensitivity analysis, we determined the conditional probability ('propensity score') of an individual to receive specialized AHT by fitting a logistic regression model comprising baseline sociodemographic and clinical characteristics as independent variables and the level of AHT expertise they received as the dependent variable (193), and adjusted the main analysis (on any-discipline AHT) for the propensity score instead of adjusting for individual covariates. In a separate sensitivity analysis, we additionally adjusted the main model for the hospital type (university medical centers vs. other centers) in which PwP received care, as a proxy for the involvement of movement disorders specialists. In another sensitivity analysis we assessed the association between AHT and the rate of PD-related complication in those who received any AHT vs. those who did not receive AHT. We included all people with PD in the time-window between January 1st, 2015 until December 31st, 2018. We chose this time period to facilitate adjustment for a clinical disease duration of >5 years, in order to minimize confounding by disease duration, as disease duration could only be determined from 2011 onwards. For this analysis we defined the follow-up start for both subgroups as the first observation in which individuals were assigned a PD diagnostic code. We followed both groups until the first of the following events: death or December 31st, 2018. We used a Poisson multivariate regression model to estimate the IRR for complications that occurred during this period, and re-ran the model once again with propensity score adjustment method. We adjusted the models for the same measured baseline covariables that we used in the main study models. The sensitivity analysis comparing the association between any AHT vs. no AHT and the rate of PD-related complications showed that the distribution of follow-up time between two groups are not equal. To correct for this imbalance we selected individuals of both groups with two years of follow-up and re-ran the analysis. We conducted all analyses in R statistical software version 3.4.3.

Supplementary figures & tables chapter 3:



Supplementary Figure 1. Venn diagram illustrates the patterns of the delivery of allied health therapy disciplines in persons with Parkinson' over study years. Of all 59,313 persons with Parkinson's disease, 51,464 were received any level of these disciplines.

Supplementary Figure 2. Forest plot shows the association between the level of expertise (specialised VS. generic) with the complications rate in different subgroups. Numbers in x-axis indicates incidence rate ratio with 95% confidence intervals

Supplementary Table 1. Complications Codes Which Used from the Vektis Database in the Analyses.

Vektis Diagnostic code	Specialty category	Complication/ Diagnosis	Complication Group
0303-0205	Surgery	Clavicle	Ortho injuries
0303-0207	Surgery	Humerus proximal and shaft	Ortho injuries
0303-0208	Surgery	Distal humerus/ (epi) condyle(s)	Ortho injuries
0303-0210	Surgery	Radius head	Ortho injuries
0303-0211	Surgery	Forearm nno	Ortho injuries
0303-0212	Surgery	Wrist	Ortho injuries
0303-0216	Surgery	Ribs, sternum	Ortho injuries
0303-0217	Surgery	Pelvis/ sacrum	Ortho injuries
0303-0218	Surgery	Femur, proximal (+ collum)	Ortho injuries
0303-0219	Surgery	Femur other	Ortho injuries
0305-1703	Orthopedics	Loosening/ infection/ malposition of pelvis/ hip/ thigh prosthesis	Ortho injuries
0305-3003	Orthopedics	Sternum/ ribs	Ortho injuries
0305-3006	Orthopedics	Clavicle	Ortho injuries
0305-3008	Orthopedics	Humerus proximal and shaft	Ortho injuries
0305-3009	Orthopedics	Distal humerus/ (epi) condyle (s)	Ortho injuries
0305-3011	Orthopedics	Radius cup	Ortho injuries
0305-3012	Orthopedics	Forearm	Ortho injuries
0305-3013	Orthopedics	Wrist	Ortho injuries
0305-3017	Orthopedics	Pelvis	Ortho injuries
0305-3018	Orthopedics	Acetabulum	Ortho injuries
0305-3019	Orthopedics	Femur proximal (+ collum)	Ortho injuries
0305-3020	Orthopedics	Femur other	Ortho injuries
0305-3207	Orthopedics	Hip, prosthesis	Ortho injuries
0313-0401	Internal med	Pneumonia nno	Pneumonia
0322-1401	Lung diseases	Pneumonia	Pneumonia

Supplementary Table 2. Characteristics of People with Parkinson's Disease, Stratified by Exposure to Any Allied Health Therapy

	AHT	**No AHT**
Age at diagnosis (SD)	73 (9.7)	69 (10.5)
Gender (female)	16393 (42%)	1630 (32%)
Individuals with at least one PD-medication at diagnosis	34111 (87%)	3806 (74%)
SES	-0.13 (1.1)	-0.16 (1.2)
CCI at diagnosis	5.1 (1.7)	4.4 (1.5)
Individuals with at least one PD-complication in year 2014	2043 (5%)	115 (2%)
N complications	1577	129
Person-years (mean)	2.0	2.0
IRR (95% CI)	1.19 (0.90-1.57)	

Population from year 2015 onwards; AHT: allied health therapy. Socioeconomic status (SES) derived from characteristics such as education, income, and labor market status of people in each neighborhood.

Supplementary Table 3. Association of Level of Allied Health Therapy and the Risk of Parkinson's Disease-related Complication Stratified by the Number of Treatment Days that Participants Received

		Any discipline					Physiotherapy			
Treatment exposure period		**N**	**N comp**	**Person-yrs (sum)**	**Rate**	**IRR (95% CI)**	**N**	**N comp**	**Person-yrs**	**IRR (95% CI)**
≤ 365 days	Total	51464	4045	53645	0.075	0.67 (0.63-0.72)*	49948	3738	50307	0.70 (0.65-0.74)*
	Sp		1630	22261	0.073			1436	19986	
	Gen		2415	31384	0.077			2302	30321	
365- 730 days	Total	31541	2363	30696	0.077	0.82 (0.75-0.89)*	30829	2269	29628	0.81 (0.74-0.89)*
	Sp		931	11967	0.078			862	11273	
	Gen		1432	18729	0.076			1407	18355	
≥730 days	Total	21047	4119	47021	0.088	0.98 (0.89-1.08)	20751	4157	47069	0.96 (0.87-1.06)
	Sp		1137	14421	0.079			1085	13975	
	Gen		2982	32600	0.091			3072	33093	

N, number of participants. N comp, number of complications. Sp, specialized. Gen, generic. CI, confidence interval. IRR, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, PD specific medications, and number of days of treatment. NA, not applicable.

	Speech & Language therapy				Occupational Therapy			
	N	**N comp**	**Person-yrs**	**IRR (95% CI)**	**N**	**N comp**	**Person-yrs**	**IRR (95% CI)**
	14113	700	7144	0.94 (0.80-1.11)	23716	1221	9553	0.88 (0.78-1.00)
		421	4298			677	5440	
		279	2845			544	4113	
	2447	170	1585	0.70 (0.50-0.98)*	1730	88	749	1.32 (0.80-2.15)
		91	972			62	486	
		79	613			26	263	
	824	103	1015	1.09 (0.62-1.93)	197	7	145	1.23(NA)
		63	591			7	102	
		40	424			0	43	

Supplementary Table 4.1. Association Between Level of Different Disciplines of Allied Health Therapy and the Rate of Complications Stratified by Different Lag Periods after Treatment Cessation

	Any discipline	**Physiotherapy**	**Speech & language therapy**	**Occupational therapy**
60 days lag	0.81(0.78-0.85)*	0.81(0.77-0.85)*	1.00(0.85-1.16)	1.03(0.92-1.15)
90 days lag	0.82(0.79-0.86)*	0.82(0.78-0.86)*	1.06(0.92-1.23)	1.11(1.00-1.23)
365 days lag (one year)	0.89(0.86-0.93)*	0.89(0.87-0.93)*	1.29(1.15-1.45)	1.59(1.46-1.72)
730 days lag (two years)	0.90(0.86-0.93)*	0.89(0.86-0.93)*	1.50(1.35-1.67)	1.86(1.73-2.00)
1460 days lag (four years)	0.91(0.87-0.94)*	0.90(0.86-0.94)*	1.66(1.51-1.84)	2.25(2.10-2.41)
1825 days lag (five years)	0.91(0.88-0.95)*	0.91(0.87-0.95)*	1.77(1.60-1.95)	2.41(2.25-2.58)

Lag period increases to different number of days of follow-up after last AHT session, specifically if individuals stop receiving specialized AHT at 30 days but we continue following patients until what extend this specialized treatment effect will sustain. CI, confidence interval. Columns indicating IRRs, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, and PD-specific medications.

Supplementary Table 4.2. Association Between Level of Different Disciplines of Allied Health Therapy and the Rate of Specific Complications Stratified by Different Lag Periods after Treatment Cessation

	Physiotherapy (and the rate of orthopedic injuries)	**Speech & language therapy (and the rate of pneumonia)**
60 days lag	0.79(0.74-0.83)*	0.90(0.70-1.15)
90 days lag	0.80(0.75-0.84)*	0.92(0.73-1.16)
365 days lag(one year)	0.87(0.83-0.92)*	1.19(1.00-1.42)
730 days lag(two years)	0.87(0.83-0.92)*	1.33(1.13-1.56)
1460 days lag	0.88(0.84-0.92)*	1.48(1.27-1.73)
1825 days lag(five years)	0.89(0.85-0.93)*	1.58(1.36-1.83)

Columns indicating IRRs, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, and PD-specific medications.

Supplementary Table 5. Association Between the Level of Allied Health Therapy and the Rate of Complications During the First-Gap-Interval*

	Any discipline		**Physiotherapy**		**Speech & Language therapy**		**Occupational Therapy**	
	Specialized	**Generic**	**Specialized**	**Generic**	**Specialized**	**Generic**	**Specialized**	**Generic**
N	12,122	28,029	11,286	27,811	7,868	5,771	12,264	10,690
Total N complications	311	1214	285	1274	661	854	1389	1452
Person-years at risk of any complication (sum)	14226	30525	13336	31129	25183	14792	41292	29150
Person-years at risk of any complication (median)	0.6	0.7	0.6	0.7	2.6	2	2.8	2.2
Rate of any complication	0.0219	0.0398	0.0213	0.0409	0.0262	0.0577	0.0336	0.0498
IRR(95% CI)	0.60(0.52-0.67)*		0.57(0.50-0.65)*		0.82(0.74-0.91)*		0.73(0.68-0.79)*	
IRR†(95% CI)	NA		NA		0.94(0.84-1.05)		0.91(0.85-1.00)	

IRR, Incidence Rate Ratio adjusted for age, gender, socioeconomic status, CCI score, and PD-specific medications. In this analysis, we only used the data of those individuals who did not receive any level allied health therapy before the diagnosis of PD. * The time interval between the diagnosis date and the first allied health therapy session; for this analysis we used the level of allied health therapy that individuals will receive right after the diagnosis date. † Analyses were additionally adjusted for exposure to Physiotherapy during the previously receiving Speech & Language therapy or Occupational therapy exposure period.

Supplementary Table 6. Level of Allied Health Therapy and the Risk of Parkinson's Disease-Related Complications with Additional Adjustment for Different Healthcare Setting

	Any discipline		**Physiotherapy**		**Speech & Language Therapy**		**Occupational Therapy**	
	Specialized	**Generic**	**Specialized**	**Generic**	**Specialized**	**Generic**	**Specialized**	**Generic**
Healthcare setting (University Medical Center %)	1327 (8.26%)	3121 (8.81%)	1181 (8.16%)	3159 (8.90%)	870 (10.13%)	515 (9.32%)	1123 (8.25%)	939 (9.30%)
IRR (95% CI)	0.80 (0.76-0.84)*		0.79 (0.75-0.84)*		0.90 (0.76-1.06)		0.87 (0.76-0.98)*	

Proportions calculated in two levels of AHT based on the predominant level of expertise of AHT received (only for descriptive purpose). CI, confidence interval.
IRR, incidence rate ratio of specialized vs. generic (reference) allied health therapy for Parkinson's Disease-related complications; adjusted for age, gender, socioeconomic status, CCI score, complications in the year before enrolment, PD-specific medication, and healthcare setting in which PwP visited by neurologist.

Online Supplementary Material Chapter 4

In a longitudinal setting with an observational study design, we need to address the possible sources of bias. Specifically, we need to address time-varying confounding, meaning confounders of the treatment-outcome relationship that could be affected by prior medication use and that also could predict the probability of receiving the next medication prescription (194, 195). Reducing these biases in our study by using (stabilized) Inverse Probability (IP) weights improves the average causal effect estimate of Levodopa initiation timing on mortality in people with Parkinson's disease (196). For our analysis, we represented the treatment history of the first two years post diagnosis as a binary time-varying variable. We split the data into discrete (quarterly) time steps from diagnosis to the first medication prescription date, meaning a maximum of nine years follow-up, for which we had 36 separate time periods that contained the data regarding the treatment status and all other co-variables. For simplicity, we assumed that the medication prescription decision took place on the first day of each quarter and that the use of medication continued until the last day of that quarter. For example, we assumed that an individual with the diagnosis date of March 1st, 2012, one Levodopa prescription during the third quarter of 2013 and another Levodopa prescription during the second quarter of 2014, was six months on treatment within 28 months of total follow-up, one from July 1st, 2013 to September 30th, 2013 and from April 1st, 2014 to June 30th, 2014. In order to define the different treatment strategies for computation of the inverse treatment probability weights, we split the first two years of follow-up period into 8 consecutive time-intervals (quarters) and defined early initiation as having received Levodopa treatment in at least one of the quarters, while late initiation meant no Levodopa was prescribed during these two years. For instance, the participant in the previous example has followed the treatment strategy of 00000100, where each binary digit shows receiving or not receiving treatment in a particular quarter within the first two years after their diagnosis, and was hence categorized into the early treatment strategy group.

Inverse Probability Weights

The role of IP weighting is to adjust for possible time-varying confounding by correcting the dependence between treatment and outcome due to covariates. This is achieved by creating a pseudo-population in which there is no association between the treatment and the covariates. The IP weighting method is explained in detail elsewhere (197). Here, we show the mathematical formula for the stabilized IP weights and briefly explain the statistical computation steps that we performed.

$$sw^{\bar{A}} = \prod_{k=0}^{K} \frac{f(A_k|\bar{A}_{k-1})}{f(A_k|\bar{A}_{k-1}, \bar{L}_k)} \qquad Equation\ 1$$

The stabilized IP weights are expressed as a product of conditional probabilities for each individual treatment value in the treatment strategy over *K* periods. The product in the denominator represents an individual's probability of receiving a particular treatment strategy () and given a particular covariate history (), while the product in the numerator represents an individual's marginal probability of receiving a particular treatment strategy and is used for numerical stability. is a binary indicator for the treatment taken at time period *k*.

For each factor in the product, corresponding to each discrete time period (quarter), we separately fit logistic regression models to estimate the probabilities in the numerator and the denominator of the stabilized IP weight equation. In the end, we obtain estimated stabilized IP weights for each combination of covariate and treatment history, based on the observed treatment and covariates status of the first two years of follow-up post-diagnosis. Notably, we removed one patient from the final analysis because the patient's IP treatment weight was very big and we decided it was an outlier.

Outcome Model: Weighted Marginal Structural Model

Marginal Structural Models (MSM) for causal survival analysis are explained in detail elsewhere (197). Here, we show the equation of the causally interpretable IP weighted MSM, and below we explain the equation in brief.

$$Pr\left[D_{k+1} = 0|\bar{L}_k = \bar{l}_k, \bar{A}_k = \bar{a}_k\right] = Pr\left[D_{k+1}^{\bar{a}_k} = 0|\bar{L}_k = \bar{l}_k\right] \qquad Equation\ 2$$

The equation above expresses the probability of survival at time period *k*+1 given a particular treatment history (and covariate history (, which under conditional exchangeability can be causally interpreted as the survival that would have been observed if someone with covariate history had received treatment strategy (see 4). To estimate the conditional probability above, we express the quantity above as a product of (one minus the) time-varying hazards at all previous time periods. For each time period *k*, we fit separate logistic regression models with mortality status at each time period as the binary outcome variable conditional on survival in the previous time period and on the previous four treatment statuses. We limited the conditioning on the last four treatment statuses to reduce model complexity, since we observed that only these coefficients were significantly associated with the probability of mortality.

For $k < 4$, there are fewer than four previous treatment statuses, so we assume no treatment pre-diagnosis. Please note that this way of conditioning was also applied in IP weighting regression models.

The mortality risk ratio for early initiators vs. late or never initiators is interpreted as the ratio of the estimated average mortality probability for early initiators divided by the estimated average mortality probability for late initiators. In the manuscript we reported this ratio for the time period nine years after the diagnosis.

People with Incomplete Treatment History

Using standard IP weighting procedures, we estimate the probability of mortality (death) given each possible treatment strategy in the first two years post-diagnosis. Since we have eight possible treatment values in the first eight time periods (quarters) after diagnosis, there are possible strategies in total. Only one strategy corresponds to late initiation, namely the strategy in which all treatment values are zero (i.e., no levodopa treatment in the first two years). The other 255 strategies all correspond to early initiation, since levodopa would have been administered at least once in the first eight quarters. Our MSM fits will give us a mortality probability for each of the 256 individual strategies. However, in order to compare the early initiators to the late initiators, we need to aggregate the results for the 255 'early initiation' strategies into a single estimate.

We proceed as follows. Using the available data, we first assess how likely each of the 255 strategies is by considering how many PwP follow these strategies in our data, as explained below.

1. For each person with complete follow-up during the first two years (complete history of treatment for the 8 time periods), their treatment strategy gets a weight of 1.
2. For each person with incomplete follow-up (i.e., incomplete history of treatment for all 8 time periods due to death or dropout from the study), we extrapolate each possible complete strategy that could have been observed. For example, if we consider a person with treatment history available for the first 6 time periods and missing for the last two, there would be possible strategies. We assign an equal weight for each strategy, which in the previous example is Here we make the simplifying assumption that each possible treatment strategy in the first two years is equally likely given incomplete data.
3. We sum all of the weights for each treatment strategy across all PwP.

4. Finally, we use these 'strategy weights' in the equation below to compute a mortality probability estimate for early initiation as the weighted mean of probability estimates for each of the 255 'early initiation' strategies.

$$1.\quad \bar{p} = \frac{\sum_s w_s p_s}{\Sigma_s w_s} \qquad \textit{Equation } 3$$

A Practical Note on Modified Charlson Comorbidity Index Score

We used a modified version of the weighted Charlson Comorbidity Index (CCI) from (198), which is derived from a combination of Pharmaceutical Cost Group (PCG) and healthcare services codes. PCG codes are special codes in the Netherlands hospital data system assigned to multiple chronic conditions for the ease of predicting future healthcare costs and to facilitate further scientific research in estimating the disease severity (131). The healthcare service codes (NL: zorgproduct) are unique numeric identifiers tracking any type of service delivered to patients each time they visit a hospital or other healthcare settings in the Netherlands (199). In our analysis, we defined an integer variable for each year which is increased as each disease condition is added to the comorbidities during the follow-up (e.g., if a person in the baseline had diabetes mellitus with no complications the CCI score was two and if they would develop myocardial infarction next year, the CCI score would be increased by two).

Handling of Missing Data

For the group of people for whom we did not have any data available regarding their treatment status, but for whom we had the data on their time-varying covariates, we assumed no Levodopa was prescribed. For the patients for whom we did not have any data on their treatment status or on their time-varying covariates, we conducted the following steps, respectively.

Socio-Economic Status (SES): The SES variable was used based on an annual measure in general. For the time periods in which the SES variable was missing, we imputed a personalized average of SES values based on the observed values in all other time periods. There was also a small number of people for whom we did not have any measure for their SES values, whom we excluded from the analyses, as mentioned in the flowchart.

CCI: For those time periods for which we did not have any observations to compute the weighted CCI, we imputed the last computed weighted values (the weighted sum of all previous comorbid disorders).

PD-related complications: In case we had no data available on PD-related complications in DBC codes data, we assumed no complications happened.

Sensitivity Table 1. Flowchart of eligible study population

(population with Parkinson's disease between years 2012-2020) – Selected by not having the PD diagnostic code during the previous recent three years

Number	Criteria & Rationale	Status
31227	Newly diagnosed people with PD based on defined criteria.	Enrolled
1389	People whom their diagnosis changed from PD to any atypical parkinsonism at the final hospital records visit they had.	Excluded
9	People of whom we do not have any data records of their SES throughout the entire available data.	Excluded
29829	Final analysed	Included
Mortality ratio [95 % CI]	Weighted for IPW	1.04 (0.93 – 1.19)

For this sensitivity analysis, we selected the newly diagnosed PwP if there was no diagnostic identifier of 30-501 observed during three years before the first ever 30-501 code

Sensitivity Table 2. Flowchart of eligible study population

(population with Parkinson's disease between years 2012-2020) – Selected by not having the PD diagnostic code during the previous recent one year

Number	Criteria & Rationale	Status
31553	Newly diagnosed people with PD based on defined criteria.	Enrolled
1405	People whom their diagnosis changed from PD to any atypical parkinsonism at the final hospital records visit they had.	Excluded
9	People of whom we do not have any data records of their SES throughout the entire available data.	Excluded
30139	Final analysed	Included
Mortality ratio [95 % CI]	Weighted for IPW	1.03 (0.90 – 1.16)

For this sensitivity analysis, we selected the newly diagnosed PwP if there was no diagnostic identifier of 30-501 observed during only one year before the first ever 30-501 code

A8. References

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