1-1-2021

SLEEP AND HEALTH-RELATED QUALITY OF LIFE AMONG PERSONS WITH PARKINSON'S DISEASE AND THEIR CAREGIVERSSLEEP AND HEALTH-RELATED QUALITY OF LIFE AMONG PERSONS WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS

Sushmitha Inguva
University of Mississippi

SLEEP AND HEALTH-RELATED QUALITY OF LIFE AMONG PERSONS WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS

A Dissertation
presented in partial fulfillment of requirements
for the Doctor of Philosophy degree
in the Department of Pharmacy Administration
The University of Mississippi

By
Sushmitha Inguva
May 2021

ABSTRACT

This dissertation aimed at filling gaps in the body of Parkinson's disease (PD) and sleep literature by synthesizing and appraising current knowledge on the influence of sleep on health-related quality of life (HRQoL) in persons with Parkinson's (PWP) and their caregivers, conducting a psychometric evaluation of a HRQoL instrument among PWP, and applying a novel method to assess the dyadic relationship between sleep and HRQoL in PWP and their caregivers.

First, the systematic literature review results showed that nocturnal and diurnal sleep problems among PWP are strong predictors of their HRQoL. Additionally, studies that focused on caregiver outcomes showed that PWP and caregivers' sleep issues were predictors of caregiver HRQoL. Results synthesized across these studies suggest that the relationship between sleep and HRQoL might be interdependent for PWP and caregivers.

Second, a cross-sectional study was conducted to evaluate the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health, a generic HRQoL instrument, among PWP. Findings from this study provide evidence that the global physical health (GPH) and global mental health (GMH) summary scores obtained from this instrument show good reliability and validity in PWP.

Finally, a cross-sectional study was conducted to assess the dyadic relationship between sleep and HRQoL among PWP and caregivers using the Actor-Partner Interdependence Model. This study used the PROMIS sleep disturbance (SD) and the PROMIS sleep-related impairment

(SRI) to measure nocturnal and diurnal sleep issues, respectively. Results showed that both SD and SRI in PWP and their caregivers are significant predictors of their own HRQoL. Additionally, caregiver's SD and SRI were found to be significant predictors of PWP's HRQoL. These results provide empirical evidence that the sleep-HRQoL relationship is not an independently occurring phenomenon for PWP and caregivers.

Study findings about the impact of sleep on HRQoL among PWP and their caregivers help provide a better understanding of this complex relationship in PD. Interventions aiming to improve PWP's HRQoL might benefit from integrating services that also address caregivers' sleep. Such interventions have the potential to reduce humanistic burden in this population and economic burden on the society by way of decreasing institutionalization rates among PWP.

DEDICATION

This dissertation is dedicated to *Amma*, *Appa*, Subodh and Kaustuv for their unconditional love, support and encouragement.

ACKNOWLEDGEMENTS

I would like to thank my dissertation co-advisors, Dr. Marie Barnard and Dr. John Bentley, for their constant guidance, encouragement, and support throughout my dissertation. I would also like to thank my committee members, Dr. Sujith Ramachandran, Dr. Amit Patel, Dr. John Green and Dr. Juebin Huang for their constructive feedback and valuable insights during the course of this project. A special thanks to Alexcia Carr for her assistance and active participation in the systematic review study.

This project would not have been possible without the data collection support provided by Rare Patient Voice, Dynata and Parkinson and Movement Disorders Alliance. A special thank you to all patients who responded to my survey and provided their input to the study. I am also grateful to the partners at Medical Marketing Economics LLC for the dissertation fellowship as well as funds from the Department of Pharmacy Administration Graduate Student Research and the University of Mississippi Graduate Student Council Research grant programs without which this project would not have been possible. I am indebted to my family and friends for their love and support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Overview of Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease condition caused by loss of dopaminergic neurons in the midbrain. This results in some of the most commonly associated symptoms with the disease such as tremors at rest, akinesia (paucity of movement), bradykinesia (slowness in movement), muscle rigidity, gait and balance problems.[1,2] PD was thought of as a purely movement-related disorder with one or more of the above symptoms. However, overwhelming evidence suggests that there are several non-motor symptoms (NMS) that occur alongside these motor symptoms such as cognitive changes, fatigue, hallucinations and delusions, mood disorders, orthostatic hypotension, pain, and sleep disorders among others.[3] Presence of motor symptoms in patients usually triggers a diagnosis for PD, however, NMS are present in a patient well before the manifestation of motor symptoms and carry on in to the final palliative stages of the disease.[4,5]

Diagnosis and treatment

The Movement Disorder Society (MDS) criteria for a PD diagnosis requires presence of parkinsonism (defined as having bradykinesia plus either tremor at rest or rigidity) accompanied by additional diagnostic features to confirm a clinically established or a clinically probable PD case, depending on the range of criteria satisfied.[6] These diagnostic features are listed below:

- *Absolute exclusion criteria* are comprised of other conditions that could explain the existing parkinsonism thereby ruling out a PD diagnosis. These conditions include but are

- not limited to presence of cerebellar abnormalities, primary progressive aphasia, cortical sensory loss, presence of drug-induced parkinsonism due to use of dopamine receptor blockers or dopamine-depleting agents.
- *Red flags* delineate criteria which must be counterbalanced by supportive criteria to allow for PD diagnosis and point to unusual patterns of disease progression following disease onset. Examples include "rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset", "recurrent falls because of impaired balance within 3 years of onset" etc.
- *Supportive criteria* define criteria that strengthen confidence in a PD diagnosis. These include characteristics such as "clear and dramatic beneficial response to dopaminergic therapy….", "presence of levodopa-induced dyskinesia" etc.

Levodopa, as dopamine replacement therapy, has remained the drug of choice for treating PD since the late 1960s when it was discovered.[7] Additional treatment options consist of dopamine agonists (DA), monoamine oxidase B (MAO-B) inhibitors, nonergot, ergot, catechol-o-methyltransferase (COMT) inhibitors, synaptic vesicle glycoprotein 2A (Sv2a) agonists/channel blockers, anticholinergics, amantadine, deep brain stimulation (DBS) and others for treating motor symptoms.[8] There are several therapies available to treat NMS, some of which are specific to individual NMS in PD patients while others might not be tailored to address these symptoms specifically in this patient population.[9]

Epidemiology

Following Alzheimer's disease, PD is the second most common degenerative disease of the central nervous system. The prevalence of the disease increases with age, with estimates ranging from 41 per 100,000 in the 40-49 years age group to 1,087 per 100,000 for 70-79

years.[10] The prevalence rate has also been reported to vary by sex and geographic location, both worldwide and within North America.[10,11] Kowal et al. reported a national prevalence of 630,000 individuals with PD in 2010 and a total economic burden of $14.4 billion in the US.[12]

Health-related quality of life of individuals with Parkinson's Disease

PD is a progressive neuromuscular disease and therefore, the main clinical priority is to restore or slow down loss of motor control. However, since this disease progresses slowly, and most PD patients live in the community, optimizing health-related quality of life (HRQoL) is also an important treatment goal. Patients' HRQoL in PD is a complex construct influenced by the following factors: motor symptoms, motor complications, deteriorating psychosocial functioning, disease severity, and NMS such as sleep disorders, depression, cognition, pain, fatigue, apathy, and speech impairment.[13–16] Moreover, several studies have shown that NMS have a greater significance for a patient's HRQoL, healthcare resource utilization, caregiver HRQoL and caregiving burden.[17–20] Among all NMS, sleep disorders are the most frequently reported symptom, with some studies estimating a prevalence rate over 90%,[17,21,22] and severely impact patient HRQoL.[23–25]

Role of caregivers in Parkinson's Disease

PD is a neurological condition where patients' symptoms, functioning and well-being deteriorate progressively with time. As a result, patients experience physical limitations including their ability to conduct activities of daily living, and cognitive and psychiatric complications.[20] PD patients may need a caregiver's assistance with activities such as personal safety, mobility, transportation, medication compliance, meal preparation, housework, chores, shopping, finances, personal care and social involvements.[20,26] Most caregivers of patients with

PD are family members.[20] Caregiving is a time-intensive activity and is an important predictor of reduced rates of institutionalization among patients.[27,28] However, caregivers of patients with PD face significant economic burden, increased caregiver burden and reduced HRQoL, as a result of caregiving.[19,29–32]

Sleep disorders in Parkinson's disease

Sleep disorders have long been studied as a frequently reported NMS among PD patients. Previous studies have estimated a 60%-90% prevalence of one or more sleep-related disorders among PD patients.[33,34] The most common sleep disorders seen among PD patients are rapid eye movement (REM) sleep behavior disorder (RBD), insomnia, nocturia, restless legs syndrome (RLS)/periodic limb movement disorder (PLMD), sleep disordered breathing (SDB), excessive daytime sleepiness (EDS), and circadian rhythm disorders.[33] There are several factors that contribute to sleep disturbances in PD patients including pathological degeneration of sleep regulation in the brainstem and thalamocortical pathways, nocturia, motor rigidity, RLS, obstructive sleep apnea, rapid onset of sleep, nocturnal recurrence of PD symptoms, certain medications, aging, anxiety and depression, and occurrence of muscle activity during REM sleep which causes disturbed sleep and dream enactment during sleep.[17,22,35] Studies suggest that some sleep disorders may be present in patients before the manifestation of PD-related motor symptoms and their frequency worsens with disease progression.[36] Sleep-related disorders among PD patients are associated with diminished sleep quality among caregivers, the prevalence of which has been estimated as 20-60% across samples.[37–40]

Diagnosis and treatment of sleep disorders

Sleep disorders are diagnosed either by using objective methods such as polysomnography (PSG), multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT), or by using subjective assessments such as self-rating scales.[41] PSG assesses nighttime sleep disturbances, while MSLT and MWT provide measures of wakefulness.[41] Different rating scales measure different sleep-related constructs and are a popular choice because they are inexpensive and relatively easy to administer in healthcare practice and research settings.[41]

The most commonly used PD-specific rating scales for sleep are the Parkinson's Disease Sleep Scale Version 2 (PDSS-2) and the Scales for Outcomes in PD-Sleep (SCOPA-S).[41,42] The PDSS-2 is a 15-item questionnaire that measures nocturnal sleep disturbances and disabling symptoms causing these disturbances.[43] It has well-established psychometric properties and it discriminates well between patients and non-diseased cohorts as well as patients at different severity levels of sleep impairment.[41–44] However, it uses a visual analog scale and might need proper instructions before administration.[41–44] The SCOPA-S has 12-items and measures overall sleep impairment by assessing nocturnal sleep quality, sleep disturbances and daytime sleepiness.[45] It has good psychometric properties and can differentiate between presence/absence of sleep impairment but not between the severity levels of impairment.[41,42,44,45] It also does not explore causes of disturbances and its responsiveness has not yet been established.[41,42,44,45]

The Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) are generic sleep measures that are routinely used across diverse populations.[41,42] The PSQI is a 19-item questionnaire that measures overall sleep impairment and other dimensions of sleep quality but has certain limitations such as its propensity to recency effects and poor discriminant validity among others.[41,42] The ESS is an 8-item scale measuring presence and severity of daytime

sleepiness, however, it has an imprecise recall period and requires the caregiver's assistance in completing certain items.[41,42]

Some pharmacological interventions for sleep disorders have been evaluated in the literature, however, MDS's guidelines deemed only rotigotine, a dopamine agonist, as "likely efficacious" for insomnia.[9] Among non-pharmacological interventions, continuous positive airway pressure has been indicated as "likely efficacious" to treat insomnia, excessive daytime somnolence and sudden onset of sleep.[9]

Impact of sleep disorders in Parkinson's disease

The impact of sleep disorders in PD is multidimensional. For patients, sleep disorders not only have a significant negative impact on their HRQoL,[23–25,33] but also on other NMS observed in PD. For example, sleep disorders have a moderate effect on patient fatigue,[46] and contribute significantly to a patient's mood disturbances[38] and cognition.[47] Enhanced sleep quality, on the other hand, has been shown to improve working memory in patients, which is an indicator of improved higher cognitive functioning involving planning, problem solving, delayed goal execution and overall fluid intelligence.[48]

Moreover, studies have shown that some sleep disorders, such as insomnia, are also prevalent among caregivers of PD patients.[37–40,49,50] Caregivers' own distress from caregiving during the day or otherwise is one probable predictor.[37] Further, Arber and Venn conducted in-depth interviews and found that nocturnal caregiving responsibilities such as attending to nocturnal physical needs of the patient, anticipation of nocturnal care needs, monitoring the patient during sleep and the patient's sleep disturbances may help explain sleep abnormalities in caregivers.[51] This negative influence of sleep disorders in patients on their caregivers' burden

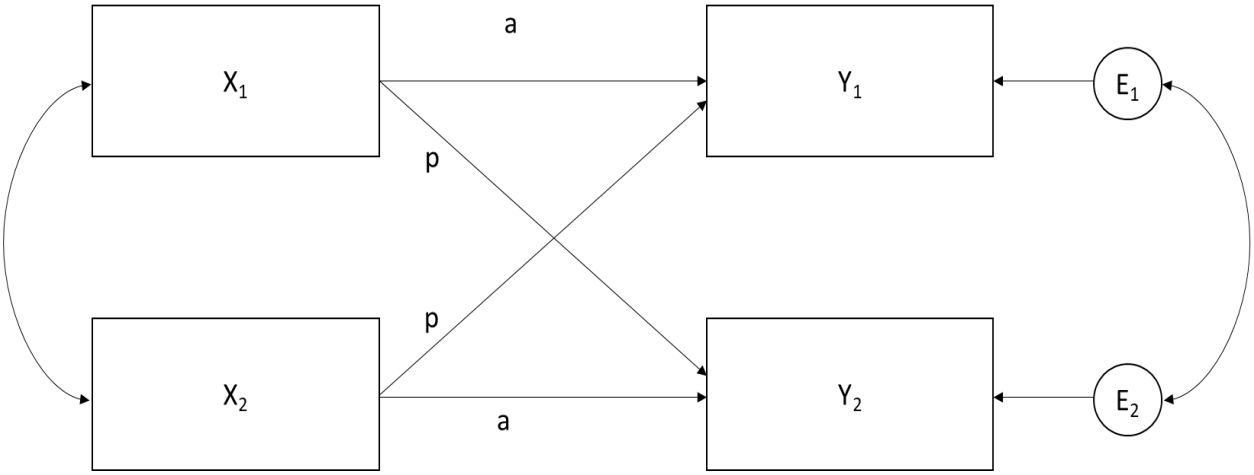
was also seen in quantitative studies.[19,39,49,52] Studies that have measured the impact of patients' sleep on caregivers' sleep and outcomes have often considered the individual (either the patient or the caregiver) as the unit of analysis rather than take on a dyadic-oriented focus.

Dyadic analysis using the Actor-Partner Interdependence Model

The Actor-Partner Interdependence Model (APIM) is a methodology developed and used extensively in psychological research to address data that involve mutual influence of thoughts, emotions and behaviors between two persons involved in close relationships.[53] The APIM is used to analyze dyadic data where the effects of interest are of mixed variables, i.e., variables that vary both between dyads and within dyads. The model has been increasingly used across research domains such as emotion, healthcare, leisure activities, communication competence, personality, commitment, interpersonal perception, relationship violence, social influence, and attachment style.[53] In healthcare, examples of studies that have used the APIM include those that aimed to understand the relationship between anxiety and HRQoL with pediatric cystic fibrosis patients and their caregivers,[54] post-traumatic stress symptoms and HRQoL in chronically critically ill patients and caregivers,[55] and patient-physician shared-decision making on their respective uncertainties of the decision being made.[56] In PD, the model has been applied to explore concepts such as benefit finding (i.e. experiencing personal growth after being faced with a challenging situation)[57] and relationship quality,[58] emotional awareness, relationship quality and satisfaction,[59] and dyadic relationship and its psychosocial impact in patients and their spousal caregivers.[60] Given the model's ability to account for interdependence in close relationships, it provides a suitable methodology to examine the impact of sleep on HRQoL in patient-caregiver dyads.

This model in Figure 1.1 below depicts two dyad members and two variables *X* and *Y*, for each member in the dyad.[53,61] X_1 and X_2 are scores on the predictor variable for dyad members 1 and 2, respectively. Y_1 and Y_2 are scores on the outcome variable for dyad members 1 and 2, respectively. *a* denotes the actor effects (X_1's effect on Y_1 and X_2's effect on Y_2) and *p* denotes partner effects (X_1's effect on Y_2 and X_2's effect on Y_1). The model allows for two correlations: correlation between the *X*'s (represented by the curved line on the left) and correlation between the *Y*'s (represented by the curved line on the right). This correlation between the *Y*'s is the residual nonindependence between the outcome variables unexplained by APIM.

Figure 1.1: Actor-Partner Interdependence Model with actor and partner effects



Need for the study

Given the multifactorial ramifications of sleep disorders in PD patients and caregivers, it is important to investigate this relationship to develop early detection strategies and appropriate care opportunities. Several studies have evaluated this relationship, albeit with significant limitations. Most studies evaluate the effect of patients' clinical characteristics on their own HRQoL or their caregivers' HRQoL or caregiver burden independently. Specifically, in the

context of sleep disorders, the correlation or the nonindependence of patients' and caregivers' sleep quality is often ignored or one of the measurements is not collected. This may give rise to biased variances and degrees of freedom in statistical significance tests, biased parameter estimates, biased statistical significance tests and standardized effect measures, loss in precision of estimates, and loss in power.[53] These biased estimates lead to inaccuracies in estimating the actual disease burden, and its spillover effects or the effect of the patients' illness on their caregiver/family. There is a need to implement appropriate statistical methodologies that account for the dyadic nature of the patient-caregiver relationship when assessing the effect of sleep disturbances on patients' and caregivers' HRQoL.

Specific aims

Considering previous literature and the above arguments, this study aimed to synthesize existing literature on the impact of sleep disorders on the HRQoL of PD patients and their caregivers, evaluate the psychometric properties of an HRQoL instrument in PD patients, and finally, assess the dyadic relationship between sleep and QoL in PD patients and caregivers using a conceptual framework. The specific aims of the study are as follows:

1. To conduct a systematic literature review to understand the relationship between sleep and HRQoL among patients with PD and their caregivers.
2. To evaluate the psychometric properties and evaluate differential item functioning of PROMIS-10 Global Health questionnaire in Parkinson's Disease patients.
3. To assess the dyadic relationship between sleep and health-related quality of life in PD patients and their caregivers using the Actor-Partner Interdependence Model (APIM).

List of References

1. Galvan and Wichmann. Pathophysiology of Parkinsonism. Clin Neurophysiol. 2008;119(7):1459-1474. doi:10.1016/j.clinph.2008.03.017

2. Merello M, Antonini A. Parkinson's Disease & Parkinsonism. International Parkinson and Movement Disorders Society. https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Parkinsons-Disease--Parkinsonism.htm. Published 2019. Accessed March 23, 2021.

3. Parkinson's Foundation. Non-Movement Symptoms. https://www.parkinson.org/Understanding-Parkinsons/Non-Movement-Symptoms. Accessed March 23, 2021.

4. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney Multicenter Study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord. 2008;23(6):837-844. doi:10.1002/mds.21956

5. Tolosa E, Gaig C, Santamaria J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. Neurology. 2009;72(Suppl 2):S12-S20.

6. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591-1601. doi:10.1002/mds.26424

7. Fahn S, Poewe W. Levodopa: 50 years of a revolutionary drug for Parkinson disease. Mov Disord. 2015;30(1):1-3. doi:10.1002/mds.26122

8. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and Movement Disorder Society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018;33(8):1248-1266. doi:10.1002/mds.27372

9. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov Disord. 2019;34(2):180-198. doi:10.1002/mds.27602

10. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2014;29(13):1583-1590. doi:10.1002/mds.25945

11. Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. npj Park Dis. 2018;4(21):1-7. doi:10.1038/s41531-018-0058-0

12. Kowal SL, Dall TM, Chakrabarti R, Storm M V., Jain A. The current and projected economic burden of Parkinson's disease in the United States. Mov Disord. 2013;28(3):311-318. doi:10.1002/mds.25292

13. Visser M, Van Rooden SM, Verbaan D, Marinus J, Stiggelbout AM, Van Hilten JJ. A comprehensive model of health-related quality of life in Parkinson's disease. J Neurol. 2008;255(10):1580-1587. doi:10.1007/s00415-008-0994-4

14. Forsaa EB, Larsen JP, Wentzel-Larsen T, Herlofson K, Alves G. Predictors and course of health-related quality of life in Parkinson's disease. Mov Disord. 2008;23(10):1420-1427. doi:10.1002/mds.22121

15. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009;24(11):1641-1649. doi:10.1002/mds.22643

16. Marras C, McDermott MP, Rochon PA, Tanner CM, Naglie G, Lang AE. Predictors of deterioration in health-related quality of life in Parkinson's disease: Results from the DATATOP trial. Mov Disord. 2008;23(5):653-659. doi:10.1002/mds.21853

17. Chaudhuri KR, Healy DG, Schapira AH V. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006;5:235-245. doi:10.4314/njm.v19i2.56496

18. Müller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. Park Relat Disord. 2013;19(11):1027-1032. doi:10.1016/j.parkreldis.2013.07.010

19. Carod-Artal FJ, Mesquita HM, Ziomkowski S, Martinez-Martin P. Burden and health-related quality of life among caregivers of Brazilian Parkinson's disease patients. Park Relat Disord. 2013;19(11):943-948. doi:10.1016/j.parkreldis.2013.06.005

20. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ. Quality of life and burden in caregivers for patients with Parkinson's disease: Concepts, assessment and related factors. Expert Rev Pharmacoeconomics Outcomes Res. 2012;12(2):221-230. doi:10.1586/erp.11.106

21. Mehta SH, Morgan JC, Sethi KD. Sleep Disorders Associated with Parkinson's Disease: Role of Dopamine, Epidemiology, and Clinical Scales of Assessment . CNS Spectr. 2008;13(S4):6-11. doi:10.1017/s1092852900017260

22. Comella CL. Sleep disorders in Parkinson's disease: An overview. Mov Disord. 2007;22(SUPPL. 17). doi:10.1002/mds.21682

23. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord. 2010;25(15):2493-2500. doi:10.1002/mds.23394

24. Avidan A, Hays RD, Diaz N, et al. Associations of sleep disturbance symptoms with health-related quality of life in parkinson's disease. J Neuropsychiatry Clin Neurosci. 2013;25(4):319-326. doi:10.1176/appi.neuropsych.12070175

25. Gómez-Esteban JC, Tijero B, Somme J, et al. Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J Neurol. 2011;258(3):494-499. doi:10.1007/s00415-010-5786-y

26. Terriff DL, Williams JVA, Patten SB, Lavorato DH, Bulloch AGM. Patterns of disability, care needs, and quality of life of people with Parkinson's disease in a general population sample. Park Relat Disord. 2012;18(7):828-832. doi:10.1016/j.parkreldis.2012.03.026

27. Abendroth M, Lutz BJ, Young ME. Family caregivers' decision process to institutionalize persons with Parkinson's disease: A grounded theory study. Int J Nurs Stud. 2012;49(4):445-454. doi:10.1016/j.ijnurstu.2011.10.003

28. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. J Am Geriatr Soc. 2000;48(8):938-942. doi:10.1111/j.1532-5415.2000.tb06891.x

29. Martínez-Martín P, Forjaz MJ, Frades-Payo B, et al. Caregiver burden in Parkinson's disease. Mov Disord. 2007;22(7):924-931. doi:10.1002/mds.21355

30. Lökk J. Caregiver strain in Parkinson's disease and the impact of disease duration. Eur J Phys Rehabil Med. 2008;44(1):39-45.

31. Peters M, Fitzpatrick R, Doll H, Playford D, Jenkinson C. Does self-reported well-being of patients with Parkinson's disease influence caregiver strain and quality of life? Park Relat Disord. 2011;17(5):348-352. doi:10.1016/j.parkreldis.2011.02.009

32. Martinez-Martin P, Macaulay D, Jalundhwala YJ, et al. The long-term direct and indirect economic burden among Parkinson's disease caregivers in the United States. Mov Disord. 2019;34(2):236-245. doi:10.1002/mds.27579

33. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev. 2017;35:33-50. doi:10.1016/j.smrv.2016.08.001

34. Suzuki K, Miyamoto M, Miyamoto T, Iwanami M, Hirata K. Sleep disturbances associated with Parkinson's disease. Parkinsons Dis. 2011;2011. doi:10.4061/2011/219056

35. Crabb L. Sleep disorders in Parkinson's disease: the nursing role. Br J Nurs. 2001;10(1):42-47. doi:10.12968/bjon.2001.10.1.5401

36. Zoccolella S, Savarese M, Lamberti P, Manni R, Pacchetti C, Logroscino G. Sleep disorders and the natural history of Parkinson's disease: The contribution of epidemiological studies. Sleep Med Rev. 2011;15(1):41-50. doi:10.1016/j.smrv.2010.02.004

37. Smith M, Ellgring H, Oertel W. Sleep disturbances in Parkinson's disease patients and spouses. J Am Geriatr Soc. 1997;45:194-199.

38. Pal PK, Thennarasu K, Fleming J, Schulzer M, Brown T, Calne SM. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. Park Relat Disord. 2004;10(3):157-168. doi:10.1016/j.parkreldis.2003.11.002

39. Cupidi C, Realmuto S, Lo Coco G, et al. Sleep quality in caregivers of patients with Alzheimers disease and Parkinsons disease and its relationship to quality of life. Int Psychogeriatrics. 2012;24(11):1827-1835. doi:10.1017/S1041610212001032

40. Drutyte G, Forjaz MJ, Rodriguez-Blazquez C, Martinez-Martin P, Breen KC. What impacts on the stress symptoms of Parkinson's carers? Results from the Parkinson's UK Members' Survey. Disabil Rehabil. 2014;36(3):199-204. doi:10.3109/09638288.2013.782363

41. Högl B, Arnulf I, Comella C, et al. Scales to assess sleep impairment in Parkinson's disease: Critique and recommendations. Mov Disord. 2010;25(16):2704-2716. doi:10.1002/mds.23190

42. Zea-Sevilla MA, Martínez-Martín P. Rating scales and questionnaires for assessment of sleep disorders in Parkinson's disease: What they inform about? J Neural Transm. 2014;121(SUPPL. 1). doi:10.1007/s00702-014-1217-z

43. Trenkwalder C, Kohnen R, Högl B, et al. Parkinson's disease sleep scale-validation of the revised version PDSS-2. Mov Disord. 2011;26(4):644-652. doi:10.1002/mds.23476

44. Martinez-Martin P, Visser M, Rodriguez-Blazquez C, et al. SCOPA-sleep and PDSS: Two scales for assessment of sleep disorder in Parkinson's disease. Mov Disord. 2008;23(12):1681-1688. doi:10.1002/mds.22110

45. Marinus J, Visser M, Van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in parkinson disease. Sleep. 2003;26(8):1049-1054. doi:10.1093/sleep/26.8.1049

46. Siciliano M, Trojano L, Santangelo G, De Micco R, Tedeschi G, Tessitore A. Fatigue in Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2018;33(11):1712-1723. doi:10.1002/mds.27461

47. Pushpanathan ME, Loftus AM, Thomas MG, Gasson N, Bucks RS. The relationship between sleep and cognition in Parkinson's disease: A meta-analysis. Sleep Med Rev. 2014;26:21-32. doi:10.1016/j.smrv.2015.04.003

48. Scullin MK, Trotti LM, Wilson AG, Greer SA, Bliwise DL. Nocturnal sleep enhances working memory training in Parkinson's disease but not Lewy body dementia. Brain. 2012;135(9):2789-2797. doi:10.1093/brain/aws192

49. Happe S, Berger K. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing. 2002;31(5):349-354. doi:10.1093/ageing/31.5.349

50. Pollak CP, Stokes PE, Wagner DR. Nocturnal interactions between community elders and caregivers, as measured by cross-correlation of their motor activity. J Geriatr Psychiatry Neurol. 1997;10(4):168-173. doi:10.1177/089198879701000408

51. Arber S, Venn S. Caregiving at night: Understanding the impact on carers. J Aging Stud. 2011;25(2):155-165. doi:10.1016/j.jaging.2010.08.020

52. Viwattanakulvanid P, Kaewwilai L, Jitkritsadakul O, et al. The impact of the nocturnal disabilities of Parkinson's disease on caregivers' burden: Implications for interventions. J Neural Transm. 2014;121(SUPPL. 1). doi:10.1007/s00702-014-1200-8

53. Kenny DA, Kashy DA, Cook WL. Dyadic Data Analysis. First ed. New York: The

Guildford Press; 2006.

54. Driscoll KA, Schatschneider C, McGinnity K, Modi AC. Application of dyadic data analysis in pediatric psychology: Cystic fibrosis health-related quality of life and anxiety in child-caregiver dyads. J Pediatr Psychol. 2012;37(6):605-611. doi:10.1093/jpepsy/jss063

55. Wintermann GB, Petrowski K, Weidner K, Strauß B, Rosendahl J. Impact of post-traumatic stress symptoms on the health-related quality of life in a cohort study with chronically critically ill patients and their partners: Age matters. Crit Care. 2019;23(1):1-10. doi:10.1186/s13054-019-2321-0

56. Turcotte S, Robitaille H, Blair L, Légaré F. The actor–partner interdependence model in shared decision-making: an illustrative example of its application to the physician–patient dyad in primary care consultations. J Clin Epidemiol. 2019;108:132-139. doi:10.1016/j.jclinepi.2018.11.027

57. Kim Y, Schulz R, Carver C. Benefit finding in the Cancer caregiving experience. Psychosom Med. 2007;69(3):283-291.

58. Mavandadi S, Dobkin R, Mamikonyan E, Sayers S, Ten Have T, Weintraub D. Benefit finding and relationship quality in Parkinson's disease: A pilot dyadic analysis of husbands and wives. J Fam Psychol. 2014;28(5):728-734. doi:10.1037/a0037847

59. Ricciardi L, Pomponi M, Demartini B, et al. Emotional Awareness, Relationship Quality, and Satisfaction in Patients with Parkinson's Disease and Their Spousal Caregivers. J Nerv Ment Dis. 2015;203(8):646-649. doi:10.1097/NMD.0000000000000342

60. Karlstedt M, Fereshtehnejad SM, Aarsland D, Lökk J. Determinants of Dyadic Relationship and Its Psychosocial Impact in Patients with Parkinson's Disease and Their Spouses. Parkinsons Dis. 2017;2017. doi:10.1155/2017/4697052

61. Kenny DA. Models of non-independence in dyadic research. J Soc Pers Relat. 1996;13(2):279-294. doi:10.1177/0265407596132007

CHAPTER 2: RELATIONSHIP BETWEEN SLEEP AND HEALTH-RELATED QUALITY OF LIFE AMONG PERSONS WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS – A SYSTEMATIC REVIEW

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease which manifests in the form of motor symptoms and non-motor symptoms (NMS). Sleep disorders are the most commonly occurring NMS among persons with PD (PWP), with a prevalence rate of ranging from 40 to 90%.[1–4] The most routinely reported sleep disorders among PWP include rapid eye movement (REM) sleep behavior disorder (RBD), insomnia, nocturia, restless legs syndrome (RLS)/periodic limb movement disorder (PLMD), sleep disordered breathing (SDB), excessive daytime sleepiness (EDS), and circadian rhythm disorders.[4] Several factors may contribute to sleep disturbances in PWP including pathological degeneration of sleep regulation in the brainstem and thalamocortical pathways, nocturia, motor rigidity, RLS, obstructive sleep apnea, rapid onset of sleep, nocturnal recurrence of PD symptoms, dopaminergic therapy, certain medications, aging, anxiety and depression, and occurrence of muscle activity during REM sleep which causes disturbed sleep and dream enactment during sleep.[2,5–8]

Researchers argue that sleep disorders in PWP may be explained by multiple modalities and that there is little evidence to indicate the correctness of one explanation over the others.[9] Hence, there is a dearth of treatment options that specifically target sleep disorders in PD. The International Parkinson's and Movement Disorder Society's Evidence-based Medicine Committee synthesized available evidence on the safety and efficacy of interventions treating PD-related sleep disorders such as continuous positive airway pressure, controlled-release

formulation of levodopa/carbidopa, some dopamine agonists (pergolide, rotigotine, piribedil), hypnotics (eszopiclone), melatonin, and psychoactive drugs (modafinil, and caffeine) and found that only a few were *"likely efficacious"*, while most had *"insufficient evidence"* to be recommended in routine use.[10]

As a result of the disease-related complications and a lack of targeted treatments, sleep disorders contribute significantly to the overall disease burden among PWP and caregivers. Several studies have highlighted the role of sleep disorders as a predictor of poor health-related quality of life (HRQoL) in PWP,[4,11–18] one of the most important outcomes of interest in chronic, progressive and complex diseases such as PD. Compared to other NMS, nighttime sleep disturbances and excessive daytime sleepiness, assessed using self-reported or clinician-reported measures, have been shown to be significantly associated with both disease-specific,[11,13,15,16,18–20] and generic HRQoL measures from patients.[14,21] However, there are studies which found contradicting evidence showing no significant relationship between sleep and HRQoL in patients.[12,25]

Similarly, there are inconsistencies in the literature regarding the role of sleep in caregiver HRQoL. Sleep disorders are very common among caregivers of PWP with estimated prevalence rates of 20-60% across samples.[23–26] Several factors may contribute to the manifestation of sleep disorders in the caregiver, such as caregivers' own distress from caregiving during the day,[23] attending to nocturnal physical needs of a patient, anticipation of nocturnal care needs, monitoring a patient during sleep, and a patient's sleep disturbances.[27] While numerous studies have identified sleep disorders as a significant predictor of increased caregiver burden or reduced HRQoL, other studies have shown a lack of support for this relationship.[25,28–32]

Despite the growth of research dedicated to understanding the role of NMS in PD, knowledge regarding the impact of sleep disorders in PWP and caregivers remains unclear. An enhanced understanding of this relationship is necessary to help advance the field of PD towards identifying therapies or innovative care programs that can help alleviate the impact of sleep disorders in PWP and their caregivers. Therefore, the current review aimed to critically and systematically evaluate the literature on the association between sleep and HRQoL in PWP and their caregivers.

Methods

A systematic review was conducted in accordance with the guidelines specified by the Meta-analyses of Observational Studies in Epidemiology (MOOSE) group.[33]

Search strategy

To identify studies assessing the relationship between sleep and HRQoL in PWP and caregivers, a literature search was conducted in June 2020 using the following databases: Medline, EMBASE, CINAHL and PsychINFO. Key search terms related to PD, sleep and HRQoL were mapped on to medical subject headings (see Table 2.1). A tailored search strategy including medical subject headings combined with subheadings and related keywords was used to capture as many studies as relevant to the current review. Truncated terms and Boolean operators were used as appropriate to ensure coverage of keywords that begin with a given string of text. A librarian was consulted during the development of the tailored search strategy in order to ensure its accuracy and efficiency. Filters were used to search for studies conducted in human subjects and published in English. Time period restrictions were not specified so as to include all studies that fall under the scope of the current review. Grey literature search was done using Google and Google Scholar. The protocol for the current systematic review was registered with

PROSPERO (protocol ID: CRD42020201837), an international database of prospectively registered systematic reviews in various fields where the outcome is related to health.[34]

Table 2.1: PubMed search terms for concepts relevant to the study objective

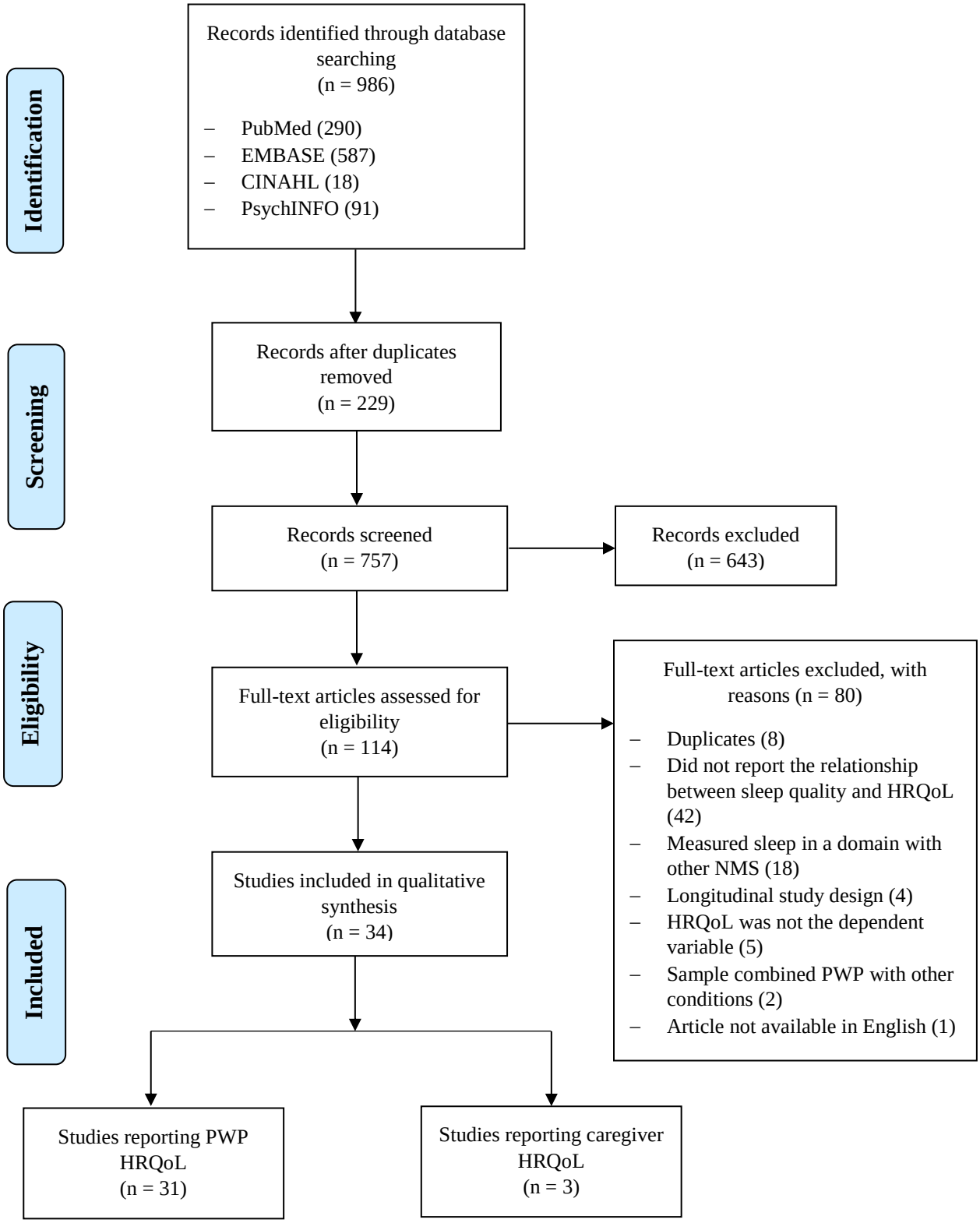
Concept	Search string
Parkinson's disease	Parkinson's Disease[MeSH Terms] OR Parkinson Disease[Tiab] OR Paralysis Agitans[Tiab] OR Idiopathic Parkinson Disease[Tiab] OR Primary Parkinsonism[Tiab]
Sleep disorders	Sleep*[tiab] OR "Sleep Wake Disorders" OR restless leg*[tiab] OR dyssomn* OR parasomn*[tiab] OR narcolep* OR somnolen*[tiab] OR hypersomn*[tiab] OR insomnolen*[tiab] OR hyposomn*[tiab] OR myoclonus syndrome[tiab] OR hypnogenic paroxysmal[tiab] OR somnamb*[tiab])
Health-related quality of life	Quality of life[MeSH Terms] OR Life quality[Tiab] OR Health-related quality of life[Tiab] OR HRQOL[Tiab] OR HRQL[Tiab]

Study selection

Inclusion criteria for studies was as follows: (1) included individuals diagnosed with idiopathic PD, (2) are cross-sectional studies, (3) evaluated the relationship between sleep and HRQoL in PWP or their caregivers or both, (4) full-text articles published in English. Longitudinal studies assessing change in any of the variables of interest, studies evaluating psychometric properties of scales related to the topic, and other reviews or expert commentaries on the topic were excluded. Longitudinal studies which reported baseline measures of sleep and HRQoL were included and only baseline data were considered in this review. Two of three reviewers (Marie Barnard, Alexcia Carr and Sushmitha Inguva) screened the title and abstract of

each article obtained from the tailored search to identify studies that were eligible based on the above criteria. Any discrepancies were resolved by a third reviewer. The reference section of each article identified for full text review was reviewed to check for articles that may not have been captured by the tailored search string. The attrition of articles excluded at each stage of the review and reasons for exclusion are presented using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2.1).

Figure 2.1: PRISMA flowchart showing article screened and included for systematic review



Data extraction and quality appraisal

A standardized electronic data extraction form was developed for the full text review to extract key information relevant to the current review. Two reviewers (Alexcia Carr and Sushmitha Inguva) independently conducted the data extraction. The following items were identified as key information to be extracted from the studies based on the Joanna Brigg's Institute's (JBI) guidelines for systematic reviews: (1) Study details: author, year, journal, funder(s), (2) Study methods/characteristics: study design, setting, recruitment procedures, sample characteristics, independent variables and how they were measured, (3) Variables: primary and secondary outcome variables and how they were measured, (4) Data analysis methods including statistical technique utilized, assessment for confounding etc., (5) Results and (6) Limitations.[35] The data extraction form was pre-tested with a few studies to ensure its validity to the aims of the current review before proceeding to extracting data from all included studies. Consensus over discrepancies between the reviewers were resolved through discussions with a third reviewer (Marie Barnard). The quality of studies was appraised using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies.[35] The tool is presented in Table 2.2.

Table 2.2: Quality appraisal form used in the systematic review based on the Joanna Briggs Institute critical appraisal checklist for analytical cross-sectional studies

Quality appraisal criteria	Response
1. Were the criteria for inclusion in the sample clearly defined?	Yes/No/Unclear/Not applicable
2. Were the study subjects and the setting described in detail?	
3. Was the exposure measured in a valid and reliable way?	
4. Were objective, standard criteria used for measurement of the condition?	
5. Were confounding factors identified?	
6. Were strategies to deal with confounding factors stated?	
7. Were the outcomes measured in a valid and reliable way?	
8. Was appropriate statistical analysis used?	
9. Overall appraisal	Include/Exclude/Seek further info
10. Comments (including reason for exclusion)	

Data synthesis

Data extracted from the included studies and their quality assessment are presented in Tables 2.3–2.8 (presented at the end of this chapter). A narrative synthesis of the results is presented below. A narrative synthesis refers to the synthesis of findings across multiple studies included in a systematic review that primarily relies on the use of text to summarize, often complemented by a series of tables.[36–38] The goal is to present a narrative of the findings of reviewed studies to guide the reader through information such as direction of effect, inconsistencies across studies etc.[36–38]

Results

Search yield

The initial electronic search yielded 986 published articles (Figure 2.1). After removing duplicates and reviewing titles and abstracts, 114 were considered suitable for full-text review. By applying a set of pre-defined inclusion and exclusion criteria as mentioned above, 34 articles in total were identified for inclusion in the current systematic review. Of them, 31 studies reported on PWP HRQoL, whereas 3 studies reported caregiver HRQoL. Characteristics of studies that assessed HRQoL of PWP are summarized in Table 2.3 and those that assessed caregiver's HRQoL are summarized in Table 2.4.

Study characteristics

While most of the studies assessing PWP HRQoL used a cross-sectional design, four articles reported sleep and HRQoL measures at the baseline from a prospective study (Table 2.3).[16,39–41] All articles assessing PWP HRQoL had sample sizes in the range of 35-1221, with the majority of the studies having a sample size of more than 100. Three studies enrolled more than 500 PWP, two of which collected data through population-based studies or registries.[20,39,42] Twenty-nine of the 31 PWP studies conducted consecutive sampling from hospitals and movement disorders or neurology clinics. While Karlsen et al.[11] used a population sample recruited from the community and Ylikoski et al.[42] used a national registry.

Among studies which measured caregiver HRQoL, all studies were cross-sectional and had sample sizes between 40-75 (Table 2.4). Two of them conducted consecutive sampling,[25,43] while all three recruited PWP-caregiver dyads through outpatient clinics for this purpose.

Sample characteristics

Most studies assessing PWP HRQoL reported the mean age of participants to be over 65 years, while one study also enrolled young-onset PWP (Table 2.3).[44] Studies that reported HRQoL of PWP mostly enrolled individuals with mild to moderate PD severity as measured by

the Hoehn and Yahr (H&Y) staging assessment. However, four studies included individuals with severe PD (H&Y stage 5) within their sample, although these individuals made up less than 5% of the total sample.[14,17,20] In studies that reported disease duration, most of the studies enrolled participants with a mean disease duration of at least 5 years. Two studies reported individuals in the earlier stages (within 5 years) of their diagnosis.[39,41,45]

Among studies that examined caregiver outcomes, the mean age of caregivers was reported to be over 50 years (Table 2.4). Only one study reported the relationship between caregivers and PWP where most caregivers were spouses, followed by children and siblings.[46]

Measurement of sleep

The studies included in this review used subjective, patient-reported sleep measures (Table 2.3). Both generic and disease-specific sleep measures were utilized. Among disease-specific measures, the Parkinson's Disease Sleep Scale (PDSS) and the Scales for Outcomes in Parkinson's Disease (SCOPA)-sleep nighttime sleep disturbances and daytime sleepiness scores were most commonly reported. Some studies reported other measures such as the United Parkinson's Disease Rating Scale (UPDRS) parts I[47] and IV,[48] the Medical Outcomes Study sleep measure,[14] and interview questions to elicit presence of sleep disturbances[11,28,42] among patients. Among generic scales, the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) were commonly used to measure sleep disturbances and EDS. The PSQI, the ESS and the Medical Outcomes Study – Sleep Scale (MOS-SS) were reported to measure sleep among caregivers (Table 2.4).

Measurement of HRQoL

Studies that reported PWP's HRQoL used measures that can be classified as health status, health utility and well-being scales. The majority of the studies used either a generic or a disease-

specific health status measure to measure HRQoL (Table 2.3). The most frequently used disease-specific measure was the Parkinson's Disease Questionnaire-39 (PDQ-39). Two studies also used another disease-specific measure – the Parkinson's Disease Quality of Life (PDQL) scale.[49,50] Among studies that used generic measures, three used the SF-36.[14,41,51] Other studies reported the EQ-5D,[39] EQ-VAS,[40] Nottingham Health Profile (NHP)[11] and World Health Organization Quality of Life Assessment for Older Adults (WHOQOL-OLD).[52]

Among caregivers, the SF-36,[43] WHOQOL-BREF[46] and McGill Quality of Life Questionnaire (MQoL)[25] were reported as HRQoL measures (Table 2.4).

Relationship between sleep and HRQoL among PWP

Results examining the relationship between sleep and HRQoL among PWP are provided in Table 2.5. There was variation in results reported across studies. The majority of the studies reported a significant impact of sleep on reduced HRQoL. However, two studies were identified which showed lack of a significant relationship between PWP sleep and their own HRQoL.[53,54] Some studies also showed the significant impact of one or more dimensions of sleep on HRQoL rather than sleep quality in general. For example, Kuhlman et al. showed that while ESS was a significant predictor of worse HRQoL, whereas SCOPA-sleep nighttime was not.[16] On the other hand, Naismith et al. noted that SCOPA-sleep nighttime was positively correlated with PDQ-39, whereas SCOPA-sleep day was not.[55]

Further, some studies used structural equation modeling (SEM) to explore the complex interrelated associations across several PD-related factors and their impact on PWP HRQoL.[40,49,56,57] In addition to sleep's direct effect on HRQoL,[56,57] these studies also pointed to indirect effects through depression,[49,56] fatigue,[56] ADL[40,56] and pain catastrophizing.[57] Moreover,

Lee et al. found significant indirect effects of disease severity, social support and pain on HRQoL through sleep disturbances.[56]

Relationship between sleep and caregiver HRQoL

Results examining the relationship between sleep and HRQoL among caregivers of PWP are provided in Table 2.6. Two of three studies identified in this review showed that sleep-related problems were common among caregivers of PWP.[25,43]

Within studies reviewed, Bartolomei et al. showed that patient sleep was associated with lower physical and mental health scores.[43] Ozdilek et al. did not show a significant relationship between PWP sleep and HRQoL.[46] Cupidi et al.[25] reported significant negative impact of caregiver sleep on their own HRQoL.

Quality appraisal

Most included articles well-addressed quality appraisal criteria related to research objectives and description of participant characteristics (Tables 2.7 for PWP studies and 2.8 for caregiver studies). The majority of articles also provided a clear explanation of the study design and recruitment strategies. All of the studies reporting caregiver outcomes used appropriate statistical methods and accounted for confounders. Studies reporting PWP's HRQoL applied statistical analysis techniques as suited to the research objectives. Twenty-six of these studies accounted for confounders statistically, while the remaining five studies did not control for confounding at the study design nor at the analysis stages.[52,55,58–60]

Discussion

There has been an increasing interest in understanding the role of NMS in PD. Sleep-related disorders are not only one of the most common NMS, but also present several challenges in PD treatment and management. Despite the significant challenges posed by sleep disturbances in PD, there is a lack of consensus on its role in relation to PWP/caregiver HRQoL and caregiver

burden. Therefore, the current review focused on critically evaluating and synthesizing current literature on the association between sleep and HRQoL among PWP and their caregivers.

Studies reporting HRQoL among PWP

Despite the heterogeneous nature of studies included in this review, the majority (29 of 31) found PWP's sleep to be a significant predictor of their own HRQoL. Two studies failed to show evidence in support of this relationship.[53,54] One of the reasons contributing to this lack of relationship could be study cohort-specific factors. For example, these two studies evaluated cohorts of individuals who reported a disease severity level of H&Y stage less than 2,[53,54] whereas the other studies enrolled PWP across all stages of the disease spectrum. Given that PD severity is one of the important factors which predict the prevalence of certain sleep disorders,[61–65] the relative frequency of sleep disturbances and their intensity in these studies may have been low.

In terms of sleep assessment, all studies provided self-reported measures of either PD-specific or generic measures of sleep among PWP. The dearth of studies using objective tools such as polysomnography or actigraphy is not surprising given the well-established, robust psychometric properties of these self-reported measures as well as practical considerations such as time and economic constraints in routine clinical practice. The PDSS/PDSS-2 was the most commonly used disease-specific measure. Most other studies included separate measures for nocturnal and diurnal sleep symptoms in their analyses. Among such studies, the results were somewhat ambiguous as some identified both nighttime and daytime sleep measures as significant predictors of HRQoL,[14,15,18,20,39,50,60,66,67] whereas some identified only nighttime[55] or daytime[16,17,40,45,68] sleep symptoms as significant contributing factors to HRQoL among PWP.

Further, most included studies conducted multivariable analytic methods to account for confounding factors. Multivariable ordinary least squares regression with HRQoL as the dependent variable was the most common choice among studies reviewed, while 5 of 31 studies merely reported bivariate analyses.[52,55,58–60] It is worth noting that there were four studies which utilized SEM in order to develop comprehensive, structural models that account for the complex interrelationships among several predictors of HRQoL simultaneously.[40,49] Significant, meaningful findings from these studies make a strong argument for use of such methods which may be better equipped to explain the multifaceted relationships encountered in PD.

Studies reporting HRQoL among caregivers

This review yielded three studies which measured caregiver-reported outcomes, which explored diverse research questions. One study evaluated the association between caregiver's sleep and caregiver HRQoL and found a significant relationship.[25] Another study evaluated the impact of PWP's sleep on caregiver outcomes and did not find a significant relationship.[46] The other study evaluated several relationships – the impact of PWP's sleep on caregiver's sleep, HRQoL and burden, respectively, as well as the impact of PWP's HRQoL on caregiver's HRQoL and burden, respectively.[43] It is interesting to note that while all these studies recruited PWP-caregiver dyads and collected data from both members, none of the studies accounted for the interdependent nature of the constructs. Specifically, the bidirectionality of sleep disturbances and their mutual influence on each dyad member's HRQoL in PWP-caregiver dyads have been ignored. Future studies should probe into this complicated phenomenon to better understand the scope of sleep disturbances and their role in the PWP-caregiver dynamic.

Moreover, the role of depression as a mediator of the relationship between sleep and their HRQoL, specifically the psychological symptoms domain, has been highlighted.[25] This

relationship was also reported in some of the PWP studies we reviewed in the context of PWP sleep and HRQoL as well.[49,56] There is some literature supporting depression or the broader mental well-being domain as a mediator in this path model in older adults, regardless of disease state.[69,70] However, there is also evidence that suggests sleep quality may in fact mediate the relationship between depression and quality of life in older adults.[71] There is a need for more empirical evidence, preferably from longitudinal studies, to evaluate the temporality and reproducibility of these results.

In accordance with the objective for this review to identify studies evaluating the impact of either PWP or caregiver's sleep on caregiver HRQoL, three studies which focused on caregiver HRQoL were identified.[25,43,46] However, while reviewing the articles, three other studies were identified which measured caregiver burden as an outcome.[28,29,32] Data extracted from these three studies are reported in the Appendix. Given the strong correlation between caregiver burden and HRQoL,[72–75] future studies may consider reviewing studies which have assessed the impact of PWP or caregiver's sleep on caregiver burden.

Limitations

There are some limitations to bear in mind while viewing these results. First, a majority of the studies that measured caregiver outcomes had low sample sizes. Consequently, the results may not be generalizable to the larger PD population. Second, this review only included cross-sectional studies and hence, results are limited to correlations between variables of interest. However, this review lays the groundwork for future research aiming to gain a better understanding of sleep patterns and their impact on humanistic outcomes in PWP and their caregivers. A review of longitudinal studies is warranted to generate evidence supporting causal inferences.

Conclusion

To our knowledge, this review is the first to summarize existing literature on the importance of sleep in the context of humanistic burden among PWP and their caregivers. Empirical evidence suggests that sleep-related issues have a significant impact on HRQoL among PWP. There is a need for more studies evaluating the impact of PWP or caregiver sleep on caregiver HRQoL. A review of studies assessing caregiver burden is required to better understand the impact of PWP or caregiver's sleep on caregivers.

Implications for clinical practice

In clinical practice, it is recommended that the input of the caregiver or the bed partner be sought for a more objective assessment of PWP's sleep and wakefulness behaviors.[76] However, at present there is no guidance on screening caregivers for sleep-related issues. Healthcare professionals may consider initiating conversations related to sleep issues with caregivers during a clinic visit, followed by either treatment initiation or referrals to specialist health services, whichever is appropriate. There are several non-pharmacological interventions such as use of melatonin supplements, practicing meditation and mindfulness techniques, and incorporating physical activity into daily routines that may help alleviate some sleep symptoms and improve HRQoL. Additionally, in case of co-occurrence of sleep disorders in PWP-caregiver dyads, optimization of anti-Parkinsonian or sleep medications to reduce symptom burden may be considered which may prove to be beneficial for both members of the dyad. Finally, sharing caregiving responsibilities with another informal or hired caregiver and seeking respite care services may also be considered to reduce the burden of sleep issues among caregivers.

Table 2.3: Methodological characteristics of included studies that reported health-related quality of life of persons with Parkinson's disease

Author, Publication Year, Country	Study design			Participant characteristics				
	Design	Recruitment method	Source of participants	Sample size	Age in years (Mean ± SD)	Female (%)	H&Y stage	Disease duration in years (Mean ± SD)
Andreadou et al.[48] 2011 Greece	CS	Consecutive	Outpatient clinic of a Neurology Department	139	69.6 ± 9.1 Range: 42-89	51	Mean = 2.1, SD = 0.8	8.5 ± 6.2
Avidan et al.[14] 2013 US	CS	Population	Neurologist clinics	371	72.2 ± 9.2	4.5	Stage 0 (0), stage 1 (7.8%), stage 1.5 (4.6%), stage 2 (32.7%), stage 2.5 (29.4%), stage 3 (19.0%), stage 4 (3.9%), stage 5 (2.6%)	4.6 ± 2.2

Baig et al.[39] 2015 UK	PS (baseline measures were reported in the study)	NR	Neurology and elderly care clinics in hospitals based in several locations across the UK	769	67.7 ± 9.5 Range: 32-89	33.9	Stage 0 (0), stage 1 (23.3%), stage 2 (69.3%), stage 3 (7.5%), stage 4-5 (0)	1.3 ± 1.0
Fan et al.[53] 2016 Taiwan	CS	NR	Outpatient clinics of a movement disorder specialist	134	64.89 ± 9.19 Range: 41-87	36.6	Mean = 1.43, SD = 0.64	7.86 ± 5.55 Range: 0-23
Gallagher et al.[17] 2010 UK	CS	NR	Three different hospitals	89	67.5 ± 9.5	31	Stage 1 (n = 1), stage 2 (n = 56), stage 3 (n = 29), stage 4 (n = 5), and stage 5 (n = 3)	7.8 ± 7.5
Gómez-Esteban et al.[13] 2010 Spain	CS	Consecutive	Movement Disorders Unit of a hospital	99	NR	NR	NR	8.7 ± 6.3

Havlikova et al.[18] 2011 Slovakia	CS	NR	1 hospital and 18 outpatient departments	93	Patients with H&Y ≤ 2: 67.8 ± 9.23 Patients with H&Y > 2: 70.3 ± 10.8	Patients with H&Y ≤ 2: 49.3% Patients with H&Y > 2: 57.1%	NR	Patients with H&Y ≤ 2: 5.43 ± 4.3 Patients with H&Y > 2: 8.06 ± 5.2
Herman et al.[58] 2015 Israel	CS	NR	Movement Disorders Clinic	110	65.13 ± 9.23	24.5	H&Y during "off" time: Mean = 2.58, SD = 0.69	5.58 ± 3.52
Karlsen et al.[77] 1999 Norway	CS	Population	County of Rogaland	233	73.6 ± 8.4	51	Mean = 2.9, SD = 1.1	6.3 ± 5.3
Kuhlman et al.[16] 2019 US	PS (baseline measures were reported in the study)	NR	Movement disorders clinic	102	68.2 ± 10.1	39.2	NR	68.2 ± 10.1

Lee et al.[49] 2014 Korea	CS	NR	Neurology outpatient department of a tertiary hospital	217	<65: N = 94 (43.3%) 65-74: N = 83 (38.2%) ≥75: N = 40 (18.4%)	52.1	NR	6.63 ± 5.31 Range: 0.08-30.0
Lee et al.[56] 2018 Korea	CS	Convenience	Inpatient and outpatient neurologic clinic of a tertiary hospital	248	65.82 ± 9.07	60.1	Modified H&Y stage: Mean = 2.64, SD = 0.80, Median = 3	7.62 ± 4.58
Lerman et al.[57] 2019 Israel	CS	NR	Tertiary neurology setting	103	65.03 ± 8.98	42		6.98 ± 4.96
Margis et al.[52] 2010 Brazil	CS	Consecutive	Movement Disorders Clinic	57	70.3 ± 6.8 Range: 60-86	47	NR	7.5 ± 5.8 Range: 1-31

Naismith et al.[55] 2010 Australia	CS	NR	Parkinson's Disease Research Clinic	35	63.91 ± 7.6 Range: 42-85	45.7	Mean = 2.2, SD = 0.6	5.8 ± 5.3 Range =1–20
Nicoletti et al.[59] 2017 Italy	CS	NR	Outpatient facilities	272	66.2 ± 9.4, Range: 37-89	65	NR	7.3 ± 5.8 Range: 1-40
Palmeri et al.[66] 2019 Italy	CS	NR	NR	48	Bad Sleepers: 71.00 ± 5.50 Good sleepers: 68.38 ± 5.77	NR	NR	Bad sleepers 10.04 ± 5.53 Good sleepers 11.43 ± 7.82
Pandey et al.[60] 2016 India	CS	NR	Department of Neurology of tertiary care teaching institute	100	59.2 ± 9.06	25	Stage 1-2 (mild PD) (n = 65), stage 2.5-3 (moderate PD) (n = 29), stage 4-	44.87 ± 44.06 (in months)

							5 (severe PD) (n = 6)	
Park et al.[44] 2018 Republic of Korea	CS	NR	Movement disorder clinic at 5 university hospitals	132	Young-onset PD: 49.1 ± 3.3 Middle-onset PD: 61.7 ± 5.5 Late-onset PD: 74.6 ± 3.6	Young-onset PD: 46.2 Middle-onset PD: 60 Late-onset PD: 50	NR	(in months) Young-onset PD: 27.5 ± 15.6 Middle-onset PD: 14.3 ± 11.0 Late-onset PD: 13.8 ± 9.6
Qin et al.[41] 2009 China	RCT (baseline measures were reported in the study)	Population	Movement Disorder Clinics	391	63.77 ± 9.80	34.5	Mean = 2.00, SD = 0.70	2.98 ± 1.92

Semiz et al.[50] 2007 Turkey	CS	NR	Movement disorder clinic	120	67.8 ± 12.5	30	Stage 1: 15 (12.5%), stage 2: 46 (38.3%), stage 3: 27 (22.5%), stage 4: 32 (26.7%)	4.7 ± 4.9
Skorvanek et al.[47] 2015 Slovakia	CS	NR	Movement Disorder Centers	291	Mean age = 68, SD = 9.0 Median age = 70 Range: 30 - 88	46.4	NR	NR
Sun et al.[68] 2018 China	CS	NR	Movement disorder specialist clinic	121	66.46 ± 8.57	44.6	Mean = 2.70, SD = 0.77	12.84 ± 2.92

Tibar et al.[54] 2018 Morocco	CS	NR	Department of Neurology and Neurogenetics in a university hospital	117	60.77 ± 11.36	44.4	H&Y stage > 2 (27.3%)	NR
Vila Cha et al.[51] 2019 UK	CS	NR	Movement Disorders Clinic	229	69 ± 11	46.7	"Off" time: Mean = 2.7, SD = 0.7 "On" time: Mean = 2.3, SD 0.5	9 ± 6
Visser et al.[40] 2008 UK	PS (baseline measures were reported in the study)	NR	University and regional hospitals	378	60.0 ± 11.2	33.9	NR	NR
Walton et al.[67] 2014 Australia	CS	NR	Parkinson's Disease Research Clinic	203	66.77 ± 8.9	32	Stage 1 (n = 39), stage 1.5 (n = 7), stage 2 (n = 98), stage 2.5 (n = 39),	61.3 ± 61.3 (in months)

							stage 3 (n = 20)	
Xiang et al.[20] 2019 China	CS	NR	Clinic or inpatient department of Department of Neurology	1221	61.5 ± 9.9	45.9	Stage 1: 178 (14.6%), stage 1.5: 161 (13.2%), stage 2: 268 (21.9%), stage 2.5: 231 (18.9%), stage 3: 314 (25.7%), stage: 53 (4.3%), stage 5: 16 (1.3%)	5.1 ± 4.5
Ylikoski et al.[42] 2017 Finland	CS	Registry	Finnish Parkinson Association Registry	684	67.8 ± 8.7	54.1	NR	6.1 ± 5.0

Yoo et al.[45] 2019 Korea	CS	NR	University hospital	198	69.1 ± 9.7	52	Mean = 1.8, SD = 0.7	0.9 ± 1.4
Yu et al.[15] 2015 Taiwan	CS	NR	Neurology outpatient clinics	211	64.08 ± 9.44	44.6	Mean = 2.25, SD = 0.84	6.02 ± 4.53

H&Y = Hoehn & Yahr, CS = Cross-sectional, SD = Standard deviation, NR = Not reported, PS = prospective, PD = Parkinson's disease, RCT = Randomized controlled trials

Table 2.4: Methodological characteristics of included studies that reported health-related quality of life and/or caregiver burden of caregivers of persons with Parkinson's disease

Author, Publication Year, Country	Study design			Participant characteristics			
	Design	Recruitment method	Source of participants	Sample size	Age in years (Mean ± SD)	Female (%)	Relationship to care recipient
Bartolomei et al.[43] 2018 Italy	CS	Consecutive	Multiple hospital clinics	75	62.0 ± 12.0	48	NR
Cupidi et al.[25] 2012 Italy	CS	Consecutive	Neurology clinic	40	64.2 ± 9.4	70	NR
Ozdilek et al.[46] 2012 Turkey	CS	NR	Neurology clinic	50	56.6 ± 13.2 Range: 20-85	78	Spouse (74%), Children (22%), Siblings (4%)

CS = Cross-sectional, SD = Standard deviation, NR = Not reported, PS = prospective

Table 2.5: Sleep and health-related quality of persons with Parkinson's disease

Author, Publication Year, Country	Sleep measurement tool & score Mean ± SD	HRQoL measurement tool and score Mean ± SD	HRQoL results	Study limitations
Andreadou et al.[48] 2011 Greece	UPDRS Part IV sleep disturbances: 43 of 139 patients reported sleep disturbances (30.9%)	PDQ-39 summary index: 22.1 ± 18.2	Sleep disturbances were significantly associated with lower HRQoL.	– Selection bias introduced due to exclusion of more severe patients (H&Y stage 5)
Avidan et al.[14] 2013 US	MOS sleep measure domains – Sleep disturbance (initiation): 21.8 ± 25.6 Sleep disturbance (maintenance): 34.9 ± 24.5 Awakening short of breath or with headache: 9.8 ± 20.0 Daytime somnolence: 39.7 ± 20.7 Sleep inadequacy: 40.8 ± 26.8 Snoring: 37.3 ± 33.4	SF-36 v.2 measure domains – Physical functioning: 36.8 ± 11.5 Physical role limitations: 39.1 ± 11.2 Emotional role limitations: 42.7 ± 11.9 Pain: 46.3 ± 10.9 Emotional well-being: 48.0 ± 10.3 Energy: 45.9 ± 11.2 General health: 42.0 ± 9.3 Social functioning: 44.3 ± 10.3	Sleep disturbance (initiation), awakening short of breath or with headache, daytime somnolence were significant negative predictors of SF-36 v.2 PCS. Sleep disturbance (initiation) and awakening short of breath or with headache were significant predictors of SF-36 v.2 MCS.	– Cross-sectional study; cannot determine causality – Lack of objective measures of sleep – MOS sleep measures were not on Movement Disorders Society taskforce review of sleep measures

		SF-36 v.2 composite scores – Physical: 39.2 ± 10.0 Mental: 48.3 ± 11.0		
Baig et al.[39] 2015 UK	Daytime somnolence (ESS): Median (IQR): 7 (4-10) RBD (RBDSQ): Median (IQR): 4 (2-7)	EQ-5D: scores not reported	Sleep disturbance, daytime somnolence and RBD were significant predictors of worse HRQoL.	– Residual confounding – Recall bias – Potential bias of mobility, comorbidity, cognition and social constraints among nonparticipants
Fan et al.[53] 2016 Taiwan	PDSS-2: 18.36 ± 16.72 Range: 1-72	PDQ-39: 37.99 ± 25.40 Range: 0-135	PDSS-2 was not a significant predictor of worse HRQoL.	– Brief self-report scales prohibited from clarifying nature of mood disorders – Cross-sectional study; cannot determine causality – Psychiatrist-based interviews may help elucidate types of mood disorders that may impact HRQoL

Gallagher et al.[17] 2010 UK	PSQI, ESS, SCOPA sleep night, SCOPA sleep daytime: scores were not reported	PDQ-39: score not reported	Two regression models were conducted – model 1 (included clinical scale summary indices only) and model 2 (included clinical scale summary indices and autonomic subscales): SCOPA sleep daytime was a significant predictor of worse HRQoL in both models.	– Use of self-reported questionnaires (potential under-representation of patients with cognitive impairment and apathy) – Selection bias arising due to inclusion of patients at movement disorder clinics who may have achieved optimization of therapy – Motor scores assessment in "on" state may lead to less between-patient variability
Gómez-Esteban et al.[13] 2010 Spain	PDSS: 108.9 ± 14.6, 95% CI: (102.9, 110.0) ESS: 8.6 ± 4.3, 95% CI: (7.9, 10.1)	PDQ-39: 24.7 ± 13.2, 95% CI: (22.1, 27.4)	Stepwise linear regression model identified four variables (in order of importance: NPI, PDSS, UPDRS IV and UPDRS I) accounting for 67.2% of the	– Use of MMSE which has low sensitivity for detecting cognitive deterioration

			variance in PDQ-39 summary index.	
Havlikova et al.[18] 2011 Slovakia	PSQI: H&Y ≤ 2 group: 8.6 ± 4.8 H&Y > 2 group: 10.2 ± 4.7 ESS: H&Y ≤ 2 group: 7.1 ± 4.4 H&Y > 2 group: 9.1 ± 5.6	PDQ-39: H&Y ≤ 2 group: 29.9 ± 17.9 H&Y > 2 group: 51.1 ± 17.8	PSQI and ESS were both significant predictors of worse HRQoL.	– Low response rate – Sample may not be representative of patients outside of outpatient clinics and those with higher disease severity levels – Use of generic instruments for sleep
Herman et al.[58] 2015 Israel	PSQI: scores were not reported	PDQ-39: PIGD group: 21.75 ± 12.25 TD group: 20.84 ± 14.90 p-PIGD group: 26.28 ± 12.46 p-TD group: 16.93 ± 12.22	PSQI was significantly correlated with lower PDQ-39.	– Cross-sectional study; cannot determine causality – Patients with dementia were excluded – NMSQuest was assessed which has a recall period of a month which encapsulated “on” and “of” periods.

Karlsen et al.[77] 1999 Norway	Presence of nocturnal sleep disturbances (60.3%)	NHP: 137.1 ± 97.3 NHP subdimensions – Emotional reactions: 13.1 ± 17.0 Energy: 26.3 ± 33.3 Pain: 22.0 ± 24.6 Physical mobility: 41.2 ± 31.7 Sleep: 27.2 ± 28.4 Social isolation: 20.4 ± 23.6	Presence of nocturnal sleep disturbance was a significant predictor of lower total NHP and subdimensions including physical mobility, sleep and social isolation.	– None reported
Kuhlman et al.[16] 2019 US	SCOPA-Sleep NS: Median (IQR): 4 (2-7) ESS: Median (IQR): 8 (5-13)	PDQ-39: Median (IQR): 13.6 (7.9-20.7)	ESS was a significant predictor of worse HRQoL, while SCOPA-sleep NS was found not to be significant.	– Cross-sectional study; cannot determine causality – Not generalizable to more advanced PD and other sub-populations – Factors such as social support and exercise were not measured
Lee et al.[49] 2014 Korea	RCSQ: 18.09 ± 5.30 Range: 5-25	PDQL: 130.83 ± 29.43 Range: 56-183	Quality of sleep did not have a significant direct effect, but had an indirect effect on	– Results are not generalizable to patients with cognitive impairment and

			HRQOL, through depression.	those with higher disease severity levels
Lee et al.[56] 2018 Korea	PDSS: 100.13 ± 29.42	PDQ-39: 33.16 ± 19.63	Sleep disturbances had a significant direct effect and indirect effect on HRQoL through depression, fatigue and ADL. Disease severity, social support and pain had indirect effects on HRQoL through sleep disturbances.	– UPDRS III was not measured – PDQ-39 items partially overlapped with several variables such as mobility, ADL, bodily discomfort and emotional well-being
Lerman et al.[57] 2019 Israel	PDSS: scores were not reported	PDQ-39: scores were not reported	Sleep disturbances (PDSS) had significant direct and indirect (through pain catastrophizing) effects on HRQoL.	– Inflated shared variance due to the use of self-report questionnaires – Other factors such as sexual dysfunction and autonomic abnormalities were not assessed – Sample included persons without severe cognitive impairment – Cross-sectional study; cannot determine causality

Margis et al.[52] 2010 Brazil	PSQI: 9.3 ± 4.6 ESS: 7.8 ± 4.4 PDSS: 91.5 ± 29.7	WHOQOL-OLD total: 63.9 ± 14.0 WHOQOL-OLD domains – Sensory capabilities: 60.8 ± 23.7 Autonomy: 61.3 ± 16.4 Past, present and future activities: 66.0 ± 18.4 Social participation: 58.3 ± 20.8 Death & dying: 67.5 ± 25.2 Intimacy: 70.2 ± 20.2	WHOQOL-OLD domains sensory capabilities and autonomy were correlated significantly with sleep measures. Specifically, sensory capabilities showed a negative association with PSQI and a positive correlation with PDSS scores, whereas those for autonomy showed an inverse association with PSQI.	– No comparator groups – Small sample size (N = 57) – Not generalizable to PD patient population at large
Naismith et al.[55] 2010 Australia	SCOPA-sleep day: 5.00 ± 3.30 Range: 1-13 SCOPA-sleep night: 6.46 ± 4.00 Range: 0-15	PDQ-39: 38.60 ± 27.60 Range: 5-98	SCOPA-sleep night was positively correlated with PDQ-39, whereas SCOPA-sleep day was not significantly correlated.	– Small sample size (N = 35) – Disease severity ranged from mild to moderate – Difficult to dissect complex interrelated multifactorial relationships in a small clinical study

Nicoletti et al.[59] 2017 Italy	PDSS: scores were not reported	PWS: 348.72 ± 46.12 Range: 222-454 Domains – Autonomy: 60.18 ± 8.60, Range: 35-84 Environmental mastery: 56.98 ± 9.51, Range: 32-83 Personal growth: 55.74 ± 8.22, Range (28-80) Positive relations: 60.03 ± 10.21, Range: 26-83 Purpose in life: 57.33 ± 9.56, Range: 28-78 Self-acceptance: 58.46 ± 10.65, Range: 19-82 PDQ-39: scores were not reported	A direct correlation was found between PWS total score and PDSS total score. PDSS was also significantly correlated with all domains of PWS.	– Cross-sectional study; cannot determine causality – Study sample mainly comprised of patients in the early stages of the disease – Uninvestigated factors contributing to PWS total score variability
Palmeri et al.[66] 2019 Italy	PSQI: Bad sleepers (PSQI > 5): 11.78 ± 4.05	PDQ-39: Total: Bad sleepers: 37.63 ± 16.37 Good sleepers: 31.69 ± 10.33	Backward linear regression in bad sleepers group showed ESS to be a significant predictor of worse	– Small sample size (N = 48) – Use of antidepressants and sleep therapy

	Good sleepers (PSQI ≤ 5): 0.76 ± 1.30 ESS: Bad sleepers: 8.59 ± 2.94 Good sleepers: 3.24 ± 2.02	Domains: Mobility, ADL, emotional well-being, stigma, social support, cognition, communication and bodily discomfort were not significantly different between bad and good sleeper groups.	cognition and bodily discomfort, respectively. Backward linear regression in bad sleepers group showed ESS and PSQI each to be significant predictors of worse ADL; ESS as a significant predictor of higher stigma, worse cognition, respectively; and PSQI as a significant predictor of communication.	were not considered
Pandey et al.[60] 2016 India	PSQI: Poor sleepers (PSQI > 5): 50% patients Good sleepers (PSQI ≤ 5): 50% patients ESS: Poor sleepers: 5.18 ± 3.45 Good sleepers: 5.34 ± 4.38	PDQ-39 summary index score: Poor sleepers: 20.14 ± 15.19 Good sleepers: 27.20 ± 16.41	Both PSQI and ESS were correlated with poor HRQoL. Compared to good sleepers, patients with poor sleep quality had worse HRQoL as determined by PDQ-39 summary index scores.	– Use of generic sleep scale

Park et al.[44] 2018 Republic of Korea	PDSS: YOPD: 127.4 ± 19.3 MOPD: 127.8 ± 19.7 LOPD: 128.3 ± 19.2	PDQ-39: YOPD: 4.4 ± 7.6 MOPD: 14.3 ± 12.4 LOPD: 12.6 ± 11.2	Sleep was a significant predictor of worse HRQoL in the MOPD group.	– Did not enroll age-matched controls – Higher frequency of comorbidities and medications for these diseases in LOPD – Mostly enrolled early stage patients therefore, advanced symptoms could not be assessed
Qin et al.[41] 2009 China	PSQI: 7.60 ± 8.60	SF-36: 63.76± 19.39 With sleep problem group: 57.68 ± 19.65 Without sleep problems group: 71.17± 16.30	Patients without sleep problems had significantly higher HRQoL than patients with sleep problems.	– Use of generic QoL instrument – Limited generalizability
Semiz et al.[50] 2007 Turkey	PDSS: 88.7 ± 32.1 PSQI: 9.0 ± 4.1 ESS: 7.3 ± 5.4	PDQL: 76.2 ± 25.3	In stepwise regression analysis, PDSS and PSQI were found to be significantly associated with worse PDQL scores.	– Lack of a control group – Recall bias – Lack of use of polysomnography to assess sleep
Skorvanek et al.[47]	UPDRS part I: 14.0 ± 7.6 Median = 13	PDQ-39: Summary index: 36.7 ± 19.7	In a multiple regression analysis model worse HRQoL as measured by the	– More motivated patients agreed to participate and were able to

2015 Slovakia	Range: 2-40	Median = 37.2 Range: 0-85	PDQ39 summary index was significantly related to the MDS–UPDRS parts I, II and IV, respectively. Within domains, PDQ-39 emotional well-being was associated with sleep problems and PDQ-39 cognition was related to daytime sleepiness.	attend the examination – Does not establish causality – Cannot generalize the results
Sun et al.[68] 2018 China	PDSS: 98.79 ± 26.83 ESS: 8.40 ± 6.24	PDQ-39: 29.98 ± 17.80	ESS was a significant predictor of worse HRQol.	– Cross-sectional study; cannot determine causality – Descriptive in nature – Patients with disease duration ≥ 10 years were evaluated during the "on" state
Tibar et al.[54] 2018 Morocco	PSQI: 9.48 ± 4.72 Median (IQR): 8 (6-12) ESS: 6.38 ± 5.35 Median (IQR): 5 (2.28-9.80)	PDQ-39: 25.83 ± 16.54 Median (IQR): 23.22 (13.36-36.69)	Neither PSQI nor ESS had a significant impact on HRQoL.	– Low disease severity (27.3% had H&Y score >2) – Patients with dementia were excluded – Cross-sectional study; cannot determine causality

Vila Cha et al.[51] 2019 UK	PDSS-2: 15 ± 10	SF-36 physical health: Group 1 (PDSS-2 < 18): Median (IQR): 42 (33-51) Group 2 (PDSS-2 ≥ 18): Median (IQR): 32 (28-42) SF-36 mental health: Group 1 (PDSS-2 < 18): Median (IQR): 50 (41-57) Group 2 (PDSS-2 ≥ 18): Median (IQR): 43 (34-49)	SF-36 physical and mental health scores were significantly lower in group 2 compared to group 1.	– Recruitment was consecutive, but a significant number of subjects were unable to complete parts of the protocol due to impaired cognition – Use of self-reported questionnaires for sleep
Visser et al.[40] 2008 UK	SCOPA-sleep NS: 4.4 ± 3.7 SCOPA-sleep DS: 4.7 ± 3.7	EQ-VAS: 67.8 ± 14.2	SCOPA-sleep DS had a significant indirect relationship on HRQoL through ADL.	– Selectively excluded patients with too many missing values – Stratification on age at onset and disease duration may make the cohort less representative of PD community
Walton et al.[67] 2014 Australia	SCOPA-sleep day: 4.29 ± 3.5	PDQ-39: 21.21 ± 14.0	Both SCOPA-sleep day and SCOPA-sleep night were significant predictors of worse HRQoL.	– Use of self-reported measures – Use of a more detailed cognitive

	SCOPA-sleep night: 4.67 ± 4.2			assessment (vs. MMSE) may have influenced the model in favor of strong impact of cognition on HRQL – Higher proportion of males (typical of the disease)
Xiang et al.[20] 2019 China	ESS: 7.6 ± 6.1 PDSS: 116.9 ± 24.8 RBD: reported in 36.9% of patients	PDQ-39: 30.1 ± 24.7	PDQ-39 score was found to be a significant predictor of worse EDS (ESS).	– Lack of subjective measures to assess sleep disorders – Cross-sectional study; cannot determine causality
Ylikoski et al.[42] 2017 Finland	Short sleepers (≤6 hours): 126 (26.2%) patients Long sleepers (≥9 hours): 192 (32.5%) patients	Self-rated health (SRH): Poor SRH: 301 (44.4%) patients WHO5: Poor QoL (WHO5 < 52): 290 (43.3%) patients	WHO5 was a significant predictor of sleep deprivation.	– Self-reported data causing possible misclassification in some participants – Data on cumulative lifetime dose for dopaminergic medication were not available

	Poor sleepers (sleep efficiency < 80%): 115 (21.2%) patients Sleep deprivation: 173 (33.8%) patients Disrupted sleep: 305 (47.4%) patients Difficulties to fall asleep: 83 (12.2%)			– Cross-sectional study; cannot determine causality – Some items were assessed using only one question
Yoo et al.[45] 2019 Korea	PDSS-2: 13.6 ± 7.2 ESS: 6.5 ± 5.7	Korean version of PDQ-39: Non-EDS group: 20.3 ± 12.3 EDS group: 37.2 ± 16.1	PDQ-39 scores were significantly higher (worse HRQoL) in the EDS group compared to the non-EDS group.	– ESS was not objectively assessed – Many comorbidities were not considered
Yu et al.[15] 2015 Taiwan	ESS: 5.85 ± 5.04 PSQI: 7.23 ± 3.51 PDSS-2:	PDQ-39: 37.64 ± 26.64 Good sleepers (PSQI ≤5): 27.11 ± 22.28 Poor sleepers (PSQI >5): 43.79 ± 27.53	Pain in arms or legs, daytime dysfunction, uncomfortable immobility at night were significant predictors of worse HRQoL.	– Patients able to come to and suitable for examination and interview were included – Dementia patients were excluded

	Factor 1 (motor symptoms at night): 2.50 ± 2.55 Factor 2 (PD symptoms at night): 2.56 ± 2.78 Factor 3 (disturbed sleep): 6.96 ± 3.59			– No control population was recruited – Apathy and depression were not evaluated – Certain confounding factors were not completely excluded – Cross-sectional study; cannot determine causality – Lack of objective measures

SD = standard deviation, HRQoL = Health-related quality of life, UPDRS = Unified Parkinson's Disease Rating Scale, PDQ = Parkinson's Disease Questionnaire, MOS = Medical Outcomes Study, SF-36 = Short Form-36, PCS = Physical Composite Score, MCS = Mental Composite Score, ESS = Epworth Sleepiness Scale, IQR = interquartile range, RBDSQ = REM sleep behavior disorder sleep questionnaire, EQ-5D = EuroQol-5 Dimension, PDSS = Parkinson's disease sleep scale, SCOPA = Scales for Outcomes in Parkinson's disease, PSQI = Pittsburgh Sleep Quality Index, PIGD = postural instability gait difficulty, TD = tremor-dominant, p-PIGD = predominantly postural instability gait difficulty, p-TD = predominantly tremor-dominant, NMSQuest = Non-Motor Symptoms Questionnaire, NHP = Nottingham health profile, PD = Parkinson's disease, RCSQ = Richards-Campbell Sleep Questionnaire, WHOQOL-OLD = World Health Organization Quality of Life Assessment for Older Adults, PWS = Psychological Wellbeing Scale, YOPD = young-onset Parkinson's disease, MOPD = middle-onset Parkinson's disease, LOPD = late-onset Parkinson's disease, NS = nighttime sleep problems, DS = daytime sleepiness, ADL = Activities of Daily Life, MMSE = Mini Mental State Examination, EDS = Excessive daytime sleepiness, WHO5 = World Health Organization Well-being Questionnaire

Table 2.6: Sleep, health-related quality of life among caregivers of persons with Parkinson's disease

Author, Publication Year, Country	Sleep measurement tool & score Mean ± SD		HRQoL and caregiver burden measurement tool and score Mean ± SD		HRQoL and caregiver burden results	Study limitations
	Patients	Caregivers	Patients	Caregivers		
Bartolomei et al.[43] 2018 Italy	PDSS: 36.7 ± 21.9 ESS: 4.8 ± 3.3	MOS-SS index II: 20.1 ± 18.1 PDSS was a significant predictor of caregiver sleep quality (MOS-SS index II).	PDQ-39: 29.8 ± 20.2	Caregiver HRQoL: SF-36 PHS: 85.9 ± 18.5 SF-36 MHS: 75.0 ± 17.7 CBI: 9.0 ± 12.5	Patient sleep (PDSS) was associated with lower caregiver physical and mental health scores, respectively. Patient HRQoL (PDQ-39) was not significantly associated with caregiver HRQoL. The relationship between PDSS and caregiver burden was not significant. Patient HRQoL was significantly associated with greater caregiver burden.	– Small sample size (N = 75) – Fewer patients with higher levels of disease severity – Cannot establish causality without longitudinal studies
Cupidi et al.[25] 2012 Italy	NR	PSQI: 6.25 ± 3.9	NR	MQoL: 7.3 ± 1.4	Poor sleepers had significantly lower QoL compared to good sleepers. The relationship between sleep and psychological	– Lack of objective sleep quality measures

				CBI: 13.4 ± 13.4	symptoms domain of QoL was mediated by depression.	– Patients' sleep was not collected
Ozdilek et al.[46] 2012 Turkey	PDSS: satisfied with sleep (N = 40, 80%) ESS: pathological sleep (N = 9, 18%)	ESS; no caregivers experienced pathological sleepiness	Turkish version of WHOQOL-BREF	Turkish version of WHOQOL-BREF ZBI: 27.6 ± 15.1	No significant relationship was found between patient and caregiver demographic characteristics and caregiver WHOQOL-BREF domain scores. Significant positive correlation was observed between patients' daytime sleepiness level (ESS) and caregiver burden.	– Relatively small sample size (N = 50) – Use of scales for psychological assessment instead of psychological-status examination measure – Patients had difficulty understanding WHOQOL-BREF questions

SD = standard deviation, HRQoL = Health-related quality of life, PDSS = Parkinson's disease sleep scale, ESS = Epworth Sleepiness Scale, MOS-SS = Medical Outcomes Study – Sleep Scale, PDQ = Parkinson's Disease Questionnaire, SF-36 = Short Form-36, PHS = Physical health scale, MHS = Mental health scale, CBI = Caregiver Burden Inventory, SCOPA = Scales for Outcomes in Parkinson's disease, NR = not reported, EQ-5D = EuroQol-5 Dimension, ZCBI = Zarit Caregiver Burden Inventory, PSQI = Pittsburgh Sleep Quality Index, MQoL = McGill Quality of Life Questionnaire, WHOQOL-BREF = World Health Organization Quality of Life Assessment-Bref, SDI = Sleep Disturbances Inventory, MPDSS = Modified Parkinson's Disease Sleep Scale

Table 2.7: Quality appraisal of included patient studies

Author	Year	Q1*	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Andreadou et al.[48]	2011	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Avidan et al.[14]	2012	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Baig et al.[39]	2015	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Fan et al.[53]	2016	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Gallagher et al.[17]	2010	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Gómez-Esteban et al.[13]	2010	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Havlikova et al.[18]	2011	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Herman et al.[58]	2015	Y	Y	Y	Y	Y	Y	Y	Y	Include	Included based on correlation results presented
Karlsen et al.[77]	1999	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Kuhlman et al.[16]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Lee et al.[49]	2014	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Lee et al.[56]	2018	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Lerman et al.[57]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Include	

Margis et al.[52]	2010	Y	Y	Y	Y	Y	Y	Y	Y	Include	Included based on correlation results presented
Naismith et al.[55]	2010	Y	Y	Y	Y	N	N	Y	Y	Include	Included based on correlation results presented
Nicoletti et al.[59]	2017	Y	Y	Y	Y	Y	Y	Y	Y	Include	Included based on correlation results presented
Palmeri et al.[66]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Pandey et al.[60]	2016	Y	Y	Y	Y	N	N	Y	Y	Include	Included based on correlation results presented
Park et al.[44]	2018	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Qin et al.[41]	2009	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Semiz et al.[50]	2007	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Skorvanek et al.[47]	2015	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Sun et al.[68]	2018	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Tibar et al.[54]	2018	Y	Y	Y	Y	Y	Y	Y	Y	Include	

Vila Cha et al.[51]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Visser et al.[40]	2008	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Walton et al.[67]	2014	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Xiang et al.[20]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Ylikoski et al.[42]	2017	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Yoo et al.[45]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Yu et al.[15]	2015	Y	Y	Y	Y	Y	Y	Y	Y	Include	

Y = Yes, N = No

* Q1-Q10 correspond to items in the quality appraisal form presented in Table 2.2.

Table 2.8: Quality appraisal of included caregiver studies

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Bartolomei et al.[43]	2018	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Cupidi et al.[25]	2012	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Ozdilek et al.[46]	2012	Y	Y	Y	Y	Y	Y	Y	Y	Include	

Y = Yes

* Q1-Q10 correspond to items in the quality appraisal form presented in Table 2.2.

List of References

1. Lees AJ, Blackburn NA, Campbell VL. The nighttime problems of Parkinson's disease. Clin Neuropharmacol. 1988;11(6):512-519.

2. Comella CL. Sleep disorders in Parkinson's disease: An overview. Mov Disord. 2007;22(SUPPL. 17). doi:10.1002/mds.21682

3. Suzuki K, Miyamoto M, Miyamoto T, Iwanami M, Hirata K. Sleep disturbances associated with Parkinson's disease. Parkinsons Dis. 2011;2011. doi:10.4061/2011/219056

4. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev. 2017;35:33-50. doi:10.1016/j.smrv.2016.08.001

5. Chaudhuri KR, Healy DG, Schapira AH V. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006;5:235-245. doi:10.4314/njm.v19i2.56496

6. Crabb L. Sleep disorders in Parkinson's disease: the nursing role. Br J Nurs. 2001;10(1):42-47. doi:10.12968/bjon.2001.10.1.5401

7. Fifel K. Alterations of the circadian system in Parkinson's disease patients. Mov Disord. 2017;32(5):682-692. doi:10.1002/mds.26865

8. Stavitsky K, Cronin-golomb A. Sleep quality in Parkinson's disease: An examination of clinical variables. Cogn Behav Neurol. 2011;24(2):43-49. doi:10.1097/WNN.0b013e31821a4a95.Sleep

9. Diederich NJ, Mcintyre DJ. Sleep disorders in Parkinson's disease: Many causes, few therapeutic options. J Neurol Sci. 2012;314:12-19. doi:10.1016/j.jns.2011.10.025

10. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov Disord. 2019;34(2):180-198. doi:10.1002/mds.27602

11. Karlsen KH, Larsen JP, Tandberg E, Mæland JG. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66(4):431-435. doi:10.1136/jnnp.66.4.431

12. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson T, Fink J, Roger D. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. Park Relat Disord. 2008;14(1):37-42. doi:10.1016/j.parkreldis.2007.05.009

13. Gómez-Esteban JC, Tijero B, Somme J, et al. Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J Neurol.

2011;258(3):494-499. doi:10.1007/s00415-010-5786-y

14. Avidan A, Hays RD, Diaz N, et al. Associations of sleep disturbance symptoms with health-related quality of life in parkinson's disease. J Neuropsychiatry Clin Neurosci. 2013;25(4):319-326. doi:10.1176/appi.neuropsych.12070175

15. Yu RL, Tan CH, Wu RM. The impact of nocturnal disturbances on daily quality of life in patients with Parkinson's disease. Neuropsychiatr Dis Treat. 2015;11:2005-2012. doi:10.2147/NDT.S85483

16. Kuhlman GD, Flanigan JL, Sperling SA, Barrett MJ. Predictors of health-related quality of life in Parkinson's disease. Park Relat Disord. 2019;65(February):86-90. doi:10.1016/j.parkreldis.2019.05.009

17. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord. 2010;25(15):2493-2500. doi:10.1002/mds.23394

18. Havlikova E, Dijk JPV, Nagyova I, et al. The impact of sleep and mood disorders on quality of life in Parkinson's disease patients. J Neurol. 2011;258(12):2222-2229. doi:10.1007/s00415-011-6098-6

19. Kadastik-Eerme L, Rosenthal M, Paju T, Muldmaa M, Taba P. Health-related quality of life in Parkinson's disease: A cross-sectional study focusing on non-motor symptoms. Health Qual Life Outcomes. 2015;13(1):1-8. doi:10.1186/s12955-015-0281-x

20. Xiang YQ, Xu Q, Sun QY, et al. Clinical features and correlates of excessive daytime sleepiness in Parkinson's disease. Front Neurol. 2019;10(FEB):1-9. doi:10.3389/fneur.2019.00121

21. Winter Y, Von Campenhausen S, Gasser J, et al. Social and clinical determinants of quality of life in Parkinson's disease in Austria: A cohort study. J Neurol. 2010;257(4):638-645. doi:10.1007/s00415-009-5389-7

22. Shibley R, Griffin HJ, Quinn NP, Jahanshahi M. Quality of life in Parkinson's disease: The relative importance of the symptoms. Mov Disord. 2008;23(10):1428-1434. doi:10.1002/mds.21667

23. Smith M, Ellgring H, Oertel W. Sleep disturbances in Parkinson's disease patients and spouses. J Am Geriatr Soc. 1997;45:194-199.

24. Pal PK, Thennarasu K, Fleming J, Schulzer M, Brown T, Calne SM. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. Park Relat Disord. 2004;10(3):157-168. doi:10.1016/j.parkreldis.2003.11.002

25. Cupidi C, Realmuto S, Lo Coco G, et al. Sleep quality in caregivers of patients with Alzheimers disease and Parkinsons disease and its relationship to quality of life. Int Psychogeriatrics. 2012;24(11):1827-1835. doi:10.1017/S1041610212001032

26. Drutyte G, Forjaz MJ, Rodriguez-Blazquez C, Martinez-Martin P, Breen KC. What impacts on the stress symptoms of Parkinson's carers? Results from the Parkinson's UK Members' Survey. Disabil Rehabil. 2014;36(3):199-204.

doi:10.3109/09638288.2013.782363

27. Arber S, Venn S. Caregiving at night: Understanding the impact on carers. J Aging Stud. 2011;25(2):155-165. doi:10.1016/j.jaging.2010.08.020

28. Happe S, Berger K. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing. 2002;31(5):349-354. doi:10.1093/ageing/31.5.349

29. Viwattanakulvanid P, Kaewwilai L, Jitkritsadakul O, et al. The impact of the nocturnal disabilities of Parkinson's disease on caregivers' burden: Implications for interventions. J Neural Transm. 2014;121(SUPPL. 1). doi:10.1007/s00702-014-1200-8

30. D'Amelio M, Terruso V, Palmeri B, et al. Predictors of caregiver burden in partners of patients with Parkinson's disease. Neurol Sci. 2009;30(2):171-174. doi:10.1007/s10072-009-0024-z

31. Martinez-Martin P, Arroyo S, Rojo-Abuin JM, et al. Burden, perceived health status, and mood among caregivers of Parkinson's disease patients. Mov Disord. 2008;23(12):1673-1680. doi:10.1002/mds.22106

32. Carod-Artal FJ, Mesquita HM, Ziomkowski S, Martinez-Martin P. Burden and health-related quality of life among caregivers of Brazilian Parkinson's disease patients. Park Relat Disord. 2013;19(11):943-948. doi:10.1016/j.parkreldis.2013.06.005

33. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. J Am Med Assoc. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

34. National Institute for Health Research. PROSPERO - International prospective register of systematic reviews. https://www.crd.york.ac.uk/prospero/. Accessed March 1, 2020.

35. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017. https://reviewersmanual.joannabriggs.org/.

36. Popay J, Roberts H, Sowden A, et al. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews - A Product from the ESRC Methods Programme.; 2006. doi:10.1001/archderm.1985.01660090059014

37. Denison HJ, Dodds RM, Ntani G, et al. How to get started with a systematic review in epidemiology: an introductory guide for early career researchers. Arch Public Heal. 2013;71(21). doi:10.1186/0778-7367-71-21

38. Thomson H, Campbell M. "Narrative Synthesis" of Quantitative Effect Data in Cochrane Reviews: Current Issues and Ways Forward.; 2020. https://training.cochrane.org/sites/training.cochrane.org/files/public/uploads/Webinar 1 Introduction 3Feb2020.pdf.

39. Baig F, Lawton M, Rolinski M, et al. Delineating nonmotor symptoms in early Parkinson's disease and first-degree relatives. Mov Disord. 2015;30(13):1759-1766. doi:10.1002/mds.26281

40. Visser M, Van Rooden SM, Verbaan D, Marinus J, Stiggelbout AM, Van Hilten JJ. A comprehensive model of health-related quality of life in Parkinson's disease. J Neurol. 2008;255(10):1580-1587. doi:10.1007/s00415-008-0994-4

41. Qin Z, Zhang L, Sun F, et al. Health related quality of life in early Parkinson's disease: Impact of motor and non-motor symptoms, results from Chinese levodopa exposed cohort. Park Relat Disord. 2009;15(10):767-771. doi:10.1016/j.parkreldis.2009.05.011

42. Ylikoski A, Martikainen K, Sieminski M, Partinen M. Sleeping difficulties and health-related quality of life in Parkinson's disease. Acta Neurol Scand. 2017;135(4):459-468. doi:10.1111/ane.12620

43. Bartolomei L, Pastore A, Meligrana L, et al. Relevance of sleep quality on caregiver burden in Parkinson's disease. Neurol Sci. 2018;39(5):835-839. doi:10.1007/s10072-018-3252-2

44. Park HR, Youn J, Cho JW, et al. Characteristic Motor and Nonmotor Symptoms Related to Quality of Life in Drug-Naïve Patients with Late-Onset Parkinson Disease. Neurodegener Dis. 2018;18(1):19-25. doi:10.1159/000484249

45. Yoo S-W, Kim J-S, Oh Y-S, Ryu D-W, Lee K-S. Excessive daytime sleepiness and its impact on quality of life in de novo Parkinson's disease. Neurol Sci. 2019;40(6):1151-1156. doi:10.1007/s10072-019-03785-8

46. Ozdilek B, Gunal DI. Motor and non-motor symptoms in Turkish patients with Parkinson's disease affecting family caregiver burden and quality of life. J Neuropsychiatry Clin Neurosci. 2012;24(4):478-483. doi:10.1176/appi.neuropsych.11100315

47. Skorvanek M, Rosenberger J, Minar M, et al. Relationship between the non-motor items of the MDS-UPDRS and Quality of Life in patients with Parkinson's disease. J Neurol Sci. 2015;353(1-2):87-91. doi:10.1016/j.jns.2015.04.013

48. Andreadou E, Anagnostouli M, Vasdekis V, et al. The impact of comorbidity and other clinical and sociodemographic factors on health-related quality of life in Greek patients with Parkinson's disease. Aging Ment Health. 2011;15(7):913-921. doi:10.1080/13607863.2011.569477

49. Lee JH, Choi MK, Jung D, Sohn YH, Hong JY. A Structural Model of Health-Related Quality of Life in Parkinson's Disease Patients. West J Nurs Res. 2014:1-19. doi:10.1177/0193945914528588

50. Semiz U, Senol M, Basoglu C, et al. Relationship of depressive symptoms and subjective sleep disturbances to the Quality of Life in patients with Parkinson's disease. Neurol Psychiatry Brain Res. 2007;14:55-58.

51. Vila-Chã N, Cavaco S, Mendes A, et al. Sleep disturbances in parkinson's disease are associated with central parkinsonian pain. J Pain Res. 2019;12:2137-2144. doi:10.2147/JPR.S206182

52. Margis R, Donis KC, Schönwald SV, Rieder CRM. WHOQOL-OLD assessment of quality of life in elderly patients with Parkinson's disease: Influence of sleep and

depressive symptoms. Rev Bras Psiquiatr. 2010;32(2):125-131. doi:10.1590/S1516-44462010005000008

53. Fan JY, Chang BL, Wu YR. Relationships among Depression, Anxiety, Sleep, and Quality of Life in Patients with Parkinson's Disease in Taiwan. Parkinsons Dis. 2016;2016. doi:10.1155/2016/4040185

54. Tibar H, El Bayad K, Bouhouche A, et al. Non-motor symptoms of Parkinson's Disease and their impact on quality of life in a cohort of Moroccan patients. Front Neurol. 2018;9(APR):1-12. doi:10.3389/fneur.2018.00170

55. Naismith S, Hickie IB, Lewis SJG. The Role of Mild Depression in Sleep Disturbance and Quality of Life in Parkinson ' s Disease. J Neuropsychiatry Clin Neurosci. 2010;22:384-389.

56. Lee SJ, Kim SR, Chung SJ, et al. Predictive model for health-related quality of life in patients with Parkinson's disease. Geriatr Nurs. 2018;39(2):204-211. doi:10.1016/j.gerinurse.2017.09.001

57. Lerman SF, Bronner G, Cohen OS, et al. Catastrophizing mediates the relationship between non-motor symptoms and quality of life in Parkinson's disease. Disabil Health J. 2019;12(4):673-678. doi:10.1016/j.dhjo.2019.03.006

58. Herman T, Weiss A, Brozgol M, Wilf-Yarkoni A, Giladi N, Hausdorff JM. Cognitive function and other non-motor features in non-demented Parkinson's disease motor subtypes. J Neural Transm. 2015;122(8):1115-1124. doi:10.1007/s00702-014-1349-1

59. Nicoletti A, Mostile G, Stocchi F, et al. Factors influencing psychological well-being in patients with Parkinson's disease. PLoS One. 2017;12(12):e0189682. doi:10.1371/journal.pone.0189682

60. Pandey S, Bajaj BK, Wadhwa A, Anand KS. Impact of sleep quality on the quality of life of patients with Parkinson's disease: a questionnaire based study. Clin Neurol Neurosurg. 2016;148:29-34. doi:10.1016/j.clineuro.2016.06.014

61. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: A community-based study. Mov Disord. 1999;14(6):922-927. doi:10.1002/1531-8257(199911)14:6<922::AID-MDS1003>3.0.CO;2-7

62. Rana AQ, Vaid H, Akhter MR, et al. Prevalence of nocturia in parkinson's disease patients from various ethnicities. Neurol Res. 2014;36(3):234-238. doi:10.1179/1743132813Y.0000000264

63. Weerkamp NJ, Tissingh G, Poels PJE, et al. Nonmotor symptoms in nursing home residents with Parkinson's disease: Prevalence and effect on quality of life. J Am Geriatr Soc. 2013;61(10):1714-1721. doi:10.1111/jgs.12458

64. Politis M, Wu K, Molloy S, Bain PG, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: The patient's perspective. Mov Disord. 2010;25(11):1646-1651. doi:10.1002/mds.23135

65. Menza M, Dobkin RDF, Marin H, Bienfait K. Sleep disturbances in Parkinson's disease.

Mov Disord. 2010;25(SUPPL. 1):1-8. doi:10.1002/mds.22788

66. Palmeri R, Lo Buono V, Bonanno L, et al. Potential predictors of quality of life in Parkinson's Disease: Sleep and mood disorders. J Clin Neurosci. 2019;70:113-117. doi:10.1016/j.jocn.2019.08.058

67. Walton CC, Shine JM, Hall JM, et al. The major impact of freezing of gait on quality of life in Parkinson's disease. J Neurol. 2015;262(1):108-115. doi:10.1007/s00415-014-7524-3

68. Sun Q, Wang T, Jiang TF, et al. Clinical profile of Chinese long-term parkinson's disease survivors with 10 years of disease duration and beyond. Aging Dis. 2018;9(1):8-16. doi:10.14336/AD.2017.0204

69. Zhi T, Sun X, Li S, et al. Associations of sleep duration and sleep quality with life satisfaction in elderly Chinese : The mediating role of depression. Arch Gerontol Geriatr. 2016;65:211-217. doi:10.1016/j.archger.2016.03.023

70. Gothe NP, Ehlers DK, Salerno EA, Fanning J, Kramer AF, Mcauley E. Physical Activity , Sleep and Quality of Life in Older Adults : Influence of Physical , Mental and Social Well-being. Behav Sleep Med. 2020;18(6):797-808. doi:10.1080/15402002.2019.1690493

71. Becker NB, de Jesus SN, Viseu JN, Stobaus CD, Guerreiro M, Domingues RB. Depression and quality of life in older adults: Mediation effect of sleep quality. Int J Clin Heal Psychol. 2018;18:8-17. doi:10.1016/j.ijchp.2017.10.002

72. Yates ME, Tennstedt S, Chang B. Contributors to and Mediators of Psychological Well-Being for Informal Caregivers. J Gerontol Psychol Sci. 1999;54B(1):12-22.

73. Chappell NL, Reid RC. Burden and Well-Being Among Caregivers : Examining the Distinction. Gerontologist. 2002;42(6):772-780.

74. Hughes SL, Giobbie-hurder A, Weaver FM, Kubal JD, Henderson W. Relationship Between Caregiver Burden and Health-Related Quality of Life. Gerontologist. 1999;39(5):534-545.

75. Martinez-Martin P, Benito-Leon J, Alonso F, et al. Quality of life of caregivers in Parkinson's disease. Qual Life Res. 2005;14:463-472.

76. Högl B, Arnulf I, Comella C, et al. Scales to assess sleep impairment in Parkinson's disease: Critique and recommendations. Mov Disord. 2010;25(16):2704-2716. doi:10.1002/mds.23190

77. Karlsen KH, Larsen JP, Tandberg E, Mæland JG. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66(4):431-435. doi:10.1136/jnnp.66.4.431

CHAPTER 3: PSYCHOMETRIC EVALUATION OF THE PROMIS® GLOBAL HEALTH QUESTIONNAIRE IN PERSONS WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS

Introduction

Parkinson's disease (PD) is a commonly occurring nervous system disorder that causes tremors, muscle stiffness, and loss of gait and balance – referred to as motor symptoms. It is accompanied by several non-motor symptoms including orthostatic hypotension, mood disorders, sleep disorders, urinary problems, difficulty swallowing, skin issues, among others. Consequently, health-related quality of life (HRQoL) is severely affected among persons with Parkinson's (PWP). PWP tend to face a similar overall economic burden when compared to certain other chronic conditions, but their HRQoL seems to be worse in comparison.[1,2]

Several patient-reported outcome (PRO) measures have been used to measure HRQoL in PD to evaluate the impact of disease from the patient's perspective. The most commonly used disease-specific measures include the Parkinson's Disease Questionnaire-39 (PDQ-39) and its short form version, the PDQ-8, both of which were developed in the 1990's.[3,4] The PDQ-39 contains 39 items measuring 8 domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. The domain scores can be combined into a single PD Summary Index (PDSI), and both the domain and the summary index are reported on a scale of 0 (perfect health) to 100 (worst health).[4,5] The PDQ-39 exhibited good internal consistency (except for the social support domain), test-retest reliability, and construct validity against the Medical Outcomes Study 36-item Short Form Health Survey (SF-36).[3] The most commonly used generic HRQoL measures in PD include the following: The

Nottingham Health Profile (NHP),[6] the Sickness Impact Profile (SIP),[7] the EuroQol (EQ-5D),[8] and the SF-36,[9] all of which have been designated as *"recommended"* scales in a critique by the Movement Disorder Society (MDS).[10] The critique concluded that these scales exhibited satisfactory psychometric properties in PD, except for the NHP which showed floor and ceiling effects compared to the PDQ-39.[10,11]

All the above-mentioned scales and their scoring algorithms were developed using Classical Test Theory (CTT) methods. However, Item-Response Theory (IRT) has gained increasing attention as a modern alternative scaling procedure to CTT.[12] While there are commonalities between the two approaches (the assumption of scale unidimensionality, for example), there are also various distinctions in their fundamental philosophies regarding scale properties. Two important differences between them include: (1) IRT's focus on individual item properties vs. CTT's focus on the scale as a whole, and (2) Scale scoring in CTT is done assuming that all individual items in the questionnaire are equally important in measuring the latent variable. However, in IRT, items have varying levels of *difficulty*, and therefore, it is possible to identify items that can differentiate between specific levels of the construct being measured.[12] Scales developed using IRT methods consider the probability a respondent selects a particular response category, given their level of the underlying latent train that the scale is measuring rather than the sample in which the trait is being measured and hence, perform better when ceiling and floor effects are expected.[12,13]

The Patient-Reported Outcomes Measurement Information System (PROMIS®) was an NIH-funded initiative established in 2004, which incorporated the use of IRT methods to develop and validate PROs used in clinical practice and research.[14,15] The PROMIS inventory comprises of over 300 measures that evaluate individuals with chronic conditions and the general

population on domains and subdomains that fall under the World Health Organization's physical, mental and social framework for health.[16] These questionnaires were developed over a few years and began by conducting extensive literature search of existing PROs to create item banks across constructs identified within domains. This was followed by qualitative item-review procedures to assess items for content validity and deletion of items which were confusing, redundant or poorly written. Finally, psychometric testing was done using CTT and IRT procedures to create final sets of item banks.[17] Moreover, since the PROMIS inventory contains generic questionnaires, they can be used across all samples (e.g., patients, healthy persons, patients at all disease severity levels) allowing us to compare diverse samples on the same scale.

Some PROMIS measures have been previously tested in subgroups of PD,[18,19] however, there are no published studies evaluating the performance of the PROMIS® Global Health measure in PWP. This measure assesses an individual's physical, mental and social health.[17,20] The PROMIS Global Health questionnaire consists of 10-items covering the following domains: physical health, mental health, pain, fatigue, social health, and overall health. The PROMIS Global Health item set includes a self-rated health item (*global01*) which has been shown to tap in to both physical health and mental health but reflects physical health more than mental health.[21] It also includes a single item for overall quality of life (*global02*). The remaining items are ratings of physical health (*global03*), mental health (*global04*), social health (*global05* and *global09R*), physical function (*global06*), pain (*global07R*), fatigue (*global08R*), and emotional distress (*global10R*). All items other than pain (*global07R*) are measured on a 5-category response scales where higher scores on responses indicate better health. Pain (*global07*) is measured on a scale of 0 – 10, where 0 = no pain and 10 = worst pain imaginable. A T-score metric is calculated for the scores which can be compared to the standard US population with a

mean of 50 and standard deviation of 10. A higher score on an instrument indicates that the respondent has "more" of the concept being measured. Summary score for global physical health (GPH) is calculated by averaging scores across 4 items: *global03* (physical health), *global06* (physical function), *global07R* (pain) and *global08R* (fatigue).[20] Similarly, global mental health (GMH) is calculated by averaging scores across the following 4 items: *global02* (quality of life), *global04* (mental health), *global05* (satisfaction with discretionary social activities) and *global10R* (emotional problems).[20] Items with the suffix "*R*" indicate reverse-coded items in the questionnaire. The current study aimed to evaluate psychometric properties of the PROMIS® Global Health measure and also evaluate differential item functioning of the measure's items in PWP.

Methods

Study sample

The current cross-sectional study was conducted by means of a web-based, self-administered survey, distributed to a national convenience sample of PWP and caregivers from Rare Patient Voice (RPV), LLC, Dynata, LLC, and Parkinson and Movement Disorder (PMD) Alliance. RPV and Dynata are market research vendor companies which maintain and provide researchers with panels of patients and caregivers across several medical conditions for conducting surveys and interviews. PMD Alliance is a national independent, not-for-profit patient advocacy group. All study participants were 50 years of age or older. The study protocol was deemed exempt by the University of Mississippi Institutional Review Board.

Study methodology

A survey with questions on respondent demographics and other required study measures was developed using Qualtrics online survey software (Qualtrics Inc., Provo, UT). The survey instrument is provided in the Appendix. A cover letter explaining the objective and scope of the

study was sent to the participants in an email. The email also contained information pertaining to eligibility criteria, nature of questions being asked, risks and benefits from the study, assurances on data security and confidentiality, participation incentive, contact information of the principal investigator and a URL link to the survey for PWP. Upon receiving adequate sample size, the survey was closed. The de-identified dataset containing the study measures was used for analysis. Each study participant was provided an incentive for completing the survey.

Study measures

The following measures were collected from PWP (See Appendix 4 for survey instrument):

PROMIS Global Health (PROMIS-GH): The PROMIS GPH and GMH summary scores were calculated from items mentioned earlier, using a web-based application the HealthMeasures Scoring Service^{SM} (HM-SS).[22] This application was developed by the PROMIS Group and is available free of cost for researchers. The other two items (*global01* – general health and *global09* – social roles) were scored individually.

Patient Global Impression of Severity (PGI-S): PGI-S is a single self-reported measure that measures a patient's self-rated symptom severity. In this study, the question was worded as "Please circle the response below that best describes the severity of your motor symptoms over the past week", with the following response categories: 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = severe, 6 = extreme. A similarly worded question was added to elicit non-motor (NM) symptom severity as well. The response categories were created based on a 2015 study which compared various commonly used disease severity measures in PD.[23]

Other measures: Information was also collected on the following characteristics: (1) age, (2) race/ethnicity, (3) sex, (4) education status, (5) employment status, (6) symptom severity (in terms of PGI-S as mentioned above), (7) current anti-parkinsonian treatment use. Additionally, because data were collected near the beginning of the Coronavirus Disease 2019 (COVID-19) pandemic, questions regarding COVID-19 were asked to understand anxiety surrounding the pandemic and the impact of the pandemic on HRQoL.

Statistical Analysis

Sample description

Descriptive statistics were calculated in the form of frequencies and percentages for categorical variables and means and standard deviations for continuous variables.

Item-level analysis

Item-level descriptive statistics were calculated in terms of means, and standard deviations (SD). Response patterns, including patterns in missing data, were examined and presented in terms of frequencies. This step is fundamental in ensuring there are no systematic patterns in responses and warrants further investigation, if any. For example, more prevalent missing data might be seen towards the end of the survey, which may signal response burden. Floor and ceiling effects were also examined at the item- and summary score-levels.

Internal consistency reliability

Ordinal alpha based on polychoric correlations was used to examine internal consistency and a minimum of 0.70 was considered as the threshold for reliable group-level measurement.[24]

Factorial validity

Categorical item, confirmatory factor analysis (CFA) based on polychoric correlations was conducted using the weighted least squares mean- and variance-adjusted estimator

(WLSMV) to evaluate the factorial validity of GPH and GMH (i.e., the existence of an underlying 2-factor measurement model). Goodness-of-fit was assessed using comparative fit index (CFI), Tucker-Lewis Index (TLI), and the root mean square error of approximation (RMSEA). The following thresholds were used for models with a good fit: CFI ≥ 0.95, TLI ≥ 0.95, and RMSEA ≤ 0.06, respectively.[25]

Differential item functioning

When a questionnaire is used in a diverse sample, the assumption is that all items in the questionnaire perform similarly across the subgroups in that sample and that the differences observed in their scores is due to a difference in the constructs being measured between the groups.[26] However, sometimes this assumption is violated, which gives rise to differential item functioning (DIF).[12,26] In the current study, we tested for age- and sex-DIF in the PROMIS Global Health measure. We used the two-factor measurement model that was estimated in the previously conducted categorical item CFA for the following steps.

Multiple-groups CFA: This step involved testing for measurement invariance and the presence of DIF using a multi-group CFA for categorical outcomes. First, a model where all the parameters are allowed to freely vary was estimated. The following stepwise approach suggested by Brown (2015)[27] was used for the next steps:

i. testing the CFA model for each group separately (for example, between males vs. females for sex-based invariance testing).
ii. establishing a baseline multiple-groups model wherein the factor loadings and thresholds are freely estimated in all groups. This model is also referred to as the *equal form* model.
iii. conducting a model in which all factor loadings and thresholds are constrained to equality across all groups (measurement invariance model). A significant degradation in model fit

was considered to indicate DIF. In case of model fit degradation, modification indices (MI) and standardized expected parameter changes (EPC) were examined to identify indicators that were noninvariant.

iv. if noninvariance was encountered in the previous step, a partial invariance model was estimated in which factor loadings and thresholds for all indicators are held equal across the groups, except for the indicator that was nonivariant. Again, model fit statistics, MI and EPC were used to identify items exhibiting further DIF.

These steps were repeated for the age variable. This approach has been used previously with other PROMIS short forms.[28–30]

Known-groups validity

Known-groups validity was assessed in PWP with respect to self-reported motor and NM symptom severity levels. Symptom severity as measured by PGI-S were collapsed in to 3 groups where response levels 1, 2, and 3 were classified as mild cases, level 4 as moderate, and levels 5 and 6 as severe. This approach was modeled after a previous study that compared severity scales in PD.[23] One-way ANOVA was used to compare GPH and GMH scores obtained from the PROMIS Global Health measure across PWP with different severity levels. Pairwise comparisons were assessed using Tukey's Honestly Significant Difference (HSD) test.

All CFA models were estimated using Mplus version 8.5 (Muthén & Muthén, Los Angeles, CA) and all other analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Sample characteristics

A total of 261 PWP responded to the survey. The majority of respondents were male (59%), 66 years or older (63%), White (77%), had less than a bachelor's degree (57%), were retired (53%), and had public insurance (66%) (Table 3.1). Sixty-two percent of participants were recruited through online panels (RPV and Dynata) and the remaining 38% were recruited from a patient advocacy group (PMD Alliance).

Table 3.1: Socio-demographic characteristics of persons with Parkinson's disease included in the study

Characteristic	Category	Patients (N = 261) N (%)
Sex	Female	105 (40.2)
	Male	154 (59.0)
	Other/prefer not to answer	2 (0.8)
Age group (in years)	50-65	96 (36.8)
	66 or older	165 (63.2)
Race	White	201 (77.0)
	Other	60 (23.0)
Highest education level	GED or High school diploma	84 (32.2)
	Associate degree	47 (18.0)
	Bachelor's degree	65 (24.9)
	Master's degree	29 (11.1)
	Terminal degree	18 (6.9)
	No degree	18 (6.9)
Employment status	Retired	138 (52.9)
	Unable to work	38 (14.6)
	Employed for wages	32 (12.3)
	Self-employed	5 (1.9)
	Out of work for 1 year or more	23 (8.8)
	Out of work for less than 1 year due to COVID-19, also known as Coronavirus or SARS-CoV-2	14 (5.4)
	Out of work for less than 1 year due to other reason(s)	5 (1.9)
Health insurance	Public insurance (e.g. Medicare, Medicaid, VA)	172 (65.9)
	Private insurance	82 (31.4)
	Other	5 (1.9)
	Uninsured	2 (0.8)

Clinical characteristics of the PWP sample

Among participants, 43% reported a moderate level of symptom severity for both motor and NM symptoms (Table 3.2). About 35% participants reported mild/borderline/normal motor

symptoms, while 22% reported severe/extreme symptoms. For NMS, 40% reported mild/borderline/normal symptoms and 17% reported sever/extreme symptoms. Respondents also reported having at least one chronic condition, other than PD. The most commonly reported chronic conditions included arthritis (28%), mood disorders (27%), heart disease (20%) and diabetes (17%).

Table 3.2: Clinical characteristics of persons with Parkinson's disease included in the study

Characteristic	Category	Patients (N = 261) N (%)
Self-reported motor symptom severity*	Normal	20 (7.7)
	Borderline	22 (8.4)
	Mild	63 (24.1)
	Moderate	86 (33.0)
	Severe	55 (21.1)
	Extreme	15 (5.8)
Self-reported non-motor symptom severity*	Normal	31 (11.9)
	Borderline	11 (4.2)
	Mild	72 (27.6)
	Moderate	110 (42.2)
	Severe	31 (11.9)
	Extreme	6 (2.3)
Number of chronic conditions (Mean ± SD, Median, Range)		1.5 ± 1.9, 1, 1-13

*Patient Global Impression of Severity (PGI-S) was used to measure motor and non-motor symptom severity.
SD = standard deviation

Item-level analysis of PROMIS Global Health questionnaire

Table 3.3 below shows item-level characteristics of the PROMIS Global Health questionnaire in the current study sample. The entire sample responded to most items, except for 1 missing response each for *global04* (mental health) and *global08R* (fatigue) items. The highest proportion of respondents with the minimum possible score was observed for the *global03* (physical health, 12%). The highest proportion of respondents who had the maximum possible

score was seen with the item *global06* (physical function, 16%). These results indicate that the floor and ceiling effects are close to the suggested threshold of 15%.[31] The lowest mean score was observed for the item *global03* (2.5 ± 0.9) and the highest mean score was observed for GLOBAL06 (3.1 ± 1.1).

Table 3.3: PROMIS Global Health-10 item-level analysis

PROMIS item identifier	N	Missing	Floor (%)	Ceiling (%)	Mean	SD	Item text
global01[*]	261	0	11.1	3.5	2.7	1.0	In general, would you say your health is
global02[*]	261	0	7.7	5.4	2.9	1.0	In general, would you say your quality of life is:
global03[*]	261	0	11.9	2.3	2.5	0.9	In general, how would you rate your physical health?
global04[*]	260	1	7.7	8.5	3.0	1.1	In general, how would you rate your mental health, including your mood and your ability to think?
global05[*]	261	0	7.3	6.1	2.9	1.0	In general, how would you rate your satisfaction with your social activities and relationships?
global09R[*]	261	0	10.0	4.6	2.8	1.0	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)
global06[†]	261	0	6.1	16.1	3.1	1.1	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?
global10R[§]	261	0	8.1	7.7	3.0	1.0	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?
global08R[‡]	260	1	5.4	3.9	2.9	0.9	How would you rate your fatigue on average?
global07R[⁑]	261	0	1.9	6.5	3.0	0.9	How would you rate your pain on average?

PROMIS = Patient Reported Outcomes Measurement Information System, GPH = Global Physical Health, GMH = Global Mental Health, SD = Standard deviation

[*]Response categories are: Excellent = 5, Very good, Good, Fair, Poor = 1.

[†]Response categories are: Completely = 5, Mostly, Moderately, A little, Not at all = 1.

[§]Response categories are: Never = 5, Rarely, Sometimes, Often, Always = 1.

[‡]Response categories are: None = 5, Mild, Moderate, Severe, Very severe = 1.

[⁑]Responses are on a scale of 0 (no pain) to 10 (worst pain imaginable), recoded as follows: 0 = 5; 1-3 = 4; 4-6 = 3; 7-9 = 2; 10 = 1.

PROMIS Global Physical and Mental health summary scores and internal consistency reliability

The mean GPH summary score in the study sample was 43.1 ± 8.5 and the mean GMH summary score was 38.7 ± 8.0 (Table 3.4). The GPH and GMH scales had an internal consistency reliability (ordinal alpha coefficient) of 0.772 and 0.843, respectively.

Table 3.4: Physical and mental health summary scores and reliability analysis for PROMIS Global Health among persons with Parkinson's disease

Component	Mean (SD)	Floor (%)	Ceiling (%)	Ordinal alpha	No. of items
PROMIS GPH	43.1 (8.5)	0	0	0.772	4
PROMIS GMH	38.7 (8.0)	1.5	0	0.843	4

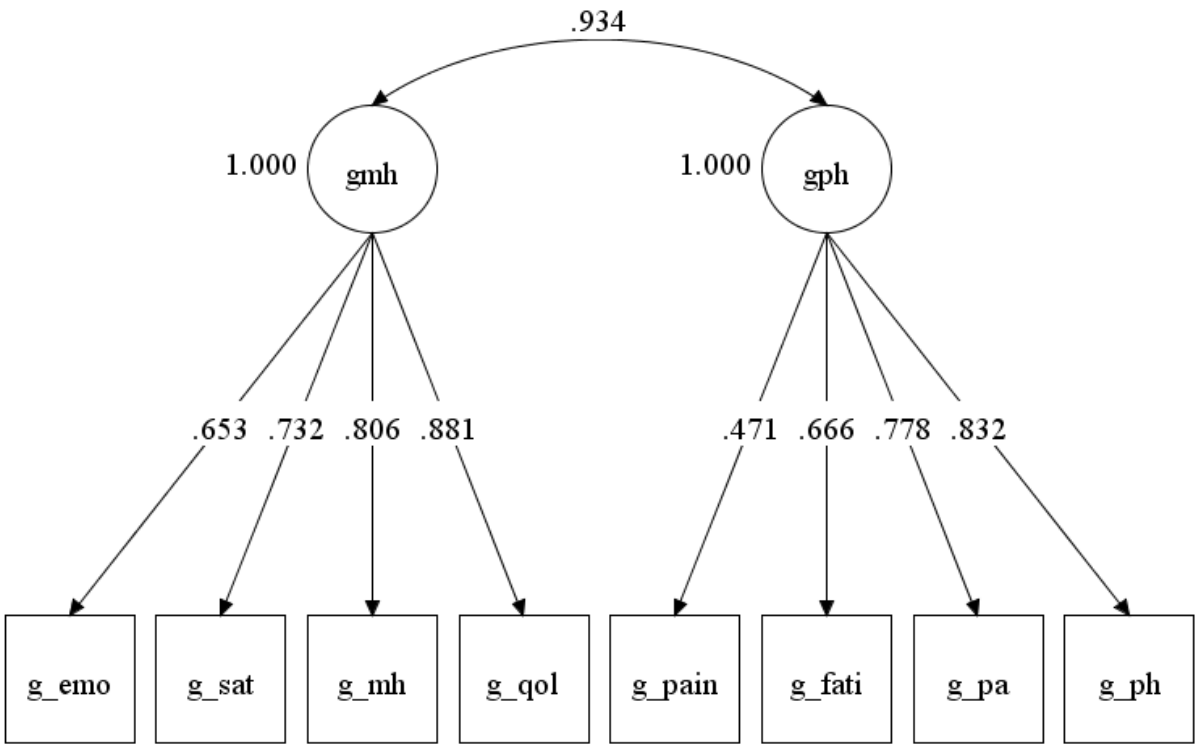
PROMIS = Patient Reported Outcomes Measurement Information System, GPH = Global Physical Health, GMH = Global Mental Health, SD = standard deviation
For GPH, the highest possible score is 67.7 and the lowest possible score is 16.2.
For GMH, the highest possible score is 67.6 and the lowest possible score is 21.2.

Factorial validity

Figures 3.1, 3.2. and 3.3 represent the models that were estimated to test the factorial validity of PROMIS Global Health among PWP. The factor loadings and goodness-of-fit indices for each of the tested models are presented in Table 3.5. The two-factor model where *global03* (physical health), *global06* (physical function), *global07R* (pain) and *global08R* (fatigue) load on GPH, and *global02* (quality of life), *global04* (mental health), *global05* (satisfaction with discretionary social activities) and *global10R* (emotional problems) load on GMH is presented in model 1 (Figure 3.1). This model did not include specifications for correlated errors between any items. Model 1 had a poor fit (Chi-square [*df*] = 222.815 [19]; CFI = 0.922; TLI = 0.885; RMSEA [90% CI] = 0.203 [0.179, 0.227]). Based on MI and standardized EPC values, a residual correlation was added between *global07R* (pain) and *global08R* (fatigue) to this model, which is represented here as model 2 (Figure 3.2). This model also had somewhat poor fit (Chi-square [*df*]

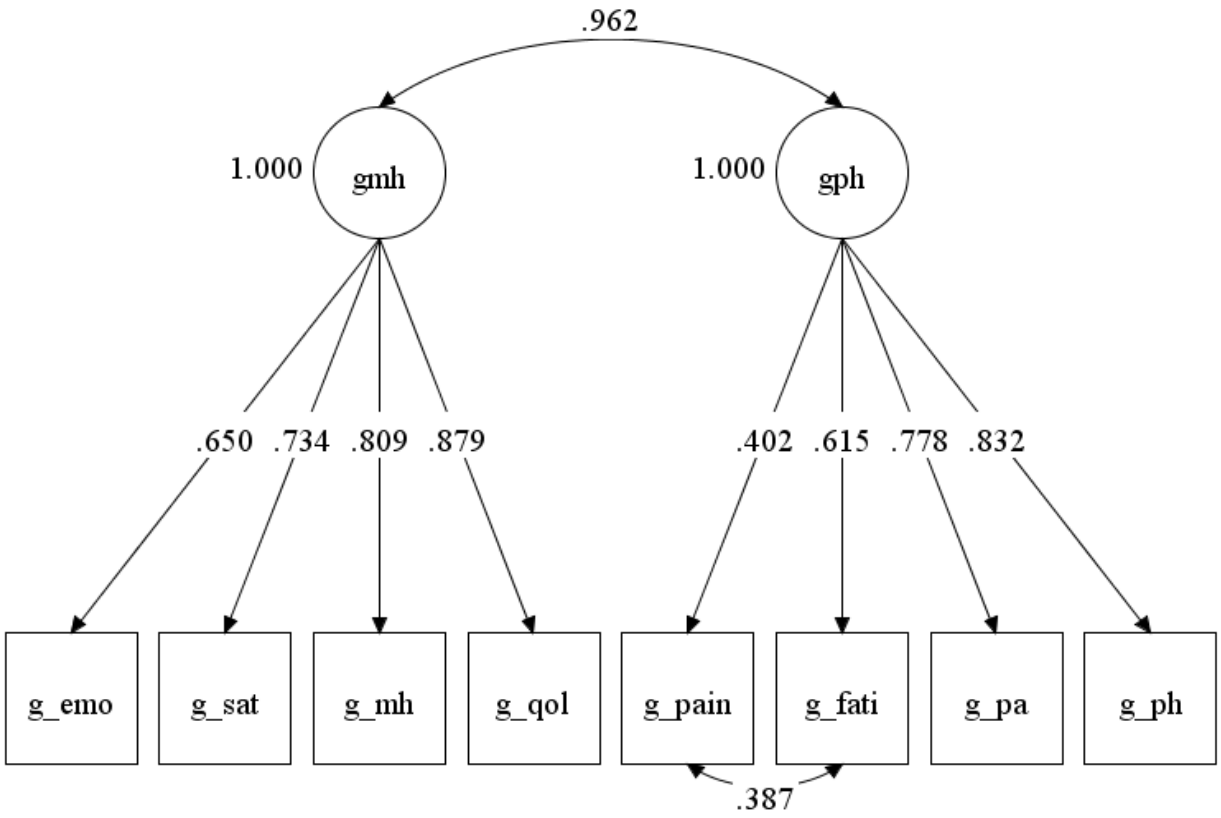
= 157.353 [18]; CFI = 0.947; TLI = 0.917; RMSEA [90% CI] = 0.172 [0.148, 0.197]). Again, modification indices and standardized EPC values were examined to identify local areas of strain. Based on these values, a method effect between reverse-coded items (*global07R* [pain] – *global10R* [emotional problems] and *global08R* [fatigue] – *global10R* [emotional problems]) was identified. Therefore, residual correlations were specified for these terms in addition to correlation between pain and fatigue to form model 3 (Figure 3.3). These specifications significantly improved model fit (Chi-square [*df*] = 44.230 [16]; CFI = 0.989; TLI = 0.981; RMSEA [90% CI] = 0.082 [0.054, 0.112]).

Figure 3.1: Model 1 – Two-factor model for PROMIS Global Health without any correlated errors between items



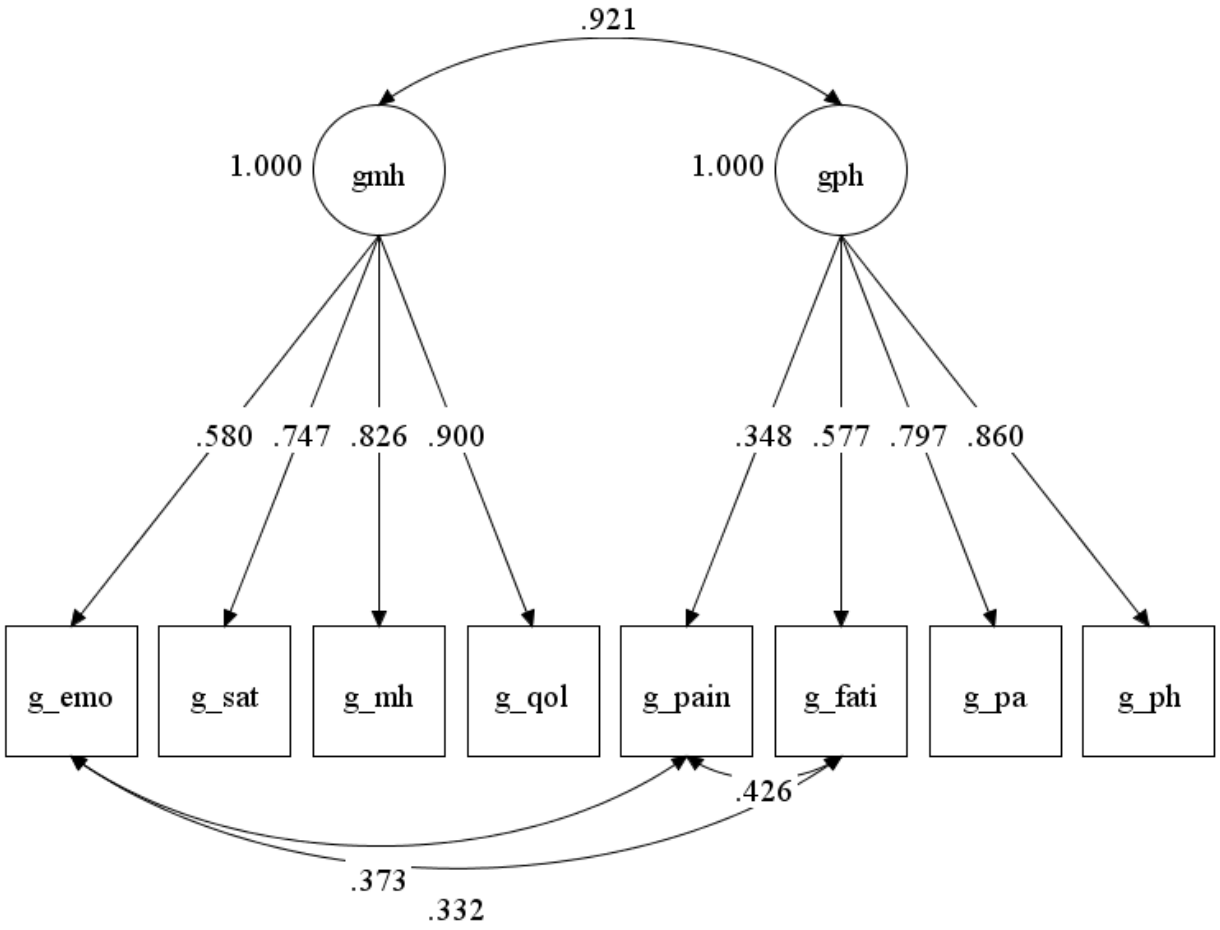
gmh = global mental health, gph = global physical health, g_emo = emotional problems (*global10R*), g_sat = satisfaction with discretionary social activities (*global05*), g_mh = mental health (*global04*), g_qol = quality of life (*global02*), g_pain = pain (*global07R*), g_fati = fatigue (*global08R*), g_pa = physical function (*global06*), g_ph = physical health (*global03*)

Figure 3.2: Model 2 – Two-factor model for PROMIS Global Health with correlated errors for *global07R* (pain) and *global08R* (fatigue)



gmh = global mental health, gph = global physical health, g_emo = emotional problems (*global10R*), g_sat = satisfaction with discretionary social activities (*global05*), g_mh = mental health (*global04*), g_qol = quality of life (*global02*), g_pain = pain (*global07R*), g_fati = fatigue (*global08R*), g_pa = physical function (*global06*), g_ph = physical health (*global03*)

Figure 3.3: Model 3 – Two-factor model for PROMIS Global Health with correlated errors for all reverse-coded items (*global07R*: pain, *global08R*: fatigue and *global10R*: emotional problems)



gmh = global mental health, gph = global physical health, g_emo = emotional problems (*global10R*), g_sat = satisfaction with discretionary social activities (*global05*), g_mh = mental health (*global04*), g_qol = quality of life (*global02*), g_pain = pain (*global07R*), g_fati = fatigue (*global08R*), g_pa = physical function (*global06*), g_ph = physical health (*global03*)

Table 3.5: Standardized factor loadings and summary of model fit indices from confirmatory factor analysis of the two-factor structures of PROMIS Global Health

Items	Estimate* (SE)		
	Model 1	Model 2	Model 3
GPH Component			
Global03	0.832 (0.025)	0.832 (0.025)	0.860 (0.025)
Global06	0.778 (0.033)	0.778 (0.033)	0.797 (0.033)
Global08R	0.666 (0.035)	0.615 (0.039)	0.577 (0.042)
Global07R	0.471 (0.041)	0.402 (0.043)	0.348 (0.045)
GMH Component			
Global02	0.881 (0.021)	0.879 (0.021)	0.900 (0.021)
Global04	0.806 (0.026)	0.809 (0.026)	0.826 (0.027)
Global05	0.732 (0.031)	0.734 (0.031)	0.747 (0.032)
Global10R	0.653 (0.034)	0.650 (0.034)	0.580 (0.038)
Latent factor correlation			
GPH with GMH	0.934 (0.023)	0.962 (0.025)	0.921 (0.024)
Correlated residuals			
Global07R with Global08R	-	0.387 (0.045)	0.426 (0.042)
Global07R with Global10R	-	-	0.0.373 (0.045)
Global08R with Global10R	-	-	0.332 (0.050)
Model fit			
Chi-square (*df*), *p*-value	222.815 (19), <0.0001	157.353 (18), <0.0001	44.230 (16), 0.0002
CFI	0.922	0.947	0.989
TLI	0.885	0.917	0.981
RMSEA (90% CI)	0.203 (0.179, 0.227)	0.172 (0.148, 0.197)	0.082 (0.054, 0.112)

SE = standard error, *df* = degrees of freedom, CFI = Comparative Fit Index, TLI = Tucker-Lewis Index, RMSEA = Root Mean Square Error of Approximation, CI = Confidence Interval

Items are as follows: G

Model 1: Two-factor structure where GLOBAL03, GLOBAL06, GLOBAL07R and GLOBAL08R load on global physical health and GLOBAL02, GLOBAL04, GLOBAL05 and GLOBAL10R load on global mental health, with no correlated errors.

Model 2: Two-factor structure as in Model 1 above with correlated errors for GLOBAL08R and GLOBAL07R.

Model 3: Two-factor structure as in Model 1 above with correlated errors among all reverse-coded items: GLOBAL08R, GLOBAL07R and GLOBAL10R.

*All factor loadings were significant at $\alpha = 0.05$.

Differential item functioning by sex and age group

Using the two-factor structure of PROMIS Global Health with the best fit specified in model 3, the possibility of DIF was explored using multi-group CFA based on sex and age group (Table 3.6). First, DIF based on sex (males vs. females) was examined. The baseline or *equal form* model, where factor loadings and thresholds were freely estimated in both groups, fit the data well (Chi-square [*df*] = 60.576 [32]; CFI = 0.989; TLI = 0.981; RMSEA [90% CI] = 0.083 [0.050, 0.115]). The measurement invariance model, where both factor loadings and thresholds were constrained to be equal across males and females, showed that the constraint did not degrade model fit relative to the baseline model (Chi-square difference [*df*] = 39.415 [28], *p*-value = 0.0745). Therefore, it was concluded that there was no indication of DIF between males and females.

Next, DIF based on age group (50-65 vs. 66+ years) was examined using model 3. The baseline model showed good fit for the data (Chi-square [*df*] = 72.712 [32]; CFI = 0.986; TLI = 0.975; RMSEA [90% CI] = 0.099 [0.069, 0.129]). The measurement invariance model showed a significant increase in chi-square (Chi-square difference [*df*] = 52.866 [28], *p*-value = 0.0030). MI and EPC indicated that the item g*lobal08R* (fatigue) was noninvariant between the two age groups. Therefore, a partial invariance model was estimated where factor loadings and thresholds for this item were freely estimated between the two groups, whereas all other items were constrained to be equal. This model did not result in a significant increase in chi-square relative to the baseline model (Chi-square difference [*df*] = 37.327 [27], *p*-value = 0.0891), providing no evidence for further DIF in the model.

Table 3.6: Differential item functioning (DIF) by sex and age group in PROMIS Global Health based on Model 3

Model	Chi-square (*df*)	*p*-value	CFI	TLI	RMSEA (90% CI)	Chi-square difference (*df*) *p*-value
Sex-based DIF						
Free parameter	60.576 (32)	0.0017	0.989	0.981	0.083 (0.050, 0.115)	-
Fixed	91.180 (60)	0.0058	0.988	0.989	0.063 (0.035, 0.089)	39.415 (28) 0.0745
Age-based DIF						
Free parameter	72.712 (32)	0.0001	0.986	0.975	0.099 (0.069, 0.129)	-
Fixed	113.343 (60)	<0.0001	0.981	0.982	0.083 (0.059, 0.106)	52.866 (28) 0.0030
Global08R	96.265 (59)	0.0016	0.987	0.987	0.070 (0.043, 0.094)	37.327 (27) 0.0891

GLOBAL08R item: "How would you rate your fatigue on average?" with response categories: None (5), Mild, Moderate, Severe, Very severe (1).

Known-groups validity

Known-groups validity was examined based on the ability of GPH and GMH to discriminate between PWP with motor and NM symptoms at mild, moderate and severe levels using one-way ANOVA (Table 3.7 and 3.8). Pairwise comparisons between the different symptom severity groups were assessed using Tukey's Honestly Significant Difference (HSD) test.

Motor symptom severity groups: The mean GPH (43.7 vs. 37.3 vs. 32.9; $p<0.0001$) and GMH (46.9 vs. 41.5 vs. 39.2; $p<0.0001$) summary scores were significantly different between the three symptom severity groups (Table 3.7). There was a reduction in GPH scores with increasing severity level. Specifically, PWP with mild symptoms had significantly higher GPH score than the moderate group (43.7 vs. 37.3) and severe group (43.7 vs. 32.9). PWP with moderate severity had significantly higher GPH than the severe group (37.3 vs. 32.9). As for GMH summary scores, the mild symptoms group had higher GMH score than the moderate (46.9 vs. 41.5) and the severe groups (46.9 vs. 39.3), but there was no evidence that the moderate and severe groups were different with respect to GMH scores (41.5 vs. 39.3, $p = 0.2092$).

Table 3.7: Known-groups validity for PROMIS Global Health components among PWP based on motor symptom severity

Motor symptom severity				
Component	Mild (N = 105)	Moderate (N = 86)	Severe (N = 70)	*p*-value
	Mean (SD)			
GPH	43.7 (7.7)[*¥]	37.3 (5.5)[*†]	32.9 (6.2)[†¥]	<0.0001
GMH	46.9 (8.6)[§‡]	41.5 (7.3)[§]	39.3 (7.5)[‡]	<0.0001

GPH = Global Physical Health, GMH = Global Mental Health, SD = standard deviation
[*]$p<0.0001$ for difference in mean GPH summary scores between the "Mild" symptom group compared to "Moderate" based on Tukey's Honestly Significant Difference (HSD) test.
[†]$p<0.0001$ for difference in mean GPH summary scores between the "Moderate" symptom group compared to "Severe" based on Tukey's HSD test.
[¥]$p<0.0001$ for difference in mean GPH summary scores between the "Mild" symptom group compared to "Severe" based on Tukey's HSD test.
[§]$p<0.0001$ for difference in mean GMH summary scores between the "Mild" symptom group compared to "Moderate" based on Tukey's HSD test.
[‡]$p<0.0001$ for difference in mean GMH summary scores between the "Mild" symptom group compared to "Severe" based on Tukey's HSD test.

Non-motor symptom severity groups: The mean GPH (42.9 vs. 37.0 vs. 30.8; p<0.0001) and GMH (46.9 vs. 41.4 vs. 36.4; p<0.0001) summary scores were significantly different between the three symptom severity groups (Table 3.8). There was a reduction in GPH and GMH scores with increasing severity level. Specifically, PWP with mild symptoms had significantly higher GPH score than the moderate group (42.9 vs. 37.0) and severe group (42.9 vs. 30.8). PWP with moderate severity had significantly higher GPH than the severe group (37.0 vs. 30.8). As for GMH summary scores, the mild symptoms group had higher GMH score than the moderate (46.9 vs. 41.4) and the severe groups (46.9 vs. 36.4). Additionally, the moderate group had significantly higher GMH score compared to the severe group (41.4 vs. 36.4).

Table 3.8: Known-groups validity for PROMIS Global Health components among PWP based on non-motor symptom severity

Component	Mild (N = 114)	Moderate (N = 110)	Severe (N = 37)	*p*-value
	Mean (SD)			
GPH	42.9 (7.4)$^{*¥}$	37.0 (6.1)*†	30.8 (6.6)$^{†¥}$	<0.0001
GMH	46.9 (8.6)§‡	41.4 (6.1)^{§ǂ}	36.4 (8.9)^{ǂ‡}	<0.0001

GPH = Global Physical Health, GMH = Global Mental Health, SD = standard deviation
$^{*}p$<0.0001 for significant difference in mean GPH summary scores between the "Mild" symptom group compared to "Moderate" based on Tukey's Honestly Significant Difference (HSD) test.
$^{†}p$<0.0001 for significant difference in mean GPH summary scores between the "Moderate" symptom group compared to "Severe" based on Tukey's HSD test.
$^{¥}p$<0.0001 for significant difference in mean GPH summary scores between the "Mild" symptom group compared to "Severe" based on Tukey's HSD test.
$^{§}p$<0.0001 for significant difference in mean GMH summary scores between the "Mild" symptom group compared to "Moderate" based on Tukey's HSD test.
^{ǂ}p = 0.0024 for significant difference in mean GMH summary scores between the "Moderate" symptom group compared to "Severe" based on Tukey's HSD test.
$^{‡}p$<0.0001 for significant difference in mean GMH summary scores between the "Mild" symptom group compared to "Severe" based on Tukey's HSD test.

Impact of COVID-19 on health-related quality of life

Results from the COVID-19 responses are presented in Table 3.9. A total of 259 survey participants responded to these questions. The mean anxiety score (on a scale of 1-10 with 1 being low and 10 being high) among the participants was 5.8 ± 2.6. When asked about how their quality of life has been impacted as a result of the COVID-19 pandemic, 69% of the participants responded "worsened" and 32% responded "remained the same", whereas less than 2% responded "improved". When asked about their agreement with the statement "The COVID-19 pandemic has had a significant impact on my quality of life", more than half of the participants answered "somewhat agree" (48%) or "strongly agree" (24%).

Table 3.9: Impact of COVID-19 on quality of life in PWP

COVID-19 related items	Category	Patients (N = 259)*
COVID-19 related anxiety (Mean ± SD, Median, Range)	On a scale of 1-10 (1 = Low, 10 = High)	5.8 ± 2.6, 6, 1-10
Change in quality of life as a result of COVID-19	Worsened	173 (66.8)
	Remained the same	82 (31.7)
	Improved	4 (1.5)
Level of agreement with statement related to the impact of COVID-19		
The COVID-19 pandemic has had a significant impact on my quality of life	Strongly disagree	23 (8.9)
	Somewhat disagree	18 (7.0)
	Neither disagree nor agree	33 (12.7)
	Somewhat agree	124 (47.9)
	Strongly agree	61 (23.6)

PWP = Persons with Parkinson's, COVID-19 = Coronavirus Disease 2019
*****259 of 261 total respondents answered the COVID-19 related questions.

Discussion

The current study aimed to assess the measurement properties of the PROMIS Global Health questionnaire in a sample of PWP. For this purpose, we analyzed primary data collected from PWP through panels and a patient advocacy group. We found that the mean GPH (43.1) and GMH (38.7) summary scores were lower than the standard US population, indicating worse physical and mental health in this sample. This difference is to be expected in a chronic, progressive neurodegenerative disease such as PD and is consistent with previous evidence.[32]

We evaluated item-level descriptive statistics as well as floor and ceiling effects and found that the instrument performed well on all these aspects. Floor and ceiling effects were minimal for each item and were non-existent at the summary score level, which highlights the advantage of instruments developed in the IRT framework compared to CTT.[12,13] Studies have shown that legacy instruments such as NHP, SF-36 etc. and also some disease-specific scales might exhibit floor and ceiling effects in PD.[33–35] PROMIS Global Health instrument could be used as an alternate generic instrument in case of severe floor and ceiling effects.

Additionally, factorial validity of PROMIS Global Health was tested by examining the proposed two-factor structure,[20] which showed poor fit. This finding was consistent with two other studies which evaluated the scale's factorial validity in samples of stroke patients by Katzan et al.[36] and pregnant and postpartum women by Slavin et al.[37] To address this issue, Slavin et al. revised items loading onto the GPH and GMH components and proposed the use of alternative versions. However in our sample, upon further investigation, we identified method effects with regards to reverse coded items (*global07R* – pain, *global08R* – fatigue and *global10R* – emotional problems) leading to model misfit. Consequently, specification of correlated residuals among these items to the model significantly improved fit. These three items

were reverse coded with the intention to score all items in PROMIS Global Health in such a way so that higher scores represent better functioning.[38] However, researchers have questioned the effectiveness of including such items and have argued that these items might in fact lead to confusion among participants.[39] In order to overcome such issues, some researchers have suggested that users could take advantage of the greater flexibility in terms of item customization allowed by PROMIS item banks and critically consider the inclusion of reverse-scored items based on the need for the particular project.[29]

The current study conducted exploratory DIF analyses and the results showed that there was no DIF across males and females. However, we did observe DIF based on age. The results indicate that for the same level of underlying latent trait of physical health, younger and older PWP scored differently on the *global08R* (fatigue) item and therefore, the observed scores may not be directly comparable between these two groups. To our knowledge, this is the first study to examine age based DIF in PD. However, studies which have evaluated PROMIS Global Health in other populations have not found evidence suggesting age-based DIF.[40,41] Further evaluations of DIF in other PD and disease samples are needed to understand if this finding was specific to the current study sample.

With regards to known-groups validity, the study findings show that PROMIS Global Health demonstrates the ability to differentiate across PWP at various levels of self-reported motor and NM symptom severity. Both GPH and GMH scores were found to be significantly different across the various levels of NM severity and direction of the effect, i.e. decreasing GPH and GMH scores with increasing symptom severity, are consistent with our expectation. While GPH scores were significantly different across all pairwise comparisons of the three motor symptom severity levels, GMH was only found to be significantly different when comparing the

mild motor symptom group to each of the higher motor symptom groups. This finding suggests that GMH summary score may not be able to discriminate between the moderate and the severe motor symptom groups.

There are some limitations in our study. First, data collection was conducted during the COVID-19 pandemic which may have affected PWP's responses to the survey questions, especially HRQoL. Additionally, participant responses to the survey questions may be prone to recall bias and social desirability bias. As this was a survey of PWP, we did not have access to clinician-reported disease severity measure (such as the Hoeh & Yahr stages). Future studies could consider evaluating the performance of the PROMIS Global Health measure against disease-specific instruments in PD.

Conclusion

This study provides evidence about the satisfactory psychometric properties of the PROMIS Global Health instrument in an online sample of PWP. It was found to have adequate internal consistency reliability, and factorial and known-groups validity among PWP in research settings. The scale showed no DIF based on sex. The presence of DIF was seen with respect to the fatigue item across age groups. Additional studies are needed to ascertain these findings in other samples and to understand the performance of the instrument in comparison to legacy instruments specific to PD.

List of References

1. Gage H, Hendricks A, Zhang S, Kazis L. The relative health related quality of life of veterans with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2003;74(2):163-169. doi:10.1136/jnnp.74.2.163

2. Chaudhuri KR, Healy DG, Schapira AH V. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006;5:235-245. doi:10.4314/njm.v19i2.56496

3. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. 1995;4(3):241-248. doi:10.1007/BF02260863

4. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire. Psychol Heal. 1997;12(6):805-814. doi:10.1080/08870449708406741

5. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's disease questionnaire (PDQ-39): Development and validation of a Parkinson's disease summary index score. Age Ageing. 1997;26(5):353-357. doi:10.1093/ageing/26.5.353

6. Hunt S, McEwen J, McKenna S. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Pr. 1985;35:185-188.

7. Bergner B, Bobbitt R, Carter W, Gilson B. The sickness impact profile: development and final revision of a health status measure. Med Care. 1981;19:787-805.

8. The EuroQol Group. EuroQol - a new facility for the measurement of health related quality of life. Health Policy (New York). 1990;16:199-208.

9. Ware J, Sherbourne C. The MOS 36-Item Short-Form Health Survey (SF-36): I. conceptual framework and item selection. Med Care. 1992;30:473-483.

10. Martinez-Martin P, Jeukens-Visser M, Lyons KE, et al. Health-related quality-of-life scales in Parkinson's disease: Critique and recommendations. Mov Disord. 2011;26(13):2371-2380. doi:10.1002/mds.23834

11. Hagell P, Whalley R, McKenna S, Lindvall O. Health status measurement in Parkinson's disease: Validity of the PDQ-39 and Nottingham Health Profile. Mov Disord. 2003;18:773-783.

12. Fayers PM, Machin D. Item response theory and differential item functioning. In: Quality of Life. Third ed. West Sussex: John Wiley & Sons, Ltd; 2016.

13. DeVellis RF. An Overview of Item Response Theory. In: Scale Development: Theory and Applications. Fourth ed. SAGE Publications; 2017.

14. National Institutes of Health. PROMIS: Clinical Outcomes Assessment. https://commonfund.nih.gov/promis/index. Published 2019. Accessed November 23, 2019.

15. Northwestern University. Intro to PROMIS. http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis. Published 2019. Accessed November 23, 2019.

16. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap Cooperative Group During its First Two Years. Medi Care. 2007;45(5 Suppl 1):S3-S11. doi:10.1097/01.mlr.0000258615.42478.55.The

17. Reeve BB, Hays RD, Bjorner JB, et al. Psychometric Evaluation and Calibration of Health-Related Quality of Life Item Banks: Plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). JSTOR. 2007;45(5 Suppl 1):S22-S31.

18. Shulman LM, Armstrong M, Ellis T, et al. Disability Rating Scales in Parkinson's Disease: Critique and Recommendations. Mov Disord. 2016;31(10):1455-1465. doi:10.1002/mds.26649

19. Shin JY, Pohlig RT, Habermann B. Feasibility of using PROMIS® in individuals with advanced parkinson's disease and their caregivers. Res Gerontol Nurs. 2018;11(3):129-136. doi:10.3928/19404921-20180329-01

20. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res. 2009;18(7):873-880. doi:10.1007/s11136-009-9496-9

21. Bjorner JB, Fayer PM, Idler EL. Self-rated health. In: Fayers PM, Hays RD, eds. Assessing Quality of Life. Oxford: Oxford University Press; 2005:309-323.

22. Cella D, Gershon R, Bass M, Rothrock N. Assessment Center Scoring Service User Manual.; 2019.

23. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez M, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. Park Relat Disord. 2015;21:50-54. doi:10.1016/j.parkreldis.2014.10.026

24. Dunn TJ, Baguley T, Brunsden V. From alpha to omega: A practical solution to the pervasive problem of internal consistency estimation. Br J Psychol. 2014;105(3):399-412. doi:10.1111/bjop.12046

25. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Model A Multidiscip J. 1999;6(1):1-55. doi:10.1080/10705519909540118

26. Cappelleri J, Zou K, Bushmakin A, Alvir J, Alemayehu D, Symonds T. Item Response Theory. In: Patient-Reported Outcomes: Measurement, Implementation and Interpretation. Raton, FL: Taylore & Francis Group, LLC; 2014.

27. Brown T. Confirmatory Factor Analysis for Applied Research. Second edi. (Little TD, ed.). New York, NY: The Guildford Press; 2015.

28. Teresi JA, Jones RN. Methodological Issues in Examining Measurement Equivalence in Patient Reported Outcomes Measures: Methods Overview to the Two-Part Series, "Measurement Equivalence of the Patient Reported Outcomes Measurement Information System® (PROMIS®) Short Forms". Psychol Test Assess Model. 2016;58(1):37-78. http://www.ncbi.nlm.nih.gov/pubmed/28983448%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5625814.

29. Jensen RE, King-Kallimanis BL, Sexton E, et al. Measurement properties of PROMIS Sleep Disturbance short forms in a large, ethnically diverse cancer cohort. Psychol Test Assess Model. 2016;58(2):353-370. http://www.psychologie-aktuell.com/fileadmin/download/ptam/2-2016_20160627/06_Jensen.pdf.

30. Jones RN, Tommet D, Ramirez M, Jensen R, Teresi JA. Differential item functioning in Patient Reported Outcomes Measurement Information System® (PROMIS®) Physical Functioning short forms: Analyses across ethnically diverse groups. Psychol Test Assess Model. 2016;58(2):371-402.

31. Terwee CB, Bot SDM, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60:34-42. doi:10.1016/j.jclinepi.2006.03.012

32. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. Mov Disord. 2000;15(6):1112-1118. doi:10.1002/1531-8257(200011)15:6<1112::AID-MDS1008>3.0.CO;2-A

33. Rubenstein LM, Voelker MD, Chrischilles EA, Glenn DC, Wallace RB, Rodnitzky RL. The usefulness of the Functional Status Questionnaire and Medical Outcomes Study Short Form in Parkinson's disease research. Qual Life Res. 1998;7(4):279-290. doi:10.1023/A:1008838317063

34. Hagell P, Törnqvist AL, Hobart J. Testing the SF-36 in Parkinson's disease: Implications for reporting rating scale data. J Neurol. 2008;255(2):246-254. doi:10.1007/s00415-008-0708-y

35. Den Oudsten BL, Van Heck GL, De Vries J. The suitability of patient-based measures in the field of Parkinson's disease: A systematic review. Mov Disord. 2007;22(10):1390-1401. doi:10.1002/mds.21539

36. Katzan IL, Lapin B. PROMIS GH (Patient-Reported Outcomes Measurement Information System Global Health) Scale in Stroke A Validation Study. Stroke. 2018;49:147-154. doi:10.1161/STROKEAHA.117.018766

37. Slavin V, Gamble J, Creedy DK, Fenwick J, Pallant J. Measuring physical and mental health during pregnancy and postpartum in an Australian childbearing population - validation of the PROMIS Global Short Form. BMC Pregnancy Childbirth. 2019;19. doi:10.1186/s12884-019-2546-6 (2019)

38. Patient-Reported Outcomes Measurement Information System. Global Health A brief guide to the PROMIS© Global Health Instruments.

39. Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common Method Biases in Behavioral Research: A Critical Review of the Literature and Recommended Remedies. J Appl Psychol. 2003;88(5):879-903. doi:10.1037/0021-9010.88.5.879

40. Lapin BR, Thompson NR, Schuster A, Katzan IL. Patient versus proxy response on global health scales: no meaningful DIFference. Qual Life Res. 2019;28(6):1585-1594. doi:10.1007/s11136-019-02130-y

41. Gregory JJ, Werth PM, Reilly CA, Jevsevar DS. Cross - specialty PROMIS - global health differential item functioning. Qual Life Res. 2021;(February). doi:10.1007/s11136-021-02812-6

CHAPTER 4: DYADIC RELATIONSHIP BETWEEN SLEEP AND HEALTH-RELATED QUALITY OF LIFE IN PERSONS WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS – AN ACTOR-PARTNER INTERDEPENDENCE MODEL APPROACH

Introduction

Parkinson's disease (PD) is the second most common disorder of the central nervous system which predominantly affects dopaminergic neurons in a specific area of the brain called substantia nigra. The disease characterized by motor symptoms such as tremors, rigidity, slowness of movement etc. and non-motor symptoms (NMS) such as sleep disorders, psychosis, mood disorders, orthostatic hypotension etc. NMS have consistently been shown to have a greater impact on health-related quality of life than motor symptoms among persons with PD (PWP).[1,2] The most frequently occurring NMS among PWP include different types of sleep disorders such as rapid eye movement (REM) sleep behavior disorder (RBD), insomnia, nocturia, restless legs syndrome (RLS)/periodic limb movement disorder (PLMD), sleep disordered breathing (SDB), excessive daytime sleepiness (EDS), and circadian rhythm disorders.[3]

Impact of sleep disorders on PWP and caregivers in PD

The impact of sleep disorders in PD is multidimensional. Sleep disorders have been shown as an important predictor of poor health-related quality of life (HRQoL) in PWP.[4–7] Moreover, previous studies have suggested that sleep disorders are also highly correlated with other NMS that contribute to poor HRQoL such as depression,[8–11] pain,[11] fatigue,[12,13] and cognitive impairment.[14,15] Enhanced sleep quality, on the other hand, has been shown to improve

working memory in PWP, which is an indicator of improved higher cognitive functioning involving planning, problem solving, delayed goal execution and overall fluid intelligence.[16]

Further, sleep-related disorders in PWP are associated with diminished sleep quality among caregivers, the prevalence of which has been estimated as 20-60% across samples.[10,17–19] Several factors may contribute to the manifestation of sleep disorders in the caregiver. Smith et al. hypothesized that caregivers' own distress from caregiving during the day could be one of the predictors.[17] Another study involving in-depth interviews with caregivers found that nocturnal caregiving responsibilities such as attending to nocturnal physical needs of a PWP, anticipation of nocturnal care needs, monitoring a PWP during sleep, and a PWP's sleep disturbances may help explain sleep abnormalities in caregivers and may contribute to caregivers' own sleep disturbances.[20] This negative influence of sleep disorders in PWP on caregivers' HRQoL has also been shown in quantitative studies.[5,8,21,22]A better understanding of this relationship can help develop interventions that can reduce the burden of sleep disorders and improve HRQoL in PWP and caregivers.

Interdependence of sleep in PWP and caregivers

Several studies have evaluated the impact of sleep on PWP and caregiver HRQoL. However, there are certain limitations to the methods used in these studies. The relationship between PWP and their caregivers involves mutuality where either of them could influence the other's behaviors. From the stresses of nocturnal caregiving needs,[10,17–19] it is evident that sleep is one such interrelated concept for the PWP-caregiver dyad and therefore, any methods evaluating its effects on PWP's HRQoL or their caregivers' HRQoL should also take this interdependence in to consideration.

Most studies assess the impact of PWP's clinical characteristics on their own HRQoL or caregivers' HRQoL independently. Specifically, in the context of sleep disorders, the nonindependence of PWP's and their caregivers' sleep quality is often ignored or one of the measurements is not collected or not used during analysis. This may give rise to biased parameter estimates and biased variances and degrees of freedom in statistical tests, which leads to biased statistical significance tests and standardized effect measures, loss in precision of estimates, and loss in power.[23] These biased estimates lead to inaccuracies in estimating the actual disease burden.

Moreover, one of the key applications of estimates of the association between sleep and HRQoL is to quantify the effect of PWP's illness (i.e., patients' sleep disorders) on caregivers' HRQoL, otherwise known as spillover effects. The National Institute of Health and Care Excellence (NICE) and the second panel of cost-effectiveness in health and medicine highlight the importance of incorporating spillover effects in pharmacoeconomic evaluations.[24–27] Unbiased estimates are needed to avoid misinterpretation of benefits of health interventions. Therefore, there is a need to identify an appropriate statistical analytic technique which accounts for the dyadic nature of the patient-caregiver relationship when assessing the effect of sleep on HRQoL of PWP and caregivers.

The current study utilizes a dyadic analytic model to assess the relationship between sleep and HRQoL in PD, an association that has traditionally been interpreted as an independent phenomenon in PWP and caregivers. However, there is a growing acceptance among researchers that sleep is influenced by social factors, such as physical comfort and emotional safety, which are regulated by close human relationships.[28,29] Therefore, there is a need to identify models that appropriately assess and enhance our understanding of sleep's impact on HRQoL in PWP-

caregiver dyads in PD. Hence, the specific aim of the study is to assess the dyadic relationship between sleep and HRQoL in PWP and their caregivers using the Actor-Partner Interdependence Model (APIM). The APIM was developed and used extensively in psychological research to address data that involve mutual influence of thoughts, emotions and behaviors between two persons involved in close relationships.[23,30] The APIM has been used to understand relational phenomena in other disease areas (to test the dyadic impact of depression and anxiety on HRQoL in HIV/AIDS,[31] for example) and to certain relationships in PD (to examine the dyadic relationship between benefit finding and relationship quality,[32] for example). The current study aimed to extend its application to study the dyadic relationship between sleep and HRQoL in PWP and caregivers.

Methods

Study sample

A national convenience sample of 108 PWP-caregiver dyads was obtained from two market research firms – Rare Patient Voice (RPV), LLC, and Dynata, LLC. All study participants were 18 years of age or older. The unit of analysis for the current study is a dyad containing a PWP and the PWP's caregiver. Therefore, PWP were linked to their family caregivers by RPV and Dynata with the use of a unique linking variable to create PWP-caregiver dyads. Since the proposed model contains variables that are distinguishable between PWP and their caregivers, survey responses were collected individually from them. Dyad members were eligible to participate in the study if the caregiver was the primary informal caregiver of the PWP, the PWP was at least 50 years old, and both members resided in the same household. The study protocol was deemed exempt by the University of Mississippi Institutional Review Board.

Study methodology

The current study used a cross-sectional study involving data collected through a web-based survey. A survey containing questions regarding participant demographics and other study measures was created using Qualtrics online survey software (Qualtrics Inc., Provo, UT). A cover letter explaining the purpose of the study, eligibility criteria, nature of questions being asked, risks and benefits from the study, details on data security and confidentiality, participation incentive, contact information of the principal investigator and the study URL link were sent in an email to PWP and caregivers. Upon receiving sufficient number of complete, usable responses the survey was closed, and the research team had access to a de-identified dataset containing the study measures with linked responses from PWP and their caregivers, which was used for analysis. Each study participant was provided an incentive for completing the survey.

Study measures

The main variables of interest in this study, HRQoL and sleep, were measured using the Patient-Reported Outcomes Measurement Information System (PROMIS^{TM}) questionnaires. PROMIS was an NIH-funded initiative established in 2004, which aimed to develop and validate patient-reported outcomes (PROs) for use in clinical practice and research.[33] The PROMIS research network focused on improving PROs using state-of-the-art psychometric methods (i.e., Item-Response Theory (IRT)).[34] The PROMIS inventory includes over 300 measures that evaluate and monitor physical, mental and social health in individuals with chronic conditions and the general population. All PROMIS scales are measured on a T-score metric which allows for comparison to the standard US population with a mean of 50 and SD of 10. A higher score indicates that the individual has "more" of the concept being measured by the scale. Moreover, since the PROMIS inventory contains generic questionnaires, they can be used across all samples (patients, healthy persons, patients at all disease severity levels etc.) allowing us to compare

these diverse samples on the same scale. For this study, the HealthMeasures Scoring Service[SM] (HM-SS), a software application developed by the PROMIS Group was used to calculate the summary scores as described below.[35]

PROMIS[TM] – Global Health: The 10-item questionnaire covering physical health, mental health, pain, fatigue, social health and overall health was used to measure HRQoL in patients and caregivers. Two summary scores were calculated using 8 of the 10-items. The Global physical health (GPH) summary score is obtained by averaging across physical health (*global03*), physical function (*global06*), pain (*global07*), and fatigue (*global08*).[34] The Global mental health (GMH) summary score is obtained by averaging scores across overall quality of life (*global02),* mental health (*global04),* social health (*global05),* and emotional distress (*global10).*[36]

PROMIS[TM] – Sleep disturbance (SD): The 8-item short form version of this questionnaire was used to measure nocturnal sleep disturbances in patients and caregivers.

PROMIS[TM] – Sleep-related impairment (SRI): The 8-item short form version of this questionnaire was used to measure daytime sleepiness in patients and caregivers.

Patient Global Impression of Severity (PGI-S): PGI-S is a single self-reported measure that measures a patient's self-rated disease severity. In this study, the question was worded as "Please circle the response below that best describes the severity of your Parkinson's disease symptoms over the past week", with the following response categories: 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = severe, 6 = extreme. The response categories were created based on a 2015 study which compared various commonly used disease severity measures in PD.[37]

Other measures: Information was also collected on the following characteristics: (1) age, (2) race/ethnicity, (3) sex, (4) education status, (5) occupational status, (6) relationship to care recipient/caregiver, (7) duration of disease, (8) disease severity (in terms of PGI-S as mentioned above), (9) current anti-parkinsonian treatment use, (10) current sleep diagnosis, (11) current sleep-related treatment use, (12) number of caregiving hours per week (only to the caregiver).

COVID-related questions: Finally, since data collection took place during the Coronavirus Disease 2019 (COVID-19) pandemic, we also included questions pertaining to anxiety related to the pandemic and its impact on sleep and HRQoL for each participant. See Appendices 4 and 5 for survey instruments for PWP and caregivers, respectively.

Statistical analysis

Sample description

Descriptive statistics were calculated in the form of frequencies and percentages for categorical variables and means and standard deviations for the continuous variables. Pearson's product-moment correlation coefficients were calculated to assess correlations between the PROMIS measures for PWP and caregivers.

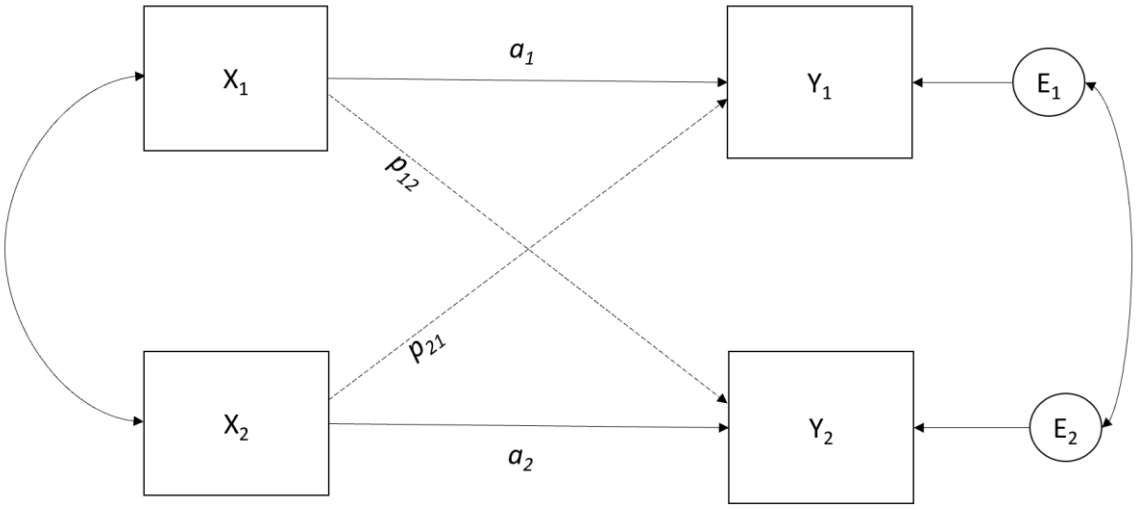
Actor-Partner Interdependence Model (APIM)

The APIM[23] is used to estimate dyadic data where the effects of interest are of mixed variables, i.e. variables that vary both between dyads and within dyads. The model allows for estimation of actor effects (the impact of an individual's independent variable on their own dependent variable) and partner effects (the impact of an individual's independent variable on the other dyad member's dependent variable). The subsequent improvement in assessing disease burden and pharmacoeconomic models could potentially translate into better policies and

healthcare interventions for PWP and caregivers. In this study, PROMIS-SD and PROMIS-SRI were considered as independent variables and PROMIS GMH and GPH summary scores were considered as dependent variables.

Figure 4.1 represents a conceptual model of the APIM for two dyad members 1 and 2. In this model, X_1 and X_2 represent the independent or predictor variables of dyad members 1 and 2, respectively. Similarly, Y_1 and Y_2 represent the dependent or outcome variables. The impact of X_1 on Y_1 represents actor effects for dyad member 1 (a_1). Similarly, the effect of X_2 on Y_2 represents actor effects for dyad member 2 (a_2). On the other hand, the effect of X_2 on Y_1 (p_{12}) and the effect of X_1 on Y_2 (p_{21}) represent their respective partner effects. In addition, the APIM allows for two correlations: (1) correlation between the independent variables (X_1 and X_2, represented by the curved line on the left), referred to as the compositional effect, where in relationships where members of a dyad were similar to each other even before pairing, (2) correlation between the dependent variables (Y_1 and Y_2 represented by the correlation between E_1 and E_2 on the right), which represents the nonindependence not explained by the model.

Figure 4.1: A conceptual model of the Actor-Partner Interdependence Model



Note: X_1 and X_2 represent the predictor variables for dyad members 1 and 2, respectively. Y_1 and Y_2 represent the dependent variables for dyad members 1 and 2 respectively. The curved double-headed arrows on the left represent the covariances between the independent variables, and the curved double-headed arrow on the right the correlation between the two error terms. The solid lines represent the actor effects (a_1 and a_2) and the dashed lines represent the partner effects (p_{12} and p_{21}).

Structural equation modeling (SEM) solution with distinguishable dyads was used to assess the models.[23,38] Within the APIM, the following four patterns have been suggested,[23] where *a* represents actor effects, *p* represents partner effects and *k* represents the ratio parameter. *k* parameter is calculated as the ratio of partner effects to actor effects for a dyad member. Dyadic patterns were assessed based on an approach suggested by Fitzpatrick et al.[39]

i. actor-oriented ($a \neq 0$, $p = 0$, $k = 0$): in this model, the person's outcomes are a function of their own characteristics and the partner's characteristics have no impact.

ii. partner-oriented ($a = 0$, $p \neq 0$, $k = 0$): in this model, the person's outcomes are purely a function of their partner's characteristics and their own characteristics have no impact.

iii. couple-oriented ($a = p$, $k = 1$): in this model, the actor and partner effects are equal, i.e. a person's outcomes are as influenced by their own characteristics as much as their partner's characteristics.

iv. social comparison ($a + p = 0$, $k = -1$): in this model, the actor and partner effects are equal in magnitude but opposite in direction. Consider the example where the actor effect is positive and partner effect is negative. In this case, the actor effect is a positive predictor of the outcome, whereas the partner effect is a negative predictor of the outcome.

Two parameters k_1 for PWP and k_2 for caregivers were estimated in the saturated model and bootstrapped 95% confidence intervals were obtained to identify possible dyadic patterns. Upon identifying a possible pattern, a model where these parameters were constrained to the hypothesized values as mentioned above was estimated to see if the model fit worsened. Model fit was assessed using the chi-square statistic, comparative fit index (CFI) and root mean square error of approximation (RMSEA). For CFI, values greater than 0.95 were considered for good fit. A 90% confidence interval for RMSEA with lower and upper bounds between 0 and 0.08, respectively, were considered to indicate good model fit. These bounds are based on the cutoffs of 0.01, 0.05 and 0.08 suggested for excellent, good and mediocre fit by MacCallum, Browne and Sugawara.[40] Data management and descriptive statistics for the sample were conducted in SAS 9.4 (SAS Institute, Cary, NC). All SEM-based analyses were conducted using Mplus version 8.5 (Muthén & Muthén, Los Angeles, CA).

Results

Socio-demographic and clinical characteristics of the PWP-caregiver dyads

A total of 108 PWP-caregiver dyads completed the online survey. Sociodemographic characteristics of the dyad members are provided in Table 4.1. Compared to their caregivers, a greater proportion of PWP were male (67% vs. 39%), had less than a bachelor's degree (53% vs. 42%), were retired (60% vs. 31%) and were enrolled in public health insurance programs (80% vs. 49%). Race was evenly distributed in both groups. The majority of the dyad members reported a household income level of $50,000 or more. Most caregivers were spouses (59%) of the PWP and were full-time caregivers (47%). The median number of chronic conditions in PWP and their caregivers was 2 and 1, respectively.

Table 4.1: Socio-demographic characteristics of persons with Parkinson's disease and their caregivers included in the study

Characteristic	Category	Patients (N = 108) N (%)	Caregivers (N = 108) N (%)
Sex	Female	35 (32.4)	66 (61.1)
	Male	72 (66.7)	42 (38.9)
	Other/prefer not to answer	1 (0.9)	-
Age group (in years)	50-65	35 (32.4)	-
	66-75	52 (48.2)	
	76-85	17 (15.7)	
	86 or older	4 (3.7)	
Age (in years) (Mean ± SD, Range)		-	56.0 ± 15.0, 28-89
Race	White	94 (87.0)	94 (87.0)
	Other	14 (13.0)	14 (13.0)
Highest education level	GED or High school diploma	39 (36.1)	20 (18.7)
	Associate degree	12 (11.1)	23 (21.5)
	Bachelor's degree	35 (32.4)	40 (37.4)
	Master's degree	8 (7.4)	16 (15.0)
	Terminal degree	8 (7.4)	6 (5.6)
	No degree	6 (5.6)	2 (1.9)
Employment status	Retired	65 (60.2)	33 (30.6)
	Unable to work	19 (17.6)	7 (6.5)
	Employed for wages	9 (8.3)	43 (39.8)
	Self-employed	2 (1.9)	5 (4.6)
	Out of work for 1 year or more	5 (4.6)	6 (5.6)
	Out of work for less than 1 year due to COVID-19, also known as Coronavirus or SARS-CoV-2	2 (1.9)	7 (6.5)
	Out of work for less than 1 year due to other reason(s)	4 (3.7)	1 (0.9)
Health insurance	Public insurance (e.g. Medicare, Medicaid, VA)	86 (79.6)	52 (48.6)
	Private insurance	21 (19.4)	48 (44.9)
	Other	-	3 (2.8)
	Uninsured	1 (0.9)	4 (3.7)

Household income (N = 107)	$15,000 to less than $25,000	11 (10.3)	
	$25,000 to less than $35,000	11 (10.3)	
	35,000 to less than $50,000	18 (16.8)	
	$50,000 or more	67 (62.6)	
Caregiver's relationship to PWP	Spouse or significant other	64 (59.3)	
	Son/daughter	19 (17.6)	
	Other relative	21 (19.4)	
	Other non-relative	4 (3.7)	
Caregiving time per week (in hours)	20 or fewer	-	31 (28.7)
	21-39	-	26 (24.1)
	40 or more	-	51 (47.2)
Number of care recipients (including primary PWP) (Mean ± SD, Median, Range)		-	1.6 ± 1.1, 1, 0-6
Number of chronic conditions (Mean ± SD, Median, Range)		1.8 ± 1.7, 2, 0-8	1.4 ± 1.4, 1, 0-8

PWP = Persons with Parkinson's

Clinical characteristics of PWP cohort

Forty-three percent of PWP reported moderate severity for both motor and NM symptoms (Table 4.2). About 35% reported normal-to-mild motor symptoms and 41% reported normal-to-mild NM symptoms. A lower proportion of PWP (22% for motor, 17% for NM) reported having severe or extreme symptoms. Within treatments, use of oral formulations of carbidopa-levodopa (44.4% for Sinemet CR, 17% for Rytary) was most commonly reported among PWP. About 23% of the PWP also reported use of melatonin supplements. Among caregivers, 31% reported having been diagnosed by a healthcare professional with a sleep disorder and 43% reported use of a medication to manage their sleep problems (Table 4.3).

Table 4.2: Clinical characteristics of PWP included in the study

Characteristic	Category	Patients (N = 108) N (%)
Self-reported motor symptom severity*	Normal	5 (4.6)
	Borderline	8 (7.4)
	Mild	25 (23.2)
	Moderate	46 (42.6)
	Severe	20 (18.5)
	Extreme	4 (3.7)
Self-reported non-motor symptom severity*	Normal	8 (7.4)
	Borderline	6 (5.6)
	Mild	30 (27.8)
	Moderate	46 (42.6)
	Severe	15 (13.9)
	Extreme	3 (2.8)
Anti-parkinsonian/sleep treatment use	Sinemet CR (carbidopa-levodopa controlled release tablets)	48 (44.4)
	Melatonin supplements	25 (23.2)
	Klonopin (clonazepam)	18 (16.7)
	Rytary (carbidopa-levodopa extended-release capsules)	18 (16.7)
	Seroquel (quetiapine)	17 (15.7)
	Mirapex (pramipexole)	16 (14.8)
	Deep-brain stimulation	12 (11.1)
	Ambien (zolpidem)	8 (7.4)
	Duopa (carbidopa-levodopa enteral suspension)	8 (7.4)
	Lunesta (eszopiclone)	8 (7.4)
	Nuplazid (pimavanserin)	8 (7.4)
	Requip (ropinirole)	7 (6.5)
	Desyrel (trazodone)	6 (5.6)
	Silenor (doxepin)	5 (4.6)
	Other+	29 (26.87)

PWP = Persons with Parkinson's

*Patient Global Impression of Severity (PGI-S) was used to measure motor and non-motor symptom severity.

+'Other' category under anti-parkinsonian/sleep treatment use included Neupro (rotigotine transdermal system), Sonata (zaleplon), Provigil (modafinil), Nuvigil (armodafinil), Ritalin (methylphenidate) and Clozaril (clozapine).

Table 4.3: Clinical characteristics of caregivers of PWP included in the study

Characteristic	Response	Caregivers (N= 108) N (%)
Sleep diagnosis	Yes	33 (30.6)
	No	68 (63.0)
	Uncertain	7 (6.5)
Current sleep medication use	Yes	46 (42.6)
	No	60 (55.6)
	Uncertain	2 (1.9)

PWP = Persons with Parkinson's

Sleep and health-related quality of life among PWP and their caregivers

The average scores for PROMIS-SD, PROMIS-SRI, PROMIS GMH and GPH measures are provided in Table 4.4. The average GPH and GMH summary scores for PWP were 46.4 (±8.6) and 40.6 (±8.4), respectively. For caregivers, the average GPH summary score was 46.2 (±8.8) and the average GMH summary score was 36.9 (±7.0). On PROMIS-SD, PWP had a mean score of 56.3 (±9.4) and caregivers had a mean score of 55.9 (±9.9). Whereas on PROMIS-SRI, PWP reported an average score of 59.5 (±10.6) and their caregivers reported 56.0 (±11.7).

PWP and caregiver responses to questions related to the impact of COVID-19 are presented in Table 4.5. On a scale of 1 (low) – 10 (high), PWP reported a mean anxiety score of 5.8 (±3.0) and caregivers reported a mean anxiety score of 5.9 (±2.8). When asked about change in sleep quality as a result of COVID-19, most PWP (68%) and caregivers (69%) reported that it remained the same. With regards to quality of life, most PWP (65%) and caregivers (62%) reported that it had worsened as a result of COVID-19. About 37% of PWP and 34% of caregivers agreed that COVID-19 had a significant impact on their sleep quality. Whereas, 67%

of PWP and 62% of caregivers agreed that COVID-19 had a significant impact on their quality of life.

Table 4.4: PROMIS global mental and physical summary scores, sleep disturbance and sleep-related impairment in PWP-caregiver dyads

Measure	Patients (N = 108) (Mean ± SD)	Caregivers (N = 108) (Mean ± SD)
PROMIS Global Mental Health Summary Score	40.6 ± 8.4	46.4 ± 8.6
PROMIS Global Physical Health Summary Score	36.9 ± 7.0	46.2 ± 8.8
Sleep Disturbance (PROMIS-SD)	56.3 ± 9.4	55.9 ± 9.9
Sleep-Related Impairment (PROMIS-SRI)	59.5 ± 10.6	56.0 ± 11.7

PWP = Persons with Parkinson's

Table 4.5: Impact of COVID-19 on sleep and quality of life in PWP-caregiver dyads

COVID-19 related items	Category	Patients (N = 107)* N (%)	Caregivers (N = 108) N (%)
COVID-19 related anxiety (Mean ± SD, Range)	On a scale of 1-10 (1 = Low, 10 = High)	5.8 ± 3.0, 1-10	5.9 ± 2.8, 1-10
Change in sleep quality as a result of COVID-19	Worsened	33 (30.8)	33 (30.6)
	Remained the same	73 (68.2)	74 (68.5)
	Improved	1 (0.9)	1 (0.9)
Change in quality of life as a result of COVID-19	Worsened	69 (64.5)	67 (62.0)
	Remained the same	38 (35.5)	39 (36.1)
	Improved	-	2 (1.9)
Level of agreement with statements related to the impact of COVID-19			
The COVID-19 pandemic has had a significant impact on the quality of my sleep	Strongly disagree	34 (31.8)	36 (33.3)
	Somewhat disagree	19 (17.8)	18 (16.7)
	Neither disagree nor agree	14 (13.1)	17 (15.7)
	Somewhat agree	26 (24.3)	22 (20.4)
	Strongly agree	14 (13.1)	15 (13.9)
The COVID-19 pandemic has had a significant impact on my quality of life	Strongly disagree	13 (12.2)	9 (8.3)
	Somewhat disagree	8 (7.5)	13 (12.0)
	Neither disagree nor agree	14 (13.1)	18 (16.7)
	Somewhat agree	45 (42.1)	36 (33.3)
	Strongly agree	27 (25.2)	32 (29.6)

PWP = Persons with Parkinson's, COVID-19 = Coronavirus Disease 2019
*****107 PWP responded to the COVID-19 related questions.

The Actor-Partner Interdependence model for sleep and HRQoL measures

Because the PROMIS-SD and PROMIS-SRI were strongly correlated within persons in our sample ($r = 0.822$, $p < 0.001$ for PWP and $r = 0.803$, $p < 0.001$ for caregivers) (Table 4.6), separate API models were conducted with PROMIS-SD and PROMIS-SRI as the independent variables to avoid potential for multicollinearity. Consequently, four separate models were conducted where two models estimated the dyadic impact of sleep disturbance on GPH and GMH, respectively, and two models estimated the impact of sleep-related impairment on GPH and GMH, respectively.

Table 4.6: Correlations of PROMIS global mental and physical health summary scores, sleep disturbance and sleep-related impairment in PWP-caregiver dyads

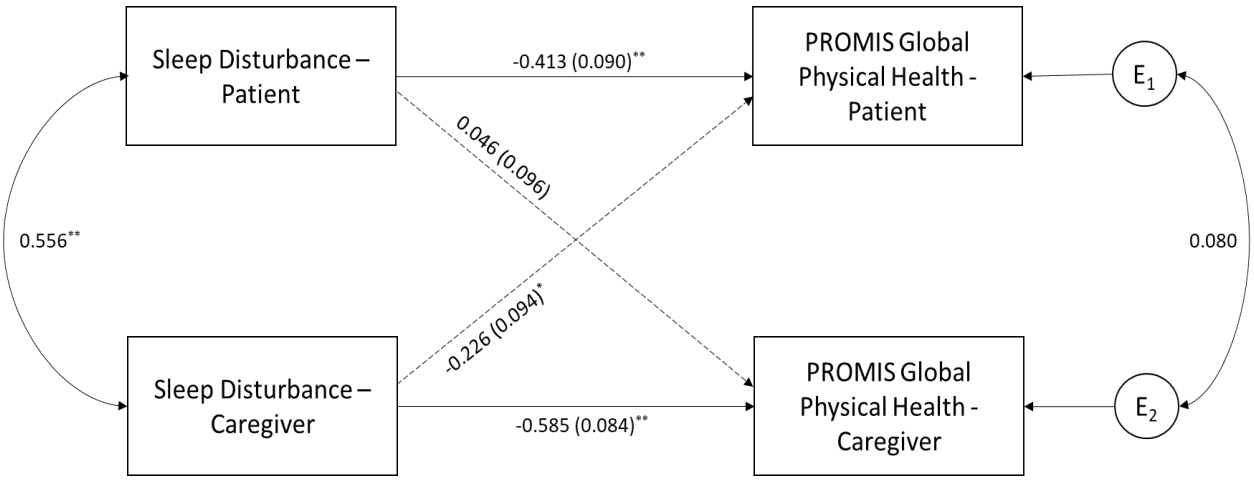
		1	2	3	4	5	6	7	8
1	PWP mental health summary score	1.000							
2	PWP physical health summary score	0.690*	1.000						
3	PWP sleep disturbance	-0.482*	-0.539*	1.000					
4	PWP sleep-related impairment	-0.471*	-0.581*	0.822*	1.000				
5	Caregiver mental health summary score	0.348*	0.297**	-0.321*	-0.265***	1.000			
6	Caregiver physical health summary score	0.182	0.296**	-0.279**	-0.278**	0.638*	1.000		
7	Caregiver sleep disturbance	-0.341*	-0.456*	0.556*	0.460*	-0.521*	-0.559*	1.000	
8	Caregiver sleep-related impairment	-0.323*	-0.427*	0.442*	0.413*	-0.499*	-0.656*	0.803*	1.000

**p ≤ 0.001, **p ≤ 0.05, ***p ≤ 0.01*

Impact of sleep disturbance on physical and mental health

APIM results for model 1 and 2 are presented in Table 4.7. In model 1 where PROMIS GPH summary score was regressed on PROMIS-SD (Figure 4.2), two significant actor effects were identified: PWP's sleep disturbance on their own physical health (unstandardized estimate = -0.309, 95% CI: [-0.446, -0.168]) and caregiver's sleep disturbance on their own physical health (unstandardized estimate = -0.517, 95% CI: [-0.680, -0.371]). Additionally, a statistically significant partner effect of caregiver's sleep disturbance on PWP's physical health (unstandardized estimate = -0.160, 95% CI: [-0.304, -0.031]) was identified. Subsequently, a model with couple-oriented ($k_1 = 1$) and actor-oriented dyadic patterns ($k_2 = 0$) was estimated for PWP and caregivers, respectively, which had a reasonably good fit.

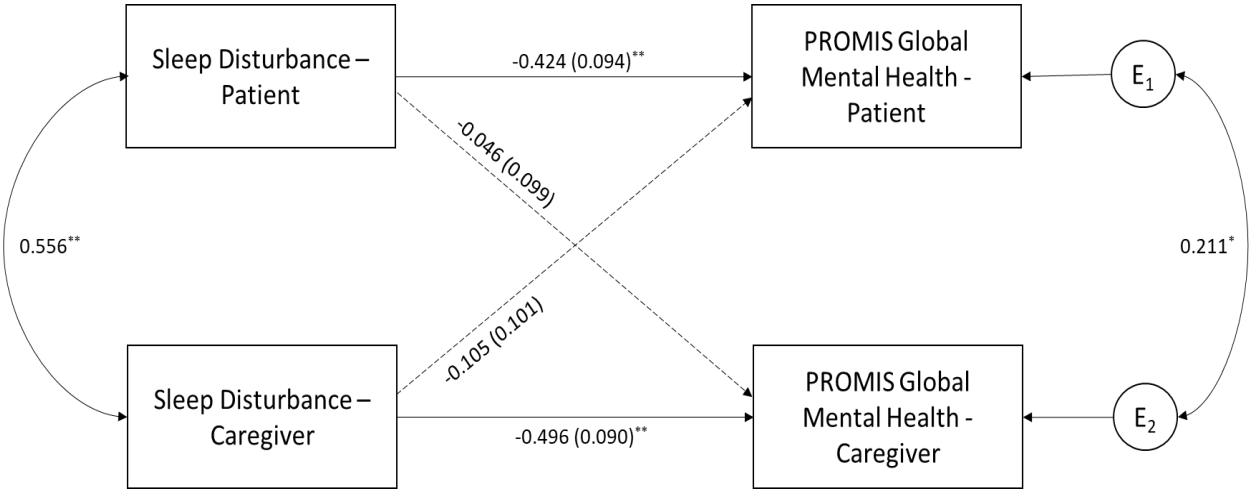
Figure 4.2: Actor-Partner Interdependence Model showing actor and partner effects for the impact of sleep disturbance on PROMIS Global Physical Health summary score



Note: Actor and partner effects of PROMIS-sleep disturbance on PROMIS global physical health summary score. In the graphical representation above, the rectangles represent the independent and dependent variables; the two circles on the right present the latent error terms; and the arrows describe the actor and partner effects. The curved double-headed arrows on the left represent the covariances between the independent variables, and the curved double-headed arrow on the right the correlation between the two error terms. The solid lines represent the actor effects and the dashed lines represent the partner effects. Standardized coefficients and standard errors are reported in parentheses. The model did not include control variables.
$^{*}p < 0.05$, $^{**}p < 0.001$

In model 2 where PROMIS GMH summary score was regressed on PROMIS-SD (Figure 4.3), two significant actor effects were identified: PWP's sleep disturbance on their own mental health (unstandardized estimate = -0.380, 95% CI: [-0.562, -0.178]) and caregiver's sleep disturbance on their own physical health (unstandardized estimate = -0.432, 95% CI: [-0.586, -0.281]) (Table 4.7). No significant partner effects were identified. Subsequently, a model with actor-oriented dyadic patterns ($k_1 = 0$, $k_2 = 0$) was estimated for PWP and caregivers, respectively, which showed good fit.

Figure 4.3: Actor-Partner Interdependence Model showing actor and partner effects for the impact of sleep disturbance on PROMIS Global Mental Health



Note: Actor and partner effects of PROMIS-sleep disturbance on PROMIS global mental health summary score. In the graphical representation above, the rectangles represent the independent and dependent variables; the two circles on the right present the latent error terms; and the arrows describe the actor and partner effects. The curved double-headed arrows on the left represent the covariances between the independent variables, and the curved double-headed arrow on the right the correlation between the two error terms. The solid lines represent the actor effects and the dashed lines represent the partner effects. Standardized coefficients and standard errors are reported in parentheses. The model did not include control variables.
$^{*}p < 0.05$, $^{**}p < 0.001$

Table 4.7: Actor-Partner Interdependence Model parameter estimates for sleep disturbance and physical and mental health

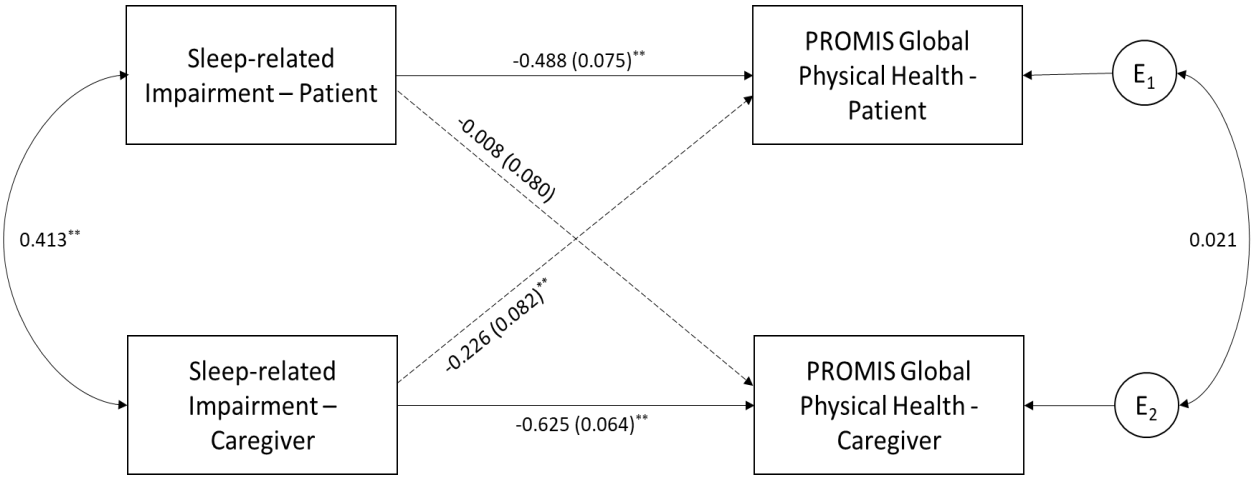
	Model 1: Physical health (PROMIS GPH summary score)		**Model 2: Mental health (PROMIS GMH summary score)**	
	Unstandardized estimate (95% CI)	***p*-value**	**Unstandardized estimate (95% CI)**	***p*-value**
Actor effects				
a_1	-0.309 (-0.446, -0.168)	<0.001	-0.380 (-0.562, -0.178)	<0.001
a_2	-0.517 (-0.680, -0.371)	<0.001	-0.432 (-0.586, -0.281)	<0.001
Partner effects				
p_{12}	-0.160 (-0.304, -0.031)	0.023	-0.089 (-0.253, 0.054)	0.246
p_{21}	0.043 (-0.129, 0.201)	0.607	-0.042 (-0.200, 0.106)	0.584
Dyadic patterns				
Hypothesis	Couple-oriented for PWP and actor-oriented for caregiver ($k_1 = 1$, $k_2 = 0$)		Actor-oriented for PWP and caregivers ($k_1 = 0$, $k_2 = 0$)	
k_1	0.517 (0.086, 1.668)		0.234 (-0.117, 1.110)	
k_2	-0.084 (-0.362, 0.283)		0.097 (-0.215, 0.566)	
Model fit				
df	2		2	
Chi-square	1.808		1.421	
RMSEA (90% CI)	0.000 (0.000, 0.185)		0.000 (0.000, 0.172)	
CFI	1.000		1.000	

a_1 = actor effect (PWP), a_2 = actor effect (caregiver), p_{12} = impact of caregiver's sleep disturbance on PWP's physical/mental health (partner effect), p_{21} = impact of PWP's sleep disturbance on their caregiver's physical/mental health (partner effect), k_1 and $k_2 = k$ (ratio) parameters to estimate dyadic patterns for PWP and caregiver, respectively, *df* = degrees of freedom, RMSEA = root mean square error of approximation, CI = confidence interval, CFI = comparative fit index
The model did not include control variables.

Impact of sleep-related impairment on physical and mental health

APIM results for model 3 and 4 are presented in Table 4.8. Model 3, where PROMIS GPH summary score was regressed on PROMIS-SRI (Figure 4.4), identified two significant actor effects: PWP's sleep-related impairment on their own physical health (unstandardized estimate = -0.323, 95% CI: [-0.461, -0.170]) and caregiver's sleep-related impairment on their own physical health (unstandardized estimate = -0.488, 95% CI: [-0.616, -0.353]). Additionally, a statistically significant partner effect of caregiver's sleep-related impairment on PWP's physical health (unstandardized estimate = -0.135, 95% CI: [-0.256, -0.013]) was identified. Subsequently, a model with couple-oriented ($k_1 = 1$) and actor-oriented dyadic patterns ($k_2 = 0$) was estimated for PWP and caregivers, respectively, which did not worsen model fit.

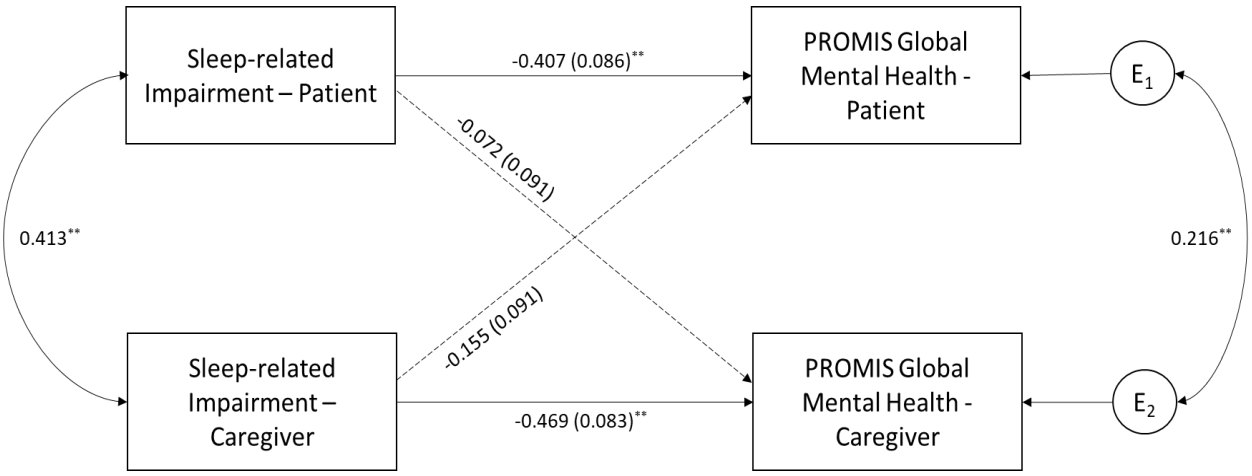
Figure 4.4: Actor-Partner Interdependence Model showing actor and partner effects for the impact of sleep-related impairment on PROMIS Global Physical Health summary score



Note: Actor and partner effects of PROMIS sleep-related impairment on PROMIS global physical health summary score. In the graphical representation above, the rectangles represent the independent and dependent variables; the two circles on the right present the latent error terms; and the arrows describe the actor and partner effects. The curved double-headed arrows on the left represent the covariances between the independent variables, and the curved double-headed arrow on the right the correlation between the two error terms. The solid lines represent the actor effects and the dashed lines represent the partner effects. Standardized coefficients and standard errors are reported in parentheses. The model did not include control variables.
$^{*}p < 0.05$, $^{**}p < 0.001$

In model 4 where PROMIS GMH summary score was regressed on PROMIS-SRI (Figure 4.5), two significant actor effects were identified: PWP's sleep-related impairment on their own mental health (unstandardized estimate = -0.322, 95% CI: [-0.485, -0.104]) and caregiver's sleep disturbance on their own physical health (unstandardized estimate = -0.346, 95% CI: [-0.469, -0.216]) (Table 4.8). No significant partner effects were identified. Subsequently, a model with actor-oriented dyadic patterns ($k_1 = 0$, $k_2 = 0$) was estimated for PWP and caregivers, respectively, which showed reasonable fit.

Figure 4.5: Actor-Partner Interdependence Model showing actor and partner effects for the impact of sleep-related impairment on PROMIS Global Mental Health



Note: Actor and partner effects of PROMIS sleep-related impairment on PROMIS global mental health summary score. In the graphical representation above, the rectangles represent the independent and dependent variables; the two circles on the right present the latent error terms; and the arrows describe the actor and partner effects. The curved double-headed arrows on the left represent the covariances between the independent variables, and the curved double-headed arrow on the right the correlation between the two error terms. The solid lines represent the actor effects and the dashed lines represent the partner effects. Standardized coefficients and standard errors are reported in parentheses. The model did not include control variables.
$^{*}p < 0.05$, $^{**}p < 0.001$

Table 4.8: Actor-Partner Interdependence Model parameter estimates for sleep-related impairment and physical and mental health

	Model 3: Physical health (PROMIS GPH summary score)		**Model 4: Mental health (PROMIS GMH summary score)**	
	Unstandardized estimate (95% CI)	***p*-value**	**Unstandardized estimate (95% CI)**	***p*-value**
Actor effects				
a_1	-0.323 (-0.461, -0.170)	<0.001	-0.322 (-0.485, -0.104)	0.001
a_2	-0.488 (-0.616, -0.353)	<0.001	-0.346 (-0.469, -0.216)	<0.001
Partner effects				
p_{12}	-0.135 (-0.256, -0.013)	0.026	-0.111 (-0.263, 0.023)	0.127
p_{21}	-0.007 (-0.144, 0.128)	0.922	-0.058 (-0.201, 0.077)	0.409
Dyadic patterns				
Hypothesis	Couple-oriented for PWP and actor-oriented for caregiver ($k_1 = 1$, $k_2 = 0$)		Actor-oriented for PWP and caregivers ($k_1 = 0$, $k_2 = 0$)	
k_1	0.419 (0.034, 1.356)		0.345 (-0.054, 2.060)	
k_2	0.014 (-0.252, 0.333)		0.169 (-0204, 0.773)	
Model fit				
df	2		2	
Chi-square	4.445		3.683	
RMSEA (90% CI)	0.106 (0.000, 0.243)		0.088 (0.000, 0.229)	
CFI	0.977		0.973	

a_1 = actor effect (PWP), a_2 = actor effect (caregiver), p_{12} = impact of caregiver's sleep-related impairment on PWP's physical/mental health (partner effect), p_{21} = impact of PWP's sleep-related impairment on their caregiver's physical/mental health (partner effect), k_1 and $k_2 = k$ (ratio) parameters to estimate dyadic patterns for PWP and caregiver, respectively, *df* = degrees of freedom, RMSEA = root mean square error of approximation, CI = confidence interval, CFI = comparative fit index
The model did not include control variables.

Discussion

Our study aimed to assess the impact of sleep disturbance and related impairment on global physical and mental health in PWP-caregiver dyads. For this purpose, we conducted an online survey in a national convenience sample of PWP and caregivers. The results indicate that both PWP and caregivers included in our study had GPH and GMH summary scores less than 50, indicating reduced physical and mental health compared to the standard US population. This finding is consistent with previous literature.[41–44] Additionally, PWP reported lower GPH and GMH summary scores than their caregivers. Both the dyad members scored higher on PROMIS-SD and PROMIS-SRI than the average for the standard US population, indicating worse sleep disturbance and related impairment in this sample.

We could not find studies which evaluated PROMIS-SD and PROMIS-SRI scores in samples comparable to our study. However, other studies conducted by Trout et al.,[45] who analyzed an early-PD cohort, and Shin et al.,[46] who analyzed an advanced PD cohort, reported PROMIS-SD scores comparable to our results. The mean PROMIS-SD scores for PWP and caregivers were similar, which was similar to the findings reported in Shin et al.[46] The mean PROMIS-SRI scores reported in the Trout et al.[45] study in an early-PD cohort (with RBD: 31, range: [27-49] and without RBD: 34, range: [26, 38]) are substantially lower than the score we found in our PWP group, which may be attributed to differences in sample characteristics and the strong correlation between disease duration and daytime sleepiness issues in PWP.[47,48] PWP reported higher scores on PROMIS-SRI than their caregivers, which was consistent with the direction reported in Shin et al.[46]

Finally, using APIM, the current study found that sleep disturbances showed significant negative actor effects on their own physical as well as mental health for both PWP and caregivers. Additionally, caregiver's sleep disturbance showed a significant negative partner effect on PWP's global physical health. Sleep-related impairment also significantly negatively impacted their own physical and mental health for both PWP and caregivers. A negative partner effect was seen between caregiver's sleep-related impairment and their PWP's global physical health. To our knowledge, the current study is the first to evaluate the dyadic relationship between sleep and HRQoL in PWP and their caregivers. Our findings provide empirical evidence to support the negative couple-oriented effects for PWP since their physical health was influenced by their own sleep measures as well as their caregiver's sleep measures. We hypothesize that sleep and wakefulness problems in caregivers might compromise their ability to provide required care to their PWP and thereby result in worse physical health outcomes for the PWP.

Since there was no precedent for this phenomenon in PD, we looked to literature outside of PD and found several studies where impact of sleep was evaluated in spousal dyads. In a study by Al-Rawashdeh et al., the authors assessed the impact of sleep disturbances on quality of life of heart failure patients and identified a couple-oriented effect for the patient's mental health.[49] Strawbridge et al. found that older adults whose spouses experienced sleep problems were at a greater odds of reporting fair or poor physical health.[50] Another dyadic study involving middle-aged and older adult couples showed that insomnia in wives increased their husband's risk of incident heart disease.[51] While most of these studies analyzed spousal dyads, we found significant partner effects in our sample where about 40% of caregivers were either adult

children, other relative or other non-relative. Further research needs to be done to evaluate the reproducibility of our results in other PD samples as well as in other disease areas.

There are some limitations in our study. First, the analysis was conducted with a convenience sample, so the results may not be generalizable to the larger PD community. As evident from the PWP and caregiver responses to COVID-19 related questions, the pandemic and the consequent restrictions may have influenced respondents' sleep and HRQoL scores and the relationships between them. Additionally, 41% of the dyads were non-spouses, which may have also affected the relationship between sleep and HRQoL. This was a cross-sectional study and therefore, causality cannot be established. PWP and caregiver responses to the survey questions may be prone to recall bias and social desirability bias.

Conclusion

Most studies usually evaluate the impact of PWP clinical factors on caregiver outcomes such as caregiver burden or HRQoL. Our results emphasize that interventions targeted at improving HRQoL in PWP may benefit from addressing sleep problems at the dyad-level, rather than the individual. Our results also underscore the importance of appropriately assessing and managing sleep problems in caregivers in a timely manner. This may help reduce distress, improve wellbeing and decrease disease burden on the society.

List of References

1. Müller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. Park Relat Disord. 2013;19(11):1027-1032. doi:10.1016/j.parkreldis.2013.07.010

2. Chaudhuri KR, Healy DG, Schapira AH V. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006;5:235-245. doi:10.4314/njm.v19i2.56496

3. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev. 2017;35:33-50. doi:10.1016/j.smrv.2016.08.001

4. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord. 2010;25(15):2493-2500. doi:10.1002/mds.23394

5. Carod-Artal FJ, Mesquita HM, Ziomkowski S, Martinez-Martin P. Burden and health-related quality of life among caregivers of Brazilian Parkinson's disease patients. Park Relat Disord. 2013;19(11):943-948. doi:10.1016/j.parkreldis.2013.06.005

6. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord. 2011;26(3):399-406. doi:10.1002/mds.23462

7. Avidan A, Hays RD, Diaz N, et al. Associations of sleep disturbance symptoms with health-related quality of life in parkinson's disease. J Neuropsychiatry Clin Neurosci. 2013;25(4):319-326. doi:10.1176/appi.neuropsych.12070175

8. Naismith S, Hickie IB, Lewis SJG. The Role of Mild Depression in Sleep Disturbance and Quality of Life in Parkinson ' s Disease. J Neuropsychiatry Clin Neurosci. 2010;22:384-389.

9. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen J. Insomnia in Parkinson's disease: frequency and progression over time. J Neurol Neurosurg Psychiatry. 2007;78:476-479. doi:10.1136/jnnp.2006.100370

10. Pal PK, Thennarasu K, Fleming J, Schulzer M, Brown T, Calne SM. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. Park Relat Disord. 2004;10(3):157-168. doi:10.1016/j.parkreldis.2003.11.002

11. Caap-Ahlgren M, Dehlin O. Insomnia and depressive symptoms in patients with Parkinson ' s disease Relationship to health-related quality of life . An interview study of patients living at home. Arch Gerontol Geriatr. 2001;32:23-33.

12. Siciliano M, Trojano L, Santangelo G, De Micco R, Tedeschi G, Tessitore A. Fatigue in

Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2018;33(11):1712-1723. doi:10.1002/mds.27461

13. Goldman SE, Ancoli-israel S, Boudreau R, et al. Sleep Problems and Associated Daytime Fatigue in Community-Dwelling Older Individuals. J Gerontol. 2008;63A(10):1069-1075.

14. Pushpanathan ME, Loftus AM, Thomas MG, Gasson N, Bucks RS. The relationship between sleep and cognition in Parkinson's disease: A meta-analysis. Sleep Med Rev. 2014;26:21-32. doi:10.1016/j.smrv.2015.04.003

15. Stavitsky K, Neargarder S, Bogdanova Y, Mcnamara P, Cronin-golomb A. The Impact of Sleep Quality on Cognitive Functioning in Parkinson ' s Disease. 2020;(2012):108-117. doi:10.1017/S1355617711001482

16. Scullin MK, Trotti LM, Wilson AG, Greer SA, Bliwise DL. Nocturnal sleep enhances working memory training in Parkinson's disease but not Lewy body dementia. Brain. 2012;135(9):2789-2797. doi:10.1093/brain/aws192

17. Smith M, Ellgring H, Oertel W. Sleep disturbances in Parkinson's disease patients and spouses. J Am Geriatr Soc. 1997;45:194-199.

18. Cupidi C, Realmuto S, Lo Coco G, et al. Sleep quality in caregivers of patients with Alzheimers disease and Parkinsons disease and its relationship to quality of life. Int Psychogeriatrics. 2012;24(11):1827-1835. doi:10.1017/S1041610212001032

19. Drutyte G, Forjaz MJ, Rodriguez-Blazquez C, Martinez-Martin P, Breen KC. What impacts on the stress symptoms of Parkinson's carers? Results from the Parkinson's UK Members' Survey. Disabil Rehabil. 2014;36(3):199-204. doi:10.3109/09638288.2013.782363

20. Arber S, Venn S. Caregiving at night: Understanding the impact on carers. J Aging Stud. 2011;25(2):155-165. doi:10.1016/j.jaging.2010.08.020

21. Happe S, Berger K. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing. 2002;31(5):349-354. doi:10.1093/ageing/31.5.349

22. Viwattanakulvanid P, Kaewwilai L, Jitkritsadakul O, et al. The impact of the nocturnal disabilities of Parkinson's disease on caregivers' burden: Implications for interventions. J Neural Transm. 2014;121(SUPPL. 1). doi:10.1007/s00702-014-1200-8

23. Kenny DA, Kashy DA, Cook WL. Dyadic Data Analysis. First ed. New York: The Guildford Press; 2006.

24. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. JAMA - J Am Med Assoc. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195

25. Neumann P, Sanders G, Rusell L, Siegel J, Ganiats T. Cost-Effectiveness in Health and Medicine. 2nd ed. New York: Oxford University Press; 2016.

26. The National Institute for Health and Care Excellence. NICE DSU Technical Support Document 8: An Introduction to the Measurement and Valuation of Health for NICE Submissions. London; 2011.

27. The National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013. London; 2013.

28. Kotronoulas G, Wengström Y, Kearney N. Sleep and sleep-wake disturbances in care recipient-caregiver dyads in the context of a chronic illness: A critical review of the literature. J Pain Symptom Manage. 2013;45(3):579-594. doi:10.1016/j.jpainsymman.2012.03.013

29. Wade R, Pachana NA, Dissanayaka N. Management of Sleep Disturbances in Parkinson's Disease Patients, Carers and the Patient and Carer Dyadic Relationship: A Scoping Review. Clin Gerontol. 2018;00(00):1-9. doi:10.1080/07317115.2018.1539424

30. Kashy DA, Kenny DA. The analysis of data from dyads and groups. In: Reis HT, Judd CM, eds. Handbook of Research Methods in Social Psychology. Cambridge University Press; 2000.

31. Bagheri Z, Taheri M, Motazedian N. The impacts of depression and anxiety on quality of life among patients with HIV/AIDS and their spouses: testing dyadic dynamics using the actor-partner interdependence model. AIDS Care - Psychol Socio-Medical Asp AIDS/HIV. 2019;31(12):1500-1508. doi:10.1080/09540121.2019.1595676

32. Mavandadi S, Dobkin R, Mamikonyan E, Sayers S, Ten Have T, Weintraub D. Benefit finding and relationship quality in Parkinson's disease: A pilot dyadic analysis of husbands and wives. J Fam Psychol. 2014;28(5):728-734. doi:10.1037/a0037847

33. National Institutes of Health. PROMIS: Clinical Outcomes Assessment. https://commonfund.nih.gov/promis/index. Published 2019. Accessed November 23, 2019.

34. Northwestern University. Patient-Reported Outcomes Measurement Information System (PROMIS). http://www.healthmeasures.net/explore-measurement-systems/promis. Published 2019. Accessed October 20, 2019.

35. Cella D, Gershon R, Bass M, Rothrock N. Assessment Center Scoring Service User Manual.; 2019.

36. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res. 2009;18(7):873-880. doi:10.1007/s11136-009-9496-9

37. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez M, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. Park Relat Disord. 2015;21:50-54. doi:10.1016/j.parkreldis.2014.10.026

38. Kenny DA. Models of non-independence in dyadic research. J Soc Pers Relat. 1996;13(2):279-294. doi:10.1177/0265407596132007

39. Fitzpatrick J, Gareau A, Lafontaine M, Gaudreau P. How to Use the Actor-Partner Interdependence Model (APIM) To Estimate Different Dyadic Patterns in MPLUS : A Step-by-Step Tutorial. Quant Methods Psychol. 2016;12(1):74-86. doi:10.20982/tqmp.12.1.p074

40. MacCallum RC, Browne MW, Sugawara HM. Power analysis and determination of sample size for covariance structure modeling. Psychol Methods. 1996;1(2):130-149. doi:10.1037/1082-989X.1.2.130

41. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. Mov Disord. 2000;15(6):1112-1118. doi:10.1002/1531-8257(200011)15:6<1112::AID-MDS1008>3.0.CO;2-A

42. Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D - q generic quality of life measure - is a useful instrument to measure quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000;69:67-73. doi:10.1136/jnnp.70.6.817

43. Haapaniemi TH, Sotaniemi KA, Sintonen H, Taimela E. The generic 15D instrument is valid and feasible for measuring health related quality of life in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004;75(7):976-983. doi:10.1136/jnnp.2003.015693

44. Martinez-Martin P, Arroyo S, Rojo-Abuin JM, et al. Burden, perceived health status, and mood among caregivers of Parkinson's disease patients. Mov Disord. 2008;23(12):1673-1680. doi:10.1002/mds.22106

45. Trout J, Christiansen T, Bulkley MB, et al. Cognitive impairments and self-reported sleep in early-stage Parkinson's disease with versus without probable REM sleep behavior disorder. Brain Sci. 2020;10(9). doi:10.3390/brainsci10010009

46. Shin JY, Pohlig RT, Habermann B. Feasibility of using PROMIS® in individuals with advanced parkinson's disease and their caregivers. Res Gerontol Nurs. 2018;11(3):129-136. doi:10.3928/19404921-20180329-01

47. Weerkamp NJ, Tissingh G, Poels PJE, et al. Nonmotor symptoms in nursing home residents with Parkinson's disease: Prevalence and effect on quality of life. J Am Geriatr Soc. 2013;61(10):1714-1721. doi:10.1111/jgs.12458

48. Wienecke M, Werth E, Poryazova R, et al. Progressive dopamine and hypocretin deficiencies in Parkinson's disease: Is there an impact on sleep and wakefulness? J Sleep Res. 2012;21:710-717. doi:10.1111/j.1365-2869.2012.01027.x

49. Al-Rawashdeh SY, Lennie TA, Chung ML. The association of sleep disturbances with quality of life in heart failure patient-caregiver dyads. West J Nurs Res. 2017;39(4):492-506. doi:10.1177/0193945916672647

50. Strawbridge WJ, Shema SJ, Roberts RE. Impact of spouses' sleep problems on partners. Sleep. 2004;27(3):527-531. doi:10.1093/sleep/27.3.527

51. Shih YC, Han SH, Burr JA. Are Spouses' Sleep Problems a Mechanism Through Which Health is Compromised? Evidence Regarding Insomnia and Heart Disease. Ann Behav Med. 2019;53:345-357. doi:10.1093/abm/kay048

CHAPTER 5: DISSERTATION SUMMARY AND FUTURE DIRECTIONS

Summary

Parkinson's disease (PD) is the second most common neurodegenerative disease. It is most commonly recognized by its motor symptoms which include motor rigidity, bradykinesia, tremors at rest, akinesia, gait and balance problems. However, evolving knowledge of the disease has brought to fore several non-motor symptoms (NMS) such as sleep disorders, psychosis, cognitive decline, mood disorders, orthostatic hypotension, pain etc. Several studies have shown the impact of these NMS as debilitating to the health-related quality of life (HRQoL) of a person with Parkinson's disease (PWP).[1] Among these NMS, sleep is particularly interesting due to its direct influence on HRQoL[2–5] and other PD symptoms such as fatigue,[6] mood disturbances[7] and cognition,[8] which may further compromise HRQoL among PWP. Additionally, PWP's sleep as well as caregiver's sleep negatively impact caregiver HRQoL and burden.[9–14] However, the biggest limitation with these studies is that the sleep-HRQoL relationship has been considered independent among PWP and their caregivers and there are no studies which have evaluated this relationship from a dyadic perspective.

Therefore, this dissertation focused on three aspects: (i) a systematic review synthesizing the literature on the impact of sleep on HRQoL in PWP and their caregivers, (ii) a cross-sectional study evaluating psychometric properties of the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health, a 10-item generic HRQoL instrument among

PWP, and (iii) a cross-sectional study assessing the dyadic relationship between sleep and HRQoL among PWP and their caregivers.

Study 1

The systematic review yielded 37 studies, of which 31 studies assessed PWP's HRQoL and six assessed HRQoL or burden among caregivers of PWP. Most studies included in the review suggested that PWP's sleep is an important predictor of their own HRQoL and their caregiver's HRQoL or burden. However, there was some ambiguity in terms of whether nighttime sleep quality or daytime wakefulness played a bigger role in influencing PWP's HRQoL. Additionally, studies also showed that both PWP's sleep and caregiver's sleep are significant predictors of caregiver HRQoL. In our review of the literature, we observed caregiver burden as one of the outcomes which has been evaluated in some studies. However, all studies viewed the sleep-HRQoL interactions to be independent for PWP and their caregivers. Multivariable methods and structural equation modeling were commonly used to analyze these data. Some studies also suggested the role of depression as a mediator in the relationship between PWP or caregiver's sleep on their own HRQoL. None of the studies evaluated the impact of caregiver's sleep on PWP outcomes.

Study 2

The cross-sectional study validating PROMIS Global Health found that the global physical health (GPH) and global mental health (GMH) summary scores obtained from this instrument showed good reliability in PWP. The instrument showed strong factorial validity and no differential item functioning (DIF) between males and females. However, the scale showed DIF by age (50-65 vs. 66+ years) on an item asking PWP to rate their fatigue. After controlling

for the noninvariance of the fatigue item, no other items showed DIF between the two age groups. PWP who are 66 years or older might have progressed to a more advanced stage of Parkinson's disease (PD) or may be experiencing additional disabilities, which could contribute to this difference in perception regarding levels of fatigue.

In our original protocol, we had proposed to evaluate DIF by race/ethnicity as well. However, the study sample mostly comprised of White/Caucasian individuals (201 of 261) and each of the racial and ethnic groups had less than 20 individuals each. A multiple-groups confirmatory factor analysis entails the simultaneous analysis of measurement models within each group being compared. Since the sample sizes for non-White racial/ethnic groups were very low, this process would not have been possible and therefore, exploring DIF by race/ethnicity was dropped from the analysis plan. However, given that the PROMIS Global Health instrument was developed and validated in a predominantly White sample,[15,16] and the evolving conversations about racial inequities,[17,18] we recognize that this is an important scale property that needs to be evaluated before this instrument can be recommended for regular use across various segments of the population in clinical practice and in research. Further studies are required to evaluate DIF in a more diverse racial and ethnic sample.

Additionally, GPH and GMH were able to discriminate between PWP with mild, moderate and severe non-motor symptoms. While GPH was sensitive to different levels of motor symptom severity, GMH was only able to discriminate mild cases from moderate and severe groups. To our knowledge, this is the first study to evaluate the psychometric properties of the PROMIS Global Health in PWP and the instrument demonstrated good factorial validity, known-groups validity and internal consistency reliability.

Study 3

This cross-sectional study assessed the dyadic relationship between sleep and HRQoL among PWP and their caregivers using the Actor-Partner Interdependence Model (APIM). PROMIS sleep disturbance (SD) and PROMIS sleep-related impairment (SRI) were used to measure nocturnal and diurnal sleep issues, respectively. Results showed significant actor effects, i.e. both SD and SRI in PWP and their caregivers were significant predictors of their respective HRQoL. Additionally, significant partner effects were observed from caregiver to patient, i.e. caregiver's SD and SRI were significant predictors of PWP's HRQoL. These findings show that caregiver's sleep issues had a negative impact on PWP's HRQoL, a relationship which is often ignored in this dynamic. This is the first study to our knowledge to use a dyadic analytic method to evaluate the sleep-HRQoL relationship in PWP-caregiver dyads. The study highlights the interdependent nature of this relationship between PWP and their caregivers and provides empirical evidence to support the important role of caregiver's sleep in affecting PWP's outcomes.

Study implications for clinical practice

These study findings have implications for clinical practice and policy. First, sleep problems are common among PWP and their caregivers. Second, sleep problems in PWP and their caregivers severely compromise their own HRQoL. Third, the study's most important contribution to the PD literature, caregiver's sleep problems negatively affect their PWP's HRQoL. Hence, it logically follows that any interventions addressing sleep issues among caregivers might, in turn, improve their PWP's HRQoL. While there are several resources made available to caregivers regarding the burdens of providing care at present, there are few

mechanisms in place to actively identify and address their health issues. One of the ways this can be addressed is by screening caregivers for sleep problems during the PWP's visit to a clinician. Another potential solution could involve healthcare professionals and researchers developing innovative models of care where the PWP-caregiver dyad is the focus of the treatment plan rather than the PWP alone. Addressing sleep problems in caregivers not only improves HRQoL in PWP, but also reduces the burden on them and the healthcare system and could potentially translate into lower healthcare resource utilization and cost of PD care.

Future directions

Our systematic review showed that sleep problems are common among PWP and their caregivers and that both PWP and caregiver's sleep negatively influence caregiver's HRQoL. A future systematic review could investigate the impact of PWP and caregiver's sleep on caregiver burden. Additionally, researchers could consider investigating the various non-pharmacological and pharmacological interventions that are currently being used to address sleep issues in this patient population and how these interventions might impact PWP outcomes. Additionally, studies could also aim to identify various treatment modalities and services (such as hired caregivers or respite services) available to caregivers, uptake of these services in PD and evaluate their impact on caregiver burden and HRQoL.

The current study evaluated internal consistency reliability, factorial validity, differential item functioning and known-groups validity of the PROMIS Global Health questionnaire in a sample of PWP. Future studies could consider evaluating other forms of validity for the scale such as convergent and discriminant validity with other measures commonly used in PD. Additionally, its performance can also be evaluated in a direct comparison to legacy HRQoL

instruments in this patient population. The scale's responsiveness to change in HRQoL over time can also be evaluated. A scale that is responsive to change would be useful in evaluating the effectiveness of any innovative patient-caregiver dyad-focused interventions in improving HRQoL. In our sample, 67% of PWP reported worsened HRQoL post-COVID-19, while 32% reported that their HRQoL remained the same. As a future study, it would be interesting to compare the GPH and GMH summary scores as well as the factor structures between these two groups.

Further, this study also provided evidence to support our hypothesis that there is a dyadic relationship between sleep and HRQoL in PWP and their caregivers. Our systematic review suggested that depression mediates the relationship between sleep and HRQoL in PWP as well as older adults. Studies could assess if depression also mediates the path from sleep to HRQoL assuming dependency between PWP and their caregivers. In addition, a test of the dyadic effect of depression and anxiety on HRQoL might also be worth investigating. Moreover, there is evolving literature that suggests that sleep plays an important role in other neurological conditions such as Alzheimer's disease and hence, future studies might consider replicating the API model suggested in our study in these conditions.

List of References

1. Soh SE, Morris ME, McGinley JL. Determinants of health-related quality of life in Parkinson's disease: A systematic review. Park Relat Disord. 2011;17(1):1-9. doi:10.1016/j.parkreldis.2010.08.012

2. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev. 2017;35:33-50. doi:10.1016/j.smrv.2016.08.001

3. Avidan A, Hays RD, Diaz N, et al. Associations of sleep disturbance symptoms with health-related quality of life in parkinson's disease. J Neuropsychiatry Clin Neurosci. 2013;25(4):319-326. doi:10.1176/appi.neuropsych.12070175

4. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord. 2010;25(15):2493-2500. doi:10.1002/mds.23394

5. Gómez-Esteban JC, Tijero B, Somme J, et al. Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J Neurol. 2011;258(3):494-499. doi:10.1007/s00415-010-5786-y

6. Siciliano M, Trojano L, Santangelo G, De Micco R, Tedeschi G, Tessitore A. Fatigue in Parkinson's disease: A systematic review and meta-analysis. Mov Disord. 2018;33(11):1712-1723. doi:10.1002/mds.27461

7. Pal PK, Thennarasu K, Fleming J, Schulzer M, Brown T, Calne SM. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. Park Relat Disord. 2004;10(3):157-168. doi:10.1016/j.parkreldis.2003.11.002

8. Pushpanathan ME, Loftus AM, Thomas MG, Gasson N, Bucks RS. The relationship between sleep and cognition in Parkinson's disease: A meta-analysis. Sleep Med Rev. 2014;26:21-32. doi:10.1016/j.smrv.2015.04.003

9. Smith M, Ellgring H, Oertel W. Sleep disturbances in Parkinson's disease patients and spouses. J Am Geriatr Soc. 1997;45:194-199.

10. Arber S, Venn S. Caregiving at night: Understanding the impact on carers. J Aging Stud. 2011;25(2):155-165. doi:10.1016/j.jaging.2010.08.020

11. Happe S, Berger K. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing. 2002;31(5):349-354. doi:10.1093/ageing/31.5.349

12. Cupidi C, Realmuto S, Lo Coco G, et al. Sleep quality in caregivers of patients with Alzheimers disease and Parkinsons disease and its relationship to quality of life. Int Psychogeriatrics. 2012;24(11):1827-1835. doi:10.1017/S1041610212001032

13. Carod-Artal FJ, Mesquita HM, Ziomkowski S, Martinez-Martin P. Burden and health-related quality of life among caregivers of Brazilian Parkinson's disease patients. Park Relat Disord. 2013;19(11):943-948. doi:10.1016/j.parkreldis.2013.06.005

14. Viwattanakulvanid P, Kaewwilai L, Jitkritsadakul O, et al. The impact of the nocturnal disabilities of Parkinson's disease on caregivers' burden: Implications for interventions. J Neural Transm. 2014;121(SUPPL. 1). doi:10.1007/s00702-014-1200-8

15. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res. 2009;18(7):873-880. doi:10.1007/s11136-009-9496-9

16. Cella D, Riley W, Stone A, et al. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63(11):1179-1194. doi:10.1016/j.jclinepi.2010.04.011

17. Borrell LN, Elhawary JR, Fuentes-Afflick E, et al. Race and Genetic Ancestry in Medicine — A Time for Reckoning with Racism. NEJM. 2021;385(4):474-480. doi:10.1056/NEJMms2029562

18. Amutah C, Greenidge K, Mante A, et al. Misrepresenting Race — The Role of Medical Schools in Propagating Physician Bias. NEJM. 2021;384(9):872-878. doi:10.1056/NEJMms2025768

APPENDIX

Appendix 1: Methodological characteristics of included studies that reported burden among caregivers of persons with Parkinson's disease

Author, Publication Year, Country	Study design			Participant characteristics			
	Design	Recruitment method	Source of participants	Sample size	Age in years (Mean ± SD)	Female (%)	Relationship to care recipient
Carod-Artal et al.[32] 2013 Brazil	CS	Consecutive	Outpatient Neurology clinic	50	55.7 ± 13.1	88	Spouse (78%), Daughter/Son (14%), Other family members/friends (8%)
Happe et al.[28] 2002 Germany	CS	NR	Outpatient clinics	101	62.3 ± 10.0	63	NR
Viwattanakulvanid et al.[29] 2014 Thailand	CS	Consecutive	Movement Disorders Clinic	85	50.8 ± 12.7 Range: 24-76	78.8	Wife (38.8%), Husband (10.6%), Sons/Daughters (37.6%), Cousins (5.9%), Friends (1.2%), Hiring caregivers (2.4%), Others (3.5%)

CS = Cross-sectional, SD = Standard deviation, NR = Not reported, PS = prospective

Appendix 2: Sleep, health-related quality of life among caregivers of persons with Parkinson's disease

Author, Publication Year, Country	Sleep measurement tool & score Mean ± SD		HRQoL and caregiver burden measurement tool and score Mean ± SD		HRQoL and caregiver burden results	Study limitations
	Patients	Caregivers	Patients	Caregivers		
Carod-Artal et al.[32] 2013 Brazil	SCOPA-sleep: 10.1 ± 6.1 Range: 0-14	NR	EQ-5D index: 0.5 ± 0.3 Range: -0.24 to 1 EQ-5D VAS: 63.6 ± 19.8 Range: 0-100	ZCBI: 20.2 ± 12.8 Range: 1-61	Patient sleep was associated with increased caregiver burden but was not significantly associated with caregiver's HRQoL.	– Small sample size (N = 50) – Increased type I error due to number of analyses performed
Happe et al.[28] 2002 Germany	Questions about sleep-related problems 34% of the patients	Questions about sleep-related problems 27% of the caregivers	NR	CBI: scores were not reported	Caregiver burden was a significant predictor of bad sleep.	– Only baseline assessments were available whereas the original study was longitudinal

	reported bad night-time sleep	reported bad night-time sleep				
Viwattanakulvanid et al.[29] 2014 Thailand	MPDSS: 146.9 ± 24.6 Range: 91-184	NR	PDQ-8: 22.7 ± 15.7 Range: 0-68.75	ZCBI: 15.9 ± 12.6 Range: 1-50	Patient's sleep (MPDSS) was a significant predictor of caregiver burden.	– Recall bias and stressful situation may result in less accurate answers

SD = standard deviation, HRQoL = Health-related quality of life, PDSS = Parkinson's disease sleep scale, ESS = Epworth Sleepiness Scale, MOS-SS = Medical Outcomes Study – Sleep Scale, PDQ = Parkinson's Disease Questionnaire, SF-36 = Short Form-36, PHS = Physical health scale, MHS = Mental health scale, CBI = Caregiver Burden Inventory, SCOPA = Scales for Outcomes in Parkinson's disease, NR = not reported, EQ-5D = EuroQol-5 Dimension, ZCBI = Zarit Caregiver Burden Inventory, PSQI = Pittsburgh Sleep Quality Index, MQoL = McGill Quality of Life Questionnaire, WHOQOL-BREF = World Health Organization Quality of Life Assessment-Bref, SDI = Sleep Disturbances Inventory, MPDSS = Modified Parkinson's Disease Sleep Scale

Appendix 3: Quality appraisal of included caregiver studies

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Carod-Artal et al.[32]	2013	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Happe et al.[28]	2002	Y	Y	Y	Y	Y	Y	Y	Y	Include	
Viwattanakulvanid et al.[29]	2014	Y	Y	Y	Y	Y	Y	Y	Y	Include	

Y = Yes

* Q1-Q10 correspond to items in the quality appraisal form presented in Table 2.2.

Appendix 4: Survey instrument for persons with Parkinson's disease

GENERAL INSTRUCTIONS: For each of the following questions please check the most appropriate response.

Are you a person living with Pakinson's disease?

- ○ Yes (1)
- ○ No (2)

Are you at least 50 years old?

- ○ Yes (1)
- ○ No (2)

Have you participated in a survey regarding sleep and quality of life with the University of Mississippi in the past one year?

- ○ Yes (1)
- ○ No (2)

End of Block: Screener

Start of Block: General instructions

INSTRUCTIONS
This survey has five sections, which contain questions about your health, sleep and quality of life as well as the impact of COVID-19 pandemic. Please note that there are no right or wrong answers to any of the following questions.

End of Block: General instructions

Start of Block: Section I: Health-related quality of life

PROMIS® Scale v1.2 – Global Health
2010-2018 PROMIS Health Organization (PHO)

INSTRUCTIONS
This survey asks about your health and quality of life. There are no right or wrong answers. For each item, please select the response that best describes your answer.

Please respond to each question or statement by marking one box per row.

	Excellent (1)	Very good (2)	Good (3)	Fair (4)	Poor (5)
In general, would you say your health is: (1)	○	○	○	○	○
In general, would you say your quality of life is: (2)	○	○	○	○	○
In general, how would you rate your physical health? (3)	○	○	○	○	○
In general, how would you rate your mental health, including your mood and your ability to think? (4)	○	○	○	○	○
In general, how would you rate your satisfaction with social activities and relationships? (5)	○	○	○	○	○
In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.) (6)	○	○	○	○	○

	Completely (1)	Mostly (2)	Moderately (3)	A little (4)	Not at all (5)
To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair? (1)	○	○	○	○	○

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
In the past 7 days, how often have you been bothered by emotional problems such as feeling anxious, depressed or irritable? (1)	○	○	○	○	○

	None (1)	Mild (2)	Moderate (3)	Severe (4)	Very severe (5)
In the past 7 days, how would you rate your fatigue on average? (1)	○	○	○	○	○

In the past 7 days, how would you rate your pain on average?

- ○ 0 (0)
- ○ 1 (1)
- ○ 2 (2)
- ○ 3 (3)
- ○ 4 (4)
- ○ 5 (5)
- ○ 6 (6)
- ○ 7 (7)
- ○ 8 (8)
- ○ 9 (9)
- ○ 10 (10)

End of Block: Section I: Health-related quality of life

Start of Block: Section II: Sleep disturbances

PROMIS® Item Bank v1.0 – Sleep Disturbance – Short Form 8a
2008-2020 PROMIS Health Organization (PHO)

INSTRUCTIONS
This survey asks about your nighttime sleep-related disturbances. There are no right or wrong answers. For each item, please select the response that best describes your answer. Please respond to each question or statement by marking one box per row.

	Very poor (1)	Poor (2)	Fair (3)	Good (4)	Very good (5)
In the past 7 days, my sleep quality was ..... (1)	○	○	○	○	○

In the past 7 days...

	Not at all (1)	A little bit (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
My sleep was refreshing (1)	○	○	○	○	○
I had a problem with my sleep (2)	○	○	○	○	○
I had difficulty falling asleep (3)	○	○	○	○	○
My sleep was restless (4)	○	○	○	○	○
I tried hard to get to sleep (5)	○	○	○	○	○
I worried about not being able to fall asleep (6)	○	○	○	○	○
I was satisfied with my sleep (7)	○	○	○	○	○

End of Block: Section II: Sleep disturbances

Start of Block: Section III: Sleep-related impairment

PROMIS Item Bank v. 1.0 – Sleep-Related Impairment – Short Form 8a
2008-2016 PROMIS Health Organization and PROMIS Cooperative Group

INSTRUCTIONS
This survey asks about your sleep-related functioning during waking hours. There are no right or wrong answers. For each item, please select the response that best describes your answer. Please respond to each question or statement by marking one box per row.

In the past 7 days...

	Not at all (1)	A little bit (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
I had a hard time getting things done because I was sleepy (1)	○	○	○	○	○
I felt alert when I woke up (2)	○	○	○	○	○
I felt tired (3)	○	○	○	○	○
I had problems during the day because of poor sleep (4)	○	○	○	○	○
I had a hard time concentrating because of poor sleep (5)	○	○	○	○	○
I felt irritable because of poor sleep (6)	○	○	○	○	○
I was sleepy during the daytime (7)	○	○	○	○	○
I had trouble staying awake during the day (8)	○	○	○	○	○

End of Block: Section III: Sleep-related impairment

Start of Block: Section IV: Information about you and your health

Q18
INSTRUCTIONS

Please answer the following questions on general information about you and your health. Please select the option that best describes your answer.

What is your sex?

- ○ Female (1)
- ○ Male (2)
- ○ Other/prefer not to answer (3)

What is your age (in years)?

- ○ 50-65 (1)
- ○ 66-75 (2)
- ○ 76-85 (3)
- ○ 86 or older (4)

Which of the following best describes your race or ethnicity? Check **ALL** that apply.

- ☐ American Indian/Alaskan Native (1)
- ☐ Asian (2)
- ☐ Black/African American (3)
- ☐ Hispanic or Latino (4)
- ☐ Native Hawaiian/Other Pacific Islander (5)
- ☐ White/Caucasian (6)
- ☐ Other (please specify) (7) _____

What is the highest level of education you have completed?

- ○ No degree (1)
- ○ GED or High school diploma (2)
- ○ Associate's degree (3)
- ○ Bachelor's degree (4)
- ○ Master's degree (5)
- ○ Terminal degree (e.g., JD, MD, PhD) (6)

What is your current primary employment status?

- ○ Employed for wages (1)
- ○ Self-employed (2)
- ○ Out of work for 1 year or more (3)
- ○ Out of work for less than 1 year due to COVID-19, also known as Coronavirus or SARS-CoV-2 (4)
- ○ Out of work for less than 1 year due to other reason(s) (5)
- ○ A homemaker (6)
- ○ A student (7)
- ○ Retired (8)
- ○ Unable to work (9)

What type of health insurance do you currently have?

- ○ Public insurance (e.g., Medicare, Medicaid, VA) (1)
- ○ Private insurance (2)
- ○ Other (please specify) (3) _____

Please choose the response below that best describes the severity of your motor symptoms over the past week.

- ○ Normal (1)
- ○ Borderline (2)
- ○ Mild (3)
- ○ Moderate (4)
- ○ Severe (5)
- ○ Extreme (6)

Please choose the response below that best describes the severity of your non-motor symptoms over the past week.

- ○ Normal (1)
- ○ Borderline (2)
- ○ Mild (3)
- ○ Moderate (4)
- ○ Severe (5)
- ○ Extreme (6)

The following list includes drugs that can help you with your Parkinson's symptoms or sleep or both. Please indicate which of the following you are currently taking. Check **ALL** that apply.

- ☐ Sinemet CR (carbidopa and levodopa) Sustained-Release Tablets (1)
- ☐ Rytary (carbidopa and levodopa) Extended-Release Capsules (10)
- ☐ Neupro (Rotigotine Transdermal System) (7)
- ☐ Requip (ropinirole) (23)
- ☐ Mirapex (pramipexole) (24)
- ☐ Silenor (doxepin) (14)
- ☐ Ambien (zolpidem) (11)
- ☐ Sonata (zaleplon) (12)
- ☐ Provigil (modafinil) (16)
- ☐ Nuvigil (armodafinil) (17)
- ☐ Ritalin (methylphenidate) (22)
- ☐ Lunesta (eszopiclone) (2)
- ☐ Klonopin (clonazepam) (18)
- ☐ Deep brain stimulation (5)
- ☐ Nuplazid (pimavanserin) (19)
- ☐ Duopa (Carbidopa and Levodopa) Enteral Suspension (3)

- [ ] Desyrel (trazodone) (15)
- [ ] Seroquel (quetiapine) (21)
- [ ] Clozaril (clozapine) (20)
- [ ] Melatonin supplements (13)
- [ ] Other (please specify) (6) _____

Have you ever had or currently have any of the following health conditions? (Check **ALL** that apply)

- [ ] None (1)
- [ ] Alzheimer's disease and other dementias (2)
- [ ] Arthritis (rheumatoid arthritis, osteoarthritis, gout etc.) (3)
- [ ] Asthma (4)
- [ ] Bone marrow or other organ transplant (5)
- [ ] Cancer (6)
- [ ] Chronic kidney disease (7)
- [ ] Chronic lung disease (COPD, emphysema, chronic bronchitis) (8)
- [ ] Diabetes (9)

- [ ] Heart disease (high blood pressure, heart failure etc.) and stroke (10)
- [ ] HIV/AIDS (11)
- [ ] Liver disease (12)
- [ ] Mood disorders (depression, anxiety etc.) (13)
- [ ] Obesity (14)
- [ ] Other chronic conditions (please specify) (15) _____

End of Block: Section IV: Information about you and your health

---

Start of Block: Section V: Impact of COVID-19

INSTRUCTIONS
Please answer the following questions to help us understand the impact of COVID-19 pandemic, also known as Coronavirus or SARS-CoV-2, on your sleep and quality of life.

Have you heard about the infectious disease called COVID-19, also known as Coronavirus or SARS-Cov-2?

- ○ Yes (1)
- ○ No (2)

How would you rate your anxiety about the COVID-19 pandemic?

- ○ 1 (Low anxiety) (1)
- ○ 2 (2)
- ○ 3 (3)
- ○ 4 (4)
- ○ 5 (5)
- ○ 6 (6)
- ○ 7 (7)
- ○ 8 (8)
- ○ 9 (9)
- ○ 10 (High anxiety) (10)

Please answer the following questions about the impact of the COVID-19 pandemic on your sleep and quality of life.

	Strongly disagree (1)	Somewhat disagree (2)	Neither agree nor disagree (3)	Somewhat agree (4)	Strongly agree (5)
The COVID-19 pandemic has had a significant impact on the quality of my sleep (1)	○	○	○	○	○
The COVID-19 pandemic has had a significant impact on my quality of life (2)	○	○	○	○	○

Please complete the following sentence: As a result of the COVID-19 pandemic, the quality of my sleep has .....

- ○ Worsened (1)
- ○ Remained the same (2)
- ○ Improved (3)

Please complete the following sentence: As a result of the COVID-19 pandemic, my quality of life has .....

- ○ Worsened (1)
- ○ Remained the same (2)
- ○ Improved (3)

End of Block: Section V: Impact of COVID-19

Appendix 5: Survey instrument for caregivers of persons with Parkinson's disease

Start of Block: Screener

GENERAL INSTRUCTIONS: For each of the following questions please check the most appropriate response.

Are you the primary informal caregiver of a family member or friend who has Parkinson's disease? An informal caregiver is someone who provides care to a care recipient with whom he/she has a personal relationship with (such as a family member, a friend etc.).

- ○ Yes (1)
- ○ No (2)

Is your primary care recipient with Parkinson's disease at least 50 years old?

- ○ Yes (1)
- ○ No (2)

Do you live in the same household as your primary care recipient with Parkinson's disease?

- ○ Yes (1)
- ○ No (2)

Have you or your primary care recipient with Parkinson's disease participated in a survey regarding sleep and quality of life with the University of Mississippi in the past one year?

- ○ Yes (1)
- ○ No (2)

End of Block: Screener

Start of Block: General instructions

INSTRUCTIONS

This survey has five sections, which contain questions about your sleep and quality of life as well as your caregiving activities. Please note that there are no right or wrong answers to any of the following questions.

End of Block: General instructions

Start of Block: Section I: Health-related quality of life

PROMIS® Scale v1.2 – Global Health
2010-2018 PROMIS Health Organization (PHO)

INSTRUCTIONS This survey asks about your health and quality of life. There are no right or wrong answers. For each item, please select the response that best describes your answer.

Please respond to each question or statement by marking one box per row.

	Excellent (1)	Very good (2)	Good (3)	Fair (4)	Poor (5)
In general, would you say your health is: (1)	○	○	○	○	○
In general, would you say your quality of life is: (2)	○	○	○	○	○
In general, how would you rate your physical health? (3)	○	○	○	○	○
In general, how would you rate your mental health, including your mood and your ability to think? (4)	○	○	○	○	○
In general, how would you rate your satisfaction with social activities and relationships? (5)	○	○	○	○	○
In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.) (6)	○	○	○	○	○

	Completely (1)	Mostly (2)	Moderately (3)	A little (4)	Not at all (5)
To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair? (1)	○	○	○	○	○

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
In the past 7 days, how often have you been bothered by emotional problems such as feeling anxious, depressed or irritable? (1)	○	○	○	○	○

	None (1)	Mild (2)	Moderate (3)	Severe (4)	Very severe (5)
In the past 7 days, how would you rate your fatigue on average? (1)	○	○	○	○	○

In the past 7 days, how would you rate your pain on average?

- ○ 0 (0)
- ○ 1 (1)
- ○ 2 (2)
- ○ 3 (3)
- ○ 4 (4)
- ○ 5 (5)
- ○ 6 (6)
- ○ 7 (7)
- ○ 8 (8)
- ○ 9 (9)
- ○ 10 (10)

End of Block: Section I: Health-related quality of life

Start of Block: Section II: Sleep disturbances

PROMIS® Item Bank v1.0 – Sleep Disturbance – Short Form 8a
2008-2020 PROMIS Health Organization (PHO)

INSTRUCTIONS
This survey asks about your nighttime sleep-related disturbances. There are no right or wrong answers. For each item, please select the response that best describes your answer. Please respond to each question or statement by marking one box per row.

	Very poor (1)	Poor (2)	Fair (3)	Good (4)	Very good (5)
In the past 7 days, my sleep quality was ..... (1)	○	○	○	○	○

In the past 7 days...

	Not at all (1)	A little bit (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
My sleep was refreshing (1)	○	○	○	○	○
I had a problem with my sleep (2)	○	○	○	○	○
I had difficulty falling asleep (3)	○	○	○	○	○
My sleep was restless (4)	○	○	○	○	○
I tried hard to get to sleep (5)	○	○	○	○	○
I worried about not being able to fall asleep (6)	○	○	○	○	○
I was satisfied with my sleep (7)	○	○	○	○	○

End of Block: Section II: Sleep disturbances

Start of Block: Section III: Sleep-related impairment

PROMIS Item Bank v. 1.0 – Sleep-Related Impairment – Short Form 8a
2008-2016 PROMIS Health Organization and PROMIS Cooperative Group

INSTRUCTIONS
This survey asks about your sleep-related functioning during waking hours. There are no right or

wrong answers. For each item, please select the response that best describes your answer. Please respond to each question or statement by marking one box per row.

In the past 7 days...

	Not at all (1)	A little bit (2)	Somewhat (3)	Quite a bit (4)	Very much (5)
I had a hard time getting things done because I was sleepy (1)	○	○	○	○	○
I felt alert when I woke up (2)	○	○	○	○	○
I felt tired (3)	○	○	○	○	○
I had problems during the day because of poor sleep (4)	○	○	○	○	○
I had a hard time concentrating because of poor sleep (5)	○	○	○	○	○
I felt irritable because of poor sleep (6)	○	○	○	○	○
I was sleepy during the daytime (7)	○	○	○	○	○
I had trouble staying awake during the day (8)	○	○	○	○	○

End of Block: Section III: Sleep-related impairment

Start of Block: Section IV: Information about you, your health and caregiving responsibilities

INSTRUCTIONS
Please answer the following questions to help us better understand your role as a caregiver. Please select the option that best describes your answer.

What is your sex?

- ○ Female (1)
- ○ Male (2)
- ○ Other/prefer not to answer (3)

What is your current age (in years)?

_____

Which of the following best describes your race or ethnicity?

- ☐ American Indian/Alaskan Native (1)
- ☐ Asian (2)
- ☐ Black/African American (3)
- ☐ Hispanic or Latino (4)
- ☐ Native Hawaiian/Other Pacific Islander (5)
- ☐ White/Caucasian (6)
- ☐ Other (please specify) (7) _____

What is the highest level of education you have completed?

- ○ No degree (1)
- ○ GED or High school diploma (2)
- ○ Associate's degree (3)
- ○ Bachelor's degree (4)
- ○ Master's degree (5)
- ○ Terminal degree (e.g., JD, MD, PhD) (6)

Are you currently ....?

- ○ Employed for wages (1)
- ○ Self-employed (2)
- ○ Out of work for 1 year or more (3)
- ○ Out of work for less than 1 year due to COVID-19, also known as Coronavirus or SARS-CoV-2 (4)
- ○ Out of work for less than 1 year due to other reason(s) (5)
- ○ A homemaker (6)
- ○ A student (7)
- ○ Retired (8)
- ○ Unable to work (9)

What is your annual household income from all sources?

- ○ Less than $15,000 (1)
- ○ $15,000 to less than $25,000 (2)
- ○ $25,000 to less than $35,000 (3)
- ○ $35,000 to less than $50,000 (4)
- ○ $50,000 or more (5)

What type of health insurance do you currently have?

- ○ Public insurance (e.g., Medicare, Medicaid, VA) (1)
- ○ Private insurance (2)
- ○ Other (please specify) (3) _____

For how many children and adults are you the primary informal caregiver (including your primary care recipient with Parkinson's disease)?

_____

Have you ever had or currently have any of the following health conditions? (Check **ALL** that apply)

- ☐ None (1)
- ☐ Alzheimer's disease and other dementias (2)
- ☐ Arthritis (rheumatoid arthritis, osteoarthritis, gout etc.) (3)
- ☐ Asthma (4)
- ☐ Bone marrow or other organ transplant (5)
- ☐ Cancer (6)
- ☐ Chronic kidney disease (7)
- ☐ Chronic lung disease (COPD, emphysema, chronic bronchitis) (8)
- ☐ Diabetes (9)
- ☐ Heart disease (high blood pressure, heart failure etc.) and stroke (10)
- ☐ HIV/AIDS (11)
- ☐ Liver disease (12)
- ☐ Mood disorders (depression, anxiety etc.) (13)
- ☐ Obesity (14)
- ☐ Other chronic conditions (please specify) (15)

_____

Has a doctor, nurse, or other health professional ever told you that you have a sleep disorder?

- ○ Yes (1)
- ○ No (2)
- ○ Uncertain (3)

Are you currently taking any medications or supplements (such as melatonin) to help with your sleep?

- ○ Yes (12)
- ○ No (13)
- ○ Uncertain (15)

INSTRUCTIONS
Please answer the following questions keeping in mind your primary care recipient with Parkinson's disease.

Which of the following best describes your relationship to your primary care recipient with Parkinson's disease?

- ○ Spouse or significant other (1)
- ○ Daughter (2)
- ○ Son (3)
- ○ Other relative (4)
- ○ Other non-relative (5)

What is the age of your primary care recipient with Parkinson's disease (in years)?

- ○ 50-65 (1)
- ○ 66-75 (2)
- ○ 76-85 (3)
- ○ 86 or older (4)

How many hours of caregiving do you provide per week to your primary care recipient with Parkinson's disease?

- ○ 20 hours or fewer (1)
- ○ 21-39 hours (2)
- ○ 40 hours or more (3)

End of Block: Section IV: Information about you, your health and caregiving responsibilities

---

Start of Block: Section V: Impact of COVID-19

INSTRUCTIONS

Please answer the following questions to help us understand the impact of COVID-19, also known as Coronavirus or SARS-CoV-2, on your caregiving responsibilities.

Have you heard about the infectious disease called COVID-19, also known as Coronavirus or SARS-Cov-2?

- ○ Yes (1)
- ○ No (2)

How would you rate your anxiety about the COVID-19 outbreak?

- ○ 1 (Low anxiety) (1)
- ○ 2 (2)
- ○ 3 (3)
- ○ 4 (4)
- ○ 5 (5)
- ○ 6 (6)
- ○ 7 (7)
- ○ 8 (8)
- ○ 9 (9)
- ○ 10 (High anxiety) (10)

Please answer the following questions about the impact of the COVID-19 pandemic on your sleep and quality of life.

	Strongly disagree (1)	Somewhat disagree (2)	Neither agree nor disagree (3)	Somewhat agree (4)	Strongly agree (5)
The COVID-19 pandemic has had a significant impact on the quality of my sleep (1)	○	○	○	○	○
The COVID-19 pandemic has had a significant impact on my quality of life (2)	○	○	○	○	○

Please complete the following sentence: As a result of the COVID-19 outbreak, the quality of sleep has .....

- ○ Worsened (1)
- ○ Remained the same (2)
- ○ Improved (3)

Please complete the following sentence: As a result of the COVID-19 outbreak, my quality of life has .....

- ○ Worsened (1)
- ○ Remained the same (2)
- ○ Improved (3)

End of Block: Section V: Impact of COVID-19

VITA

SUSHMITHA INGUVA, M.S., Ph.D.

PROFESSIONAL SUMMARY

- 4+ years' experience generating real-world evidence for reimbursement and policy decisions for a government payer
- Experience collaborating and communicating projects and findings to cross-functional and external stakeholders
- Experience partnering with key opinion leaders, leading and managing project and vendor teams
- Excellent written and oral communication skills and ability to work independently with minimal supervision
- Software: SAS, R, STATA, Instant Health Data, MPlus, SPSS and TreeAge Pro
- **Areas of specialty:** Observational research, Retrospective analysis of claims data (Medicare, Medicaid, Truven/IBM Marketscan) and complex survey databases, Patient-reported outcomes and psychometrics, Data analysis of prospective observational cohort studies, Statistical programming, Economic modeling, Systematic and targeted literature reviews, Developing and reviewing product value dossiers, Qualitative research methods

EDUCATION

University of Mississippi — University, MS
PhD candidate in Pharmaceutical Sciences — May 2021
Concentration: Pharmacy Administration; Track: Health Outcomes Research
Dissertation: Sleep and health-related quality of life among persons with Parkinson's disease and their caregivers
Advisors: Dr. John Bentley and Dr. Marie Barnard

Philadelphia College of Pharmacy, University of the Sciences — Philadelphia, PA
M.S. in Pharmacy Administration & Pharmacy Policy — May 2016
Advisor: Dr. Brandon Patterson

Birla Institute of Technology and Science (BITS), Pilani — Pilani, India
Bachelors in Pharmaceutical Sciences — May 2013

PROFESSIONAL AND RESEARCH EXPERIENCE

Center for Pharmaceutical Marketing & Management, University of Mississippi University, MS
Research Analyst, Mississippi Medicaid Drug Utilization Review team August 2016 – August 2020
Therapeutic area(s): Diabetes, Vaccines, Infectious diseases, Dermatology, Mental health, Substance use disorders, Oncology

- Conceptualizing studies using claims data to assess burden of illness, treatment patterns, health outcomes, costs and healthcare resource utilization based on areas of interest to Medicaid
- Executing studies and communicating findings to internal and external stakeholders
- Translating evidence generated in to actionable insights and recommending policies to improve access and reimbursement decisions

Center for Population Studies, University of Mississippi University, MS
Research Assistant August 2018 – August 2020
Therapeutic area(s): Maternal and Child health

- Lead analyst on Right! from the Start, a community-focused intervention to improve breastfeeding rates in MS
- Analyzed clinical and PRO data to assess participant
- Compiled and communicated findings to funding agency, and scientific and community-based audiences

AbbVie Inc. North Chicago, IL
Health Economics and Outcomes Research Intern June 2018 – August 2018
Therapeutic area(s): Neuroscience

- Contributed to the planning and execution of HEOR strategy for advanced Parkinson's disease (APD)
- Developed a protocol to assess economic burden among APD patients using Medicare and Truven Marketscan data
- Synthesized evidence supporting clinical efficacy for the product dossier to demonstrate value to payers
- Analyzed PRO measures from a pragmatic trial to generate real-world effectiveness data and communicated results to internal stakeholders
- Co-authored poster abstract, presentation and manuscript to communicate project findings to clinical audiences

Regeneron Pharmaceuticals, Inc. Tarrytown, NY
Health Economics and Outcomes Research Intern June 2017 – August 2017
Therapeutic area(s): Musculoskeletal disorders and Chronic pain

- Developed and executed a protocol to evaluate real-world treatment patterns and unmet need in patients with osteoarthritis-related pain using commercial claims data
- Collaborated with vendor teams for developing and reviewing protocols, study design and results
- Communicated findings to internal stakeholders and contributed to presentation at a national, clinical conference

RESEARCH

Peer-reviewed publications

- **Inguva S**, Sautter JM, Chun GJ, Patterson BJ, McGhan WF. Population characteristics associated with pharmacy-based influenza vaccination in United States survey data. *Journal of the American Pharmacists Association*. 2017;57(6):654-660. https://doi.org/10.1016/j.japh.2017.07.007
- **Inguva S**, Barnard M, Ward LM, Yang Y, Pittman E, Banahan III BF, Kirby TR, Noble SN. Factors influencing Human Papillomavirus (HPV) vaccination series completion in Mississippi Medicaid. *Vaccine*. 2020;38(8):2051-2057. https://doi.org/10.1016/j.vaccine.2019.12.030

Manuscripts in progress

- Rosenthal M, Goswami S, Nair S, **Inguva S**, Hamarneh Y, Tsuyuki R. Applying the Stages of Implementation Completion (SIC) framework retrospectively to a community pharmacy clinical intervention implementation project for scaling up future success. (under review with the *Journal of Pharmacy Practice*)
- Antonini A, Odin P, Pahwa R, Aldred J, Alobaidi A, Jalundhwala YJ, Kukreja P, Bergmann L, **Inguva S**, Bao Y, Chaudhuri KR. The long-term impact of levodopa/carbidopa intestinal gel on 'off'-time in patients with advanced Parkinson's disease: a systematic review. (under review with the *Advances in Therapy* journal*)*
- **Inguva S**, Bhattacharya K, Priyadarshini M, Shah R. Financial toxicity of cancer care among survivors and its effect on patient-reported outcomes and caregiver burden. (submitted to the *Cancer* journal)

Oral presentations

- Woo L, Parks V, **Inguva S**, Bush S. Right! from the Start NICU breastfeeding and care coordination initiative. Plenary session at Delta Directions Forum hosted by the Delta Directions Consortium, Clarksdale, MS: July 18-19, 2019.
- **Inguva S**, Yang Y, Barnard M, Pittman E. Risk of pneumonia due to incident antipsychotic drug use among older adults with Parkinson's disease. Podium at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting. New Orleans, LA: May 19-23, 2019.
- **Inguva S**, Green J, Allen III D, Snell S, Famuyide M. Right! from the Start – Serving the needs of mothers and low birthweight babies in the Mississippi Delta. Maternal and child health session at Alabama-Mississippi Sociological Association (A-MSA) 50th Anniversary Conference, Starkville, MS: February 21-22, 2019.

Posters

- Thompson W, Green J, Deleveaux J, Kerstetter K, Haggard R, Myers J, **Inguva S**. Can Medicaid policies disrupt the association between socioeconomic context and poor birth outcomes? Assessing state policy variation and birth outcomes. American Public Health Association 2020 Virtual Annual Meeting and Expo. October 24-28, 2020.
- Antonini A, Odin P, Pahwa R, Aldred J, Alobaidi A, Jalundhwala YJ, Kukreja P, Bergmann L, **Inguva S**, Bao Y, Chaudhuri KR. Long-term impact of Levodopa Carbidopa Intestinal Gel (LCIG) on reducing "Off" time: Results from a systematic review of studies with ≥ 12 months of follow-up. International Congress of Parkinson's Disease and Movement Disorders. Nice, France: September 22-26, 2019.
- **Inguva S**, Gangan N, Pittman E, Banahan BF III, Noble S. Prescription Opioid use before and after an Overdose event in Mississippi Medicaid. ***Semi-finalist for Research Poster Presentation Award.*** International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting. Baltimore, MD: May 19-23, 2018.

- **Inguva S**, Allen DD, Ramachandran S, Pittman E, Banahan BF III, Noble S. Opioid Overdose risk factors: A matched case control study in Mississippi Medicaid. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting. Baltimore, MD: May 19-23, 2018.
- Korgaonkar S, **Inguva S**, Yang Y. Cost-effectiveness of mepolizumab versus omalizumab as an adjunct therapy in patients with uncontrolled allergic asthma. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting. Baltimore, MD: May 19-23, 2018.
- Huang A, Wei W, Gandhi K, Wang L, **Inguva S**, Katz NP. Opioid use intensity and its association with opioid overdose risk and abuse and hospitalization among patients with hip/knee Osteoarthritis: A retrospective analysis of real-world data. American Academy of Pain Medicine 34th Annual Meeting. Vancouver, Canada: April 25-29, 2018.
- **Inguva S**, Ramachandran S, Banahan BF III. Impact of using Affiliate IDs On PQA's Opioid Multiple Provider Measure Among Medicaid Beneficiaries. ***Top 10% ribbon winner.*** International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual International Meeting. Boston, MA: May 20-24, 2017.
- Ramachandran S, **Inguva S**, Banahan BF III, Kirby TR, Noble SL. Evaluating the effect of Prescription Monitoring Program Cash Prescriptions on the PQA Measure: Use of Opioids from Multiple Providers in Persons Without Cancer. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual International Meeting. Boston, MA: May 20-24, 2017.
- Ramachandran S, **Inguva S**, Banahan BF III, Kirby TR, Noble S. Impact of Cash Prescriptions and Use of Affiliate Provider Identifiers (IDs) on measures of Opioid use from Multiple Providers. ***Silver Ribbon Winner.*** Academy of Managed Care Pharmacy (AMCP) Annual Meeting. Denver, CO: March 27-30, 2017.

GRANTS/FELLOWSHIPS

- MME Endowed Fellowship, Medical Marketing Economics (MME) LLC., 2020
    - Competitive fellowship awarded by the Fellowship Selection Committee based on academic performance, research, and service
    - Amount awarded: $6,000

- Graduate Student Research Grant Recipient, Department of Pharmacy Administration, University of Mississippi, 2020
    - Competitive funding awarded by the GSRG Subcommittee based on quality of proposed research
    - Amount awarded: $2,500

- Graduate Student Council Research Grant Recipient, Office of Research and Sponsored Programs and the Graduate School, University of Mississippi, 2020
    - Competitive funding awarded by the review committee based on novelty or originality, marketability and competitiveness of proposed research for extramural funding
    - Amount awarded: $1,000

- Augustus T. Pollard Fellowship, Office of Graduate Education, University of the Sciences in Philadelphia, 2015-2016
    - Competitive fellowship awarded by OGE to a student performing research in areas related to pharmacy
    - Amount awarded: $2,000

TEACHING

University of Mississippi University, MS

- Social and Administrative Pharmacy I (PHCY 431) – Guest Lecturer 2019 - 2020
- Pharmacy Ethics (PHAD 395) – Graduate Teaching Assistant Fall 2017
- Professional Communications in Pharmacy (PHAD 390) – Graduate Teaching Assistant Fall 2016

HONORS AND AWARDS

- Sigma Xi, The Scientific Research Honor Society Initiate, 2020
- Travel Grant Recipient, ISPOR Annual International Meeting, New Orleans, LA: May 19-23, 2019
- Healthcare Quality Innovation Challenge Third place, Pharmacy Quality Alliance Annual Meeting, Baltimore, MD: May 16-18, 2018
- Rho Chi Honor Society Initiate, 2018
- The Honor Society of Phi Kappa Phi Initiate, 2018
- Gelb Scholar, Office of Graduate Education, University of the Sciences in Philadelphia, 2014-2015

SERVICE AND LEADERSHIP

Refereeing – Adhoc reviewer

- *Preventing Chronic Disease*
- *Journal of Adolescent Health*
- *Journal of American Pharmacists Association*
- *Vaccine*
- *Journal of Managed Care Pharmacy*
- *Quality of Life Research*
- *Research in Social and Administrative Pharmacy*
- *Exploratory Research in Clinical and Social Pharmacy*

Department/University service

- Member, Strategic Planning Committee, Department of Pharmacy Administration, University of Mississippi, 2020
- Member, Center for Pharmaceutical Marketing and Management Director Search Committee, 2018
- Member, Graduate Education Committee, Philadelphia College of Pharmacy, 2016
- Graduate Representative, Strategic Planning Council, University of the Sciences in Philadelphia, 2014-2016
- Coordinator, Ragamalika (classical dance and music club), BITS-Pilani (India), 2011-2012

Professional Association Membership/Leadership roles

- Abstract reviewer, ISPOR Europe 2020
- President, University of Mississippi ISPOR Student Chapter, 2018-2019
- Member, ISPOR Student Network Survey Committee, 2018-2019
- Member, American Association of Colleges of Pharmacy, 2020
- Member, Alabama-Mississippi Sociological Association, 2018-Present
- Member, International Society for Pharmacoeconomics and Outcomes Research, 2015-Present