Curriculum Vitae

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Education

2009	BA, Biology, Boston University, Boston, MA, *Summa cum laude, Phi Beta Kappa*
2011	MPH, Epidemiology, University of Minnesota-Twin Cities, Minneapolis, MN, *Delta Omega*
2012	Non-Degree Seeking Student, Epidemiology, State University of New York at Albany, Albany, NY
2018	PhD, Epidemiology, University of Maryland School of Medicine, Baltimore, MD

Thesis Work

Master's Thesis Title: "Elucidating Possible Causes of Significant Increases in Hepatitis C Infection Rates Post Kidney Transplant in the United States"
Thesis Advisor: Jon Snyder, PhD, MS

Employment History

Academic Appointments

05/09-08/09	Research Assistant, Department of Health Sciences, Boston University, Boston, MA
09/13-Present	Graduate Research Assistant, Department of Epidemiology & Public Health, University of Maryland School of Medicine, Baltimore, MD
03/15-02/18	Pre-Doctoral Trainee, Department of Epidemiology & Public Health, University of Maryland School of Medicine, Baltimore, MD

Other Employment

05/07-08/07	Summer Program for Undergraduate Research Intern, Department of Renal Physiology, Medical College of Wisconsin, Milwaukee, WI
05/08-08/08	Summer Program for Undergraduate Research Intern, Rat Genome Database, Medical College of Wisconsin, Milwaukee, WI

07/09-08/09	Epidemiology Intern, Cambridge Public Health Department, Cambridge Health Alliance, Cambridge, MA
08/09-06/11	Student Worker Paraprofessional, Vector-borne Disease Subunit, Infectious Disease Epidemiology Prevention and Control, Minnesota Department of Health, St. Paul, MN
05/10-07/10	Field Experience Intern, Unexplained Critical Illnesses and Deaths of Possible Infectious Etiology & Medical Examiner Surveillance Programs, Infectious Disease Epidemiology Prevention and Control, Minnesota Department of Health, St. Paul, MN
07/11-07/13	Centers for Disease Control & Prevention/Council of State and Territorial Epidemiologists Applied Epidemiology Fellow, Emerging Infectious Program, New York State Department of Health, Albany, NY
07/13-08/13	Hourly Research Assistant, Emerging Infectious Program, Bureau of Communicable Disease Control, New York State Department of Health, Albany, NY

Professional Society Memberships

2011-2013	Council of State and Territorial Epidemiologists
2014-Present	Gerontological Society of America
2015-Present	Society for Epidemiologic Research
2017-Present	PROMIS® Health Organization

Honors and Awards

2005	Frank Parker Junior Girl Awardee, Wisconsin Tennis Association
2005-2009	Full Athletic Scholarship Awardee, Boston University Varsity Women's Tennis Team
2005-2009	Academic All-American, Intercollegiate Tennis Association
2006	Distinguished Sophomore, Boston University College of Arts & Sciences
2006, 2009	First Team All-Conference (Tennis), America East Conference
2008, 2009	All-Academic Selection (Tennis), America East Conference
2009	Inductee, Phi Beta Kappa Academic Honor Society
2009	National Collegiate Athletic Association (NCAA) Postgraduate Scholarship Awardee
2011	Inductee, Delta Omega National Honor Society in Public Health
2014	Commissioner's Recognition Award, New York State Department of Health
2014	Health Sciences Travel Award, the Gerontological Society of America
2015	Trudy Bush Award, Department of Epidemiology & Public Health, University of Maryland School of Medicine
2015	PhD Scholar Award Nominee, Program in Epidemiology & Human Genetics, University of Maryland, Baltimore Graduate Program in Life Sciences

2016	Renée Royak-Schaler Award, Department of Epidemiology & Public Health, University of Maryland School of Medicine
2016	Otani Award Nominee, Program in Epidemiology & Human Genetics, University of Maryland, Baltimore Graduate Program in Life Sciences
2017	Dorothy and Morris Magaziner Scholarship Endowment Award, Department of Epidemiology & Public Health, University of Maryland School of Medicine

Administrative Service

Institutional Service

2005-2008	Student-Athlete Advisory Council Representative, Boston University
2007-2008	Freshman Resource Advisor, Boston University College of Arts & Sciences
2007-2009	Member, Boston University Undergraduate Public Health Association
2007-2009	Co-Captain, Boston University Varsity Women's Tennis Team
2009-2011	Member, University of Minnesota-Twin Cities Tennis Club
2010-2011	Executive Board Member (Gopher Invitational Coordinator), University of Minnesota-Twin Cities Tennis Club
2009-2011	Epidemiology Representative, University of Minnesota School of Public Health Student Senate
2010-2011	Planning Committee Member, University of Minnesota National Public Health Week Film Festival
2010-2011	School of Public Health Representative, University of Minnesota Graduate and Professional Student Assembly
2013-2017	Volunteer, University of Maryland, Baltimore Graduate Program in Life Sciences Student Recruitment
2014-2015	Student Co-Coordinator, Epidemiology of Aging Training Grant, University of Maryland School of Medicine Department of Epidemiology & Public Health
2015-2016	Program in Epidemiology & Human Genetics Student Representative, University of Maryland, Baltimore Graduate Student Association
2015-2016	Epidemiology Student Representative, University of Maryland, Baltimore Graduate Program in Epidemiology & Human Genetics Council
2015-2017	Member, Students for Non-Academic Careers, University of Maryland, Baltimore
2015-Present	Member, International Society for Pharmacoepidemiology, University of Maryland, Baltimore Student Chapter
2015-Present	Member, Women in Biology – Mentors, Advisors, and Peers, University of Maryland, Baltimore Chapter
2016-Present	Co-Coordinator, Women in Biology – Mentors, Advisors, and Peers, University of Maryland, Baltimore Chapter

2017-Present	Member, Career Advisory Group, University of Maryland, Baltimore Graduate Program in Life Sciences

Local Service

2011-2013	Volunteer, Medical Reserve Corps
2013-2014	Vaccine Clinic Volunteer, Baltimore Animal Rescue and Care Shelter (BARCS)
2015-2016	Volunteer & Young Professional Social Tennis Representative, United States Tennis Association Mid-Atlantic Section
2015-Present	Volunteer Tennis Coach, The Active Children Excel (ACE) Project

Teaching Service

Fall 2010	Teaching Assistant, Fundamentals of Epidemiology (PUBH 6320), University of Minnesota-Twin Cities Department of Epidemiology & Community Health
Summer 2011	Teaching Assistant, Zoonoses Epidemiology (EPI 625), State University of New York at Albany Department of Epidemiology & Biostatistics
Spring 2012	Teaching Assistant, Zoonoses Epidemiology (EPI 625), New York at Albany Department of Epidemiology & Biostatistics
Fall 2014	Teaching Assistant, Principles of Biostatistics (PREV/PH 620), University of Maryland School of Medicine Department of Epidemiology & Public Health
Spring 2015	Teaching Assistant, Research Practicum I (PREV 747), University of Maryland School of Medicine Department of Epidemiology & Public Health
Summer 2015	Teaching Assistant, Research Practicum II (PREV 748), University of Maryland School of Medicine Department of Epidemiology & Public Health
Fall 2015	Teaching Assistant, Health Services Policy, Management, and Finance (PREV 648), University of Maryland School of Medicine Department of Epidemiology & Public Health
Spring 2016	Teaching Assistant, Research Practicum I (PREV 747), University of Maryland School of Medicine Department of Epidemiology & Public Health
Summer 2016	Teaching Assistant, Research Practicum II (PREV 748), University of Maryland School of Medicine Department of Epidemiology & Public Health
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Fall 2016	Teaching Assistant, Health Survey Research Methods (PREV 758), University of Maryland School of Medicine Department of Epidemiology & Public Health

Spring 2017	Teaching Assistant, Research Practicum I (PREV 747), University of Maryland School of Medicine Department of Epidemiology & Public Health
Summer 2017	Teaching Assistant, Research Practicum II (PREV 748), University of Maryland School of Medicine Department of Epidemiology & Public Health
Spring 2018	Invited Lecturer, Research Practicum I (PREV 747), University of Maryland School of Medicine Department of Epidemiology & Public Health

Grants

Completed

03/01/16-02/28/18 Role: Pre-doctoral Trainee
Research Training in the Epidemiology of Aging
5T32 AG000262
P.I.: Jay Magaziner; National Institute on Aging

Submitted, Unfunded

Role: Pre-doctoral Fellow
Differences in Multiple Domains of Disease Progression by Sex and Menopause Type among a Cohort of Clinically Managed Parkinson's Disease Patients
F31AG056074-01
P.I.: Danielle Abraham; National Institute on Aging

Publications

Peer-Reviewed Journal Articles

1. Berges IM, Amr S**, Abraham DS**, Cannon DL, Ostir GV. Associations between Depressive Symptoms and 30-day Hospital Readmission among Older Adults. J Depress Anxiety 2015; 4:2. doi:10.4172/2167-1044.1000185
2. Evans CF, Sorkin JD, **Abraham DS**, Wehman B, Kaushal S Rosenthal GL. Interstage Weight Gain is Associated with Survival after First-Stage Single-Ventricle Palliation. Ann Thorac Surg 2017. doi: 10.1016/j.athoracsur.2016.12.031
3. Tanaka K, Moser K, **Abraham D**, Sniecinski, Mazzeffi M. Off-label PCC-Buyer be careful! J Cardiothorac Vasc Anesth 2017. doi: 10.1053/j.jvca.2017.01.004
4. **Abraham DS,** Gruber-Baldini AL, Harrington D, Shulman, LM. The Factor Structure of the Brief Symptom Inventory-18 in Parkinson Disease Patients. J Psychosom Res 2017; 96. doi:10.1016/j.jpsychores.2017.03.002

Poster & Oral Presentations

1. Nadeau JA, Currenti SA, **Abraham DS**, Solghan SM, Zansky SM. "Antimicrobial Resistance among Isolates of Invasive Pneumococcal Disease in New York State from 1999 through August 2011". International Conference on Emerging Infectious Diseases, Atlanta, GA, March 11-14, 2012.

2. Burzlaff KE, Smith GL, Malloy K, **Abraham DS**, Karr JB, Spina NL, Zansky SM. "Diabetes as an Underlying Health Condition among New York State Emerging Infection Program ABCs Pathogens: 2000-2009". International Conference on Emerging Infectious Diseases, Atlanta, GA, March 11-14, 2012.
3. Smith GL, **Abraham DS**, Karr JB, Spina NL, Burzlaff KE, Kolherschmidt D, Zansky SM. "Invasive GAS Cases in the New York State Emerging Infections Program 2000-2009: *emm* Types as Indicators for Virulence". International Conference on Emerging Infectious Diseases, Atlanta, GA, March 11-14, 2012.
4. **Abraham DS,** Eidson M, Clancy KA, Lin S, Zansky SM, Freed HA, Birkhead GS. "Evaluating the Utility of State Health Department Surveillance Systems for Monitoring Climate Change-related Human Health Impacts". Council of State and Territorial Epidemiologists Annual Conference, Omaha, NE, June 3-5, 2012.
5. **Abraham DS**, Eidson M, McGuire SM, Nattanmai GV, Spina NL, Zansky SM. "Antimicrobial Non-Sensitivity Trends Among Invasive Group A and Group B *Streptococcus* Isolates in New York State". Council of State and Territorial Epidemiologists Annual Conference, Pasadena, CA, June 9-13, 2013.
6. **Abraham DS**, Eidson M, Giambrone GP, Giambrone AE, SM Zansky. "Estimating Inpatient Costs of Group A *Streptococcus*—an Application Utilizing the National Inpatient Sample". Council of State and Territorial Epidemiologists Annual Conference, Pasadena, CA, June 9-13, 2013.
7. Santos RP, Spina NL, **Abraham DS**, Simmerly DA, Zansky SM, Elmendorf SL. "Epidemiology and Early Clinical Presentations of Invasive Group A Streptococcal Diseases". ID Week 2013 Conference, San Francisco, CA, October 2-6, 2013.
8. **Abraham DS**, Gruber-Baldini AL, Armstrong MJ, Barr EA, Shulman LM. "Self-Efficacy and Disability in Parkinson's Disease". The Gerontological Society of America Annual Conference, Washington, D.C., November 5-9, 2014.
9. Smith G, **Abraham D**, Auman K, Greene C, Dischinger P. "Linking Trauma Registry with national Death Index: Why are Some Inhospital Deaths Missing?" International Collaborative Effort on Injury Statistics and Methods, Washington, D.C., October 22-24, 2014.
10. Cannon DL, **Abraham DS**, Ostir GV. "Do Depressive Symptoms Predict 30-Day Rehospitalization?" Preventive Medicine 2015, Atlanta, GA, February 25-28, 2015.
11. Smith G, **Abraham D**, Auman K, Greene C, Dischinger P. "Linking Trauma Registry with National Death Index: Why are Some Inhospital Deaths Missing?" Society for Advancement of Violence and Injury Research Conference, New Orleans, LA, March 11-13, 2015.
12. Pimentel L, Ostir G, Schenkel S, **Abraham DS**, Berges IM, Kostelec T. "Cognition and Risk of Revisits to an Emergency Department in Ambulatory

Geriatric Patients". American College of Emergency Physicians Research Forum, Boston, MA, October 26-27, 2015.

13. Evans CF, **Abraham DS**, Kaushal S, Rosenthal G. "Interstage Growth Trajectory is Associated with Interstage Survival in the Absence of Post-Operative Complications Following the Norwood Procedure". American Heart Association Scientific Sessions, Orlando, FL, November 7-11, 2015.
14. **Abraham DS**, Berges IM, Guralnik JM, Ostir GV. "Sex Differences in the Association between In-Hospital Gait Speed and Post-Discharge Mortality". The Gerontological Society of America Annual Conference, Orlando, FL, November 18-22, 2015.
15. Le N, Cappola AR, **Abraham D**, Huang Y, Hochberg M, Miller R, Shardell M, Eastlack M, Hicks G, Orwig D, Magaziner J. "Testosterone, Estrogen, and IGF-1 in Men and Women Following Hip Fracture". Endocrine Society, Boston, MA, April 1-4, 2016.
16. **Abraham DS**, Pimentel L, Schenkel SM, Ostir GV. "Racial Disparities in Emergency Department Revisits among Older Adults". The Gerontological Society of America Annual Conference, New Orleans, LA, November 16-20, 2016.
17. **Abraham DS,** Orwig D, Hoghberg M, Magaziner J. "Sex Differences in Recovery Trajectories among Hip Fracture Patients". 21st International Association of Gerontology & Geriatrics World Congress of Gerontology and Geriatrics, San Francisco, CA, July 23-27, 2017.
18. **Abraham DS**, Gross AL, Gruber-Baldini A, Shulman LM. "Cross-Linking Legacy Questionnaires with PROMIS® Measures in Parkinson Disease Patients. PROMIS® Health Organization 2017 Conference, Philadelphia, PA, October 17, 2017.
19. Keshtkar Jahromi M, **Abraham D**, Gruber-Baldini A, Barr E, Schrader K, Savitt J, von Coelln R, Shulman L. "Parkinson's Diagnostic Accuracy – What diagnoses cause the most diagnostic-switches by Movement Disorder Specialists". American Academy of Neurology Annual Meeting, Los Angeles, CA, April 21-27, 2018.

Abstract

Title of Dissertation: Differences in Parkinson Disease Presentation and Progression by Sex and Reproductive Health Characteristics

Danielle S. Abraham, Doctor of Philosophy, 2018

Dissertation Directed by: Ann L. Gruber-Baldini PhD

Professor

Department of Epidemiology & Public Health

Background: Female sex and reproductive health characteristics indicative of higher estrogen exposure are associated with a reduced risk of Parkinson disease (PD). However, it is unclear if those risk factors also act as prognostic factors. Past studies examining PD progression have methodological limitations or have only focused on physician assessed, impairment progression.

Objective: To examine differences in physician assessed and patient reported PD presentation and progression by sex and reproductive health characteristics.

Methods: Analysis was conducted on PD patients who sought care at the University of Maryland PD and Movement Disorders Center. Bivariate analysis was used to compare patient sociodemographics, clinical characteristics, care patterns, and outcomes by sex and reproductive health characteristics. Multiple models of PD progression were explored; linear mixed-effects models with five year spline intervals were selected to examine patient impairment, disability, and health-related quality of life progression and heterogeneity. Sex and reproductive health characteristic interaction terms were added to the mixed-effects models to examine differences.

Results: The final study sample included 914 males, 549 females, and 463 post-menopausal females. Females had less social support, more psychological distress, and worse self-reported (but not physician assessed) disability and health-related quality of life at initial PD visits, compared to males. Progression patterns differed by outcome measure and were heterogeneous. For all outcome measures but one, patients improved in the first year of clinical care at the Center. However, there were minimal differences in PD progression by sex and inconsistent differences by reproductive health characteristics. A mediation analysis demonstrated that managing patient psychological distress had the largest impact on reducing sex differences in self-reported disability and health-related quality of life at initial PD visits.

Conclusions: The findings emphasize the difference in patient-reported and physician assessed outcome measures as well as the challenge of prognostic counseling in PD. The improvement seen in the first year of care at the Center highlights the need for specialist referral in PD. Females perceived their disease to be worse than males. To improve this difference, psychological distress interventions and management, particularly targeting females, should be implemented as part of PD clinical care.

Differences in Parkinson Disease Presentation and Progression by Sex and Reproductive Health Characteristics

by
Danielle S. Abraham

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2018

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Thank you to the faculty across campus that have mentored me as part of the Epidemiology of Aging T32, involved me in their varied projects, or allowed me to serve as a teaching assistant. A special thank you goes out to Dr. Jay Magaziner, Dr. Jack Guralnik, Dr. Braxton Mitchell, Dr. Geoff Rosenthal, Dr. Surbhi Leekha, and Dr. John Sorkin. You have provided me with such enriching experiences and greatly advanced my analysis, writing, teaching, and mentorship skills.

I would like to acknowledge the patients at the University of Maryland Parkinson Disease and Movement Disorders Center. Their selfless willingness to participate in research to benefit others is truly inspiring. Additionally, I would like to recognize all of the assistance from the clinical and research staff who work for and collaborate with the Center, especially Erik Barr and Katrina Schrader.

Lastly, I would like to thank Dr. Shelley Zansky for being a mentor at multiple stages of my career and encouraging me to take the plunge and pursue a doctoral degree.

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List of Abbreviations

ADLs	Activities of Daily Living
AES	Apathy Evaluations Scale
BLUP	Best Linear Unbiased Predictor
BMI	Body Mass Index
BSI-18	Brief Symptom Inventory-18
CDE	Controlled Direct Effect
CI	Confidence Interval
CIRS-G	Cumulative Illness Rating Scale-Geriatric
COMT	Catechol-O-methyltransferase
DAG	Directed Acyclic Graph
DBS	Deep Brain Stimulation
DF	Degrees of Freedom
ENT	Ear, Nose, and Throat
FSS	Fatigue Severity Scale
HOME	The University of Maryland Parkinson Disease and Movement Disorders Center Health Outcomes Measurements Study
HRT	Hormone Replacement Therapy
IADLs	Instrumental Activities of Daily Living
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
MAO_B	Monoamine Oxidase B
MD	Medical Doctor
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MVN	Multivariate Normal
MQL	Marginal Quasi-Likelihood
N/A	Not Applicable
Neuro-QoL	Quality of Life in Neurological Disorders
NM	Natural Menopause
NSDA	Nigrostriatal dopaminergic pathway
OARS	Older Americans Resources and Services Multidimensional Functional Assessment Questionnaire
PD	Parkinson disease
PDQ-39	39-Item PD Questionnaire
PET	Positron Emission Tomography
PIGD	Postural instability and gait difficulty dominant
PQL	Penalized Quasi-Likelihood
PROMIS	Patient Reported Outcomes Measurement Information System
RS-15	Resilience Scale 15
S&E	Schwab & England Scale
SAS	Social Activities Scale
SD	Standard Deviation
SF-12 MH	12 Item Short Form Health Survey Mental Health Scale
SF-12 PH	12 Item Short Form Health Survey Physical Health Scale

SF-36	36-Item Short Form Survey
SM	Surgical Menopause
SPECT	Single-photon emission computed tomography
TD	Tremor dominant
UPDRS	Unified Parkinson Disease Rating Scale
VAS	Visual Analog Scale

CHAPTER 1. INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Studies of factors that impact disease progression are limited in both scope and methodology. Although females are less likely to be diagnosed with PD, potentially due to the neuroprotective effects of estrogen, once diagnosed, it is unclear if females experience disease progression differently than males. Similarly, among females, various reproductive health characteristics increase the risk of diagnosis with PD, but the impact on progression is unclear. This study will examine whether PD presentation and progression, as measured by various domains (i.e., impairment, disability, health-related quality of life), differs between males and females clinically managed in a tertiary care center and how sex differences can be addressed. Furthermore, this study will explore if reproductive health characteristics (menopause type, hormone replacement therapy, parity) impact disease presentation and progression among post-menopausal females. These research questions will be explored via the following specific aims:

Aim 1. To estimate the rate and variability of disease progression in multiple domains over time among a cohort of clinically managed, PD patients.

Aim 1.1. To estimate the rate and variability of disease progression over time as measured by impairment.

Aim 1.2. To estimate the rate and variability of disease progression over time as measured by disability.

Aim 1.3. To estimate the rate and variability of disease progression over time as measured by health-related quality of life.

Hypothesis: *The rate of progression will be fastest later in the disease course and the variability in progression will be greatest early in the disease course for all outcomes.*

Aim 2. To determine if there are sex differences in disease presentation or rate of PD progression and what factors explain any differences.

Aim 2.1. To determine whether differences exist between males and females with respect to sociodemographics, clinical characteristics, impairment, disability, and health-related quality of life at the time of diagnosis and upon PD care initiation at a tertiary care center.

Aim 2.2. To compare males and females with respect to the rate of disease progression over time as captured by impairment, disability, and health-related quality of life.

Aim 2.3. To conduct a mediation analysis to understand underlying drivers of sex differences in disease presentation or rate of disease progression.

Hypothesis: *Females will have more severe disease at care milestones (diagnosis, initiation of PD tertiary clinical care), longer care delays (e.g., time from diagnosis to specialist visit), and a faster rate of disease progression for disability and health-related quality of life, compared to males. Males will have a faster rate of impairment progression, compared to females. The difference will be mediated by multiple factors.*

Aim 3. To determine if there are differences in the presentation and rate of Parkinson disease progression among post-menopausal females by reproductive health characteristics.

Aim 3.1. To describe the sociodemographics, clinical characteristics, impairment, disability, and health-related quality of life of post-menopausal females at the time of diagnosis and upon PD care initiation at a tertiary care center by menopause type, parity, and hormone replacement therapy usage.

Aim 3.2. To compare disease progression as captured by impairment, disability, and health-related quality of life among post-menopausal females by menopause type, parity, and hormone replacement usage, after adjustment for confounders.

Hypothesis: *Females with reproductive health characteristics indicative of greater endogenous and exogenous estrogen exposure will have a more mild presentation and a slower rate of disease progression than females with lower exposure.*

CHAPTER 2. BACKGROUND AND SIGNIFICANCE

A. Parkinson Disease

Overview

Dr. James Parkinson first described Parkinson disease (PD) in 1817 (1). PD is a progressive, neurodegenerative disease that results in motor along with nonmotor symptoms (1, 2). Among neurodegenerative disorders, PD is second only to Alzheimer's disease in terms of prevalence (3). In 2010, PD patients incurred almost $14 billion in medical expenses and over $6.3 billion in indirect costs (4).

Pathogenesis

PD is caused by neurodegeneration of the substantia nigra pars compacta within the basal ganglia. The neurons in this portion of the brain are vital to dopamine production as part of the nigrostriatal dopaminergic pathway (NSDA) (1, 2, 5). This pathway is essential for motor control (6). The disease has an extended prodromal period before motor symptoms develop (7).

Although this is the prime etiology of PD, additional neurodegeneration occurs outside of the substantia nigra (2, 5). This neurodegeneration results in additional dysfunction (2). For example, one review established that some symptoms of PD may be due to neurodegeneration of areas of the brain that control acetylcholine production (8). Formation of protein inclusions called Lewy bodies in neurons are an additional histological feature of PD (2).

The drivers behind neuronal losses in PD at the cellular level are thought to be multi-factorial and include mitochondrial dysfunction, oxidative stress, ubiquitin-proteasome pathway defects, and autophagy (5). While the majority of cases are sporadic

in nature (90%), mutations in several genes are associated with familial PD cases (e.g., *PINK1*, *LRRK-2*) (3, 5). Although dopaminergic cells are lost with natural aging, the region of the substantia nigra impacted by PD seems to be distinct from natural aging (9).

Presentation

Diagnosis of PD is challenging and can only be confirmed postmortem (1, 3). Diagnosis relies on clinical evaluation and neuroimaging (1). Key symptoms of PD include bradykinesia, tremor at rest, rigidity, and postural instability/gait impairment (1, 2, 7). Diagnosis of PD can be challenging as multiple system atrophy, progressive supranuclear palsy, and essential tremor can share features with PD (1, 10, 11). Based on autopsy, on average, 83.9% of PD patients followed by movement disorder experts have received a correct diagnosis of PD (11). In addition to these cardinal symptoms, other motor symptoms seen in patients include freezing, hypomimia, micrographia, hypophonia, dysphagia, and camptocormia, among others (1, 2). Motor symptoms that do not respond well to treatment, such as gait and postural disorders, are common in advanced disease (12).

In a study of incident, treatment-naïve patients, 52.4% developed any motor complication, 42.9% developed motor fluctuations, and 24.3% developed dyskinesias within 5 years of diagnosis (13). Risk factors for the development of motor complications include diagnosis at a younger age, female sex, and higher Unified Parkinson Disease Rating Scale (UPDRS) motor score at diagnosis (13).

Nonmotor symptoms are also very burdensome to PD patients, and clinicians may underappreciate these symptoms (14). Nonmotor symptoms negatively affect health-related quality of life in PD patients (7). Nonmotor symptoms can be grouped into

several classes: cognitive (e.g., cognitive impairment, dementia), autonomic (e.g., orthostatic hypotension, genitourinary dysfunction), psychological (e.g., depression), sensory (e.g., anosmia), and sleep-related (e.g., daytime sleepiness) (1, 2, 14). In a nationally representative German study of PD outpatients, 71% had dementia, depression, and/or other neuropsychiatric symptoms (15). The development of dementia is very common in PD patients; individuals have between 1.7 and 5.9 times the risk of developing dementia, compared to healthy controls (3). Although the aforementioned nonmotor symptoms are seen in older adults not taking medications for chronic conditions, these symptoms are significantly more common in PD patients (16).

PD symptomatology is heterogeneous (17). Several efforts have been made to define clinical subtypes of PD that capture such heterogeneity. One such clinical distinction based on the Unified Parkinson Disease Rating Scale (UPDRS) is the tremor-dominant (TD) and postural instability/gait difficulty (PIGD) phenotype dichotomy (7, 18). Other studies have identified subtypes with cluster analysis (17, 19). Cluster analysis defined some subtypes by more severe nonmotor symptoms (19). For example, patients particularly burdened by PIGD symptoms and psychopathology formed one cluster (19).

Treatment

The main treatment for the motor symptoms of PD is levodopa, a dopaminergic medication (20). In a cohort study of newly diagnosed PD patients, 85% were taking levodopa by five years from diagnosis (13). Over time, individuals develop side effects of levodopa treatment, which include dyskinesias, nausea, and dystonia (21). Higher doses of levodopa result in more improvement in motor symptoms; however, patients are

more likely to have medication side effects (21). Dyskinesias are detrimental to quality of life and result in increased costs, particularly non-medical costs (22).

Motor symptoms are treated with many additional medications in conjunction with, or instead of, levodopa (20, 23). Two such classes of drugs are dopamine agonists and monoamine oxidase B (MAO_B) inhibitors (20, 23). Catechol-O-methyltransferase (COMT) inhibitors are used in conjunction with levodopa to increase dopamine levels (20). Surgical treatments, including deep brain stimulation (DBS), are also available (20, 23). However, DBS is typically reserved for patients with advanced disease after receiving conventional treatment (20).

Much like some motor symptoms (e.g., gait and postural instability), many nonmotor symptoms (e.g., cognitive, autonomic, sensory) are not improved with dopaminergic therapy (2). Additional medications are prescribed to treat the nonmotor symptoms of PD (20). For example, clonazepam may be effective at treating rapid eye movement sleep behavior disorder and clozapine is efficacious in the treatment of psychosis in PD patients (20).

B. Epidemiology

Based on United States survey data, there were 630,000 individuals with PD in 2010 with 15% of afflicted individuals residing in a nursing home (4). The cost and burden of the disease is expected to increase; in 2050, it is estimated that 1.34 million people will have a diagnosis of PD (4). With respect to incidence, a literature review found that the incidence rate of PD is between 16 to 19 newly diagnosed cases per 100,000 person-years (24). A different review article states that the incidence ranges between 8 to18 cases per 100,000 person-years (3). Determining the true incidence and

prevalence of PD is challenging as studies have utilized different diagnostic criteria and case finding methodologies (3).

Active surveillance is particularly difficult with PD. It is very expensive and time consuming to find patients via door-to-door evaluations (25, 26). These strategies find many more cases than passive case-finding strategies (25). One study found that active case-finding resulted in 1.7 times higher estimates of PD than traditional case-finding via clinical practices (25). An Italian study that conducted screening and clinical follow-up of older adults (65-84 years of age) (27). After follow-up of those without PD at baseline, the researchers found an incidence rate of 326.3 cases per 100,000 person-years (27). This higher estimate, compared to other studies, is likely because the population studied was older.

Passive surveillance strategies include case finding via physician records (i.e., diagnostic codes) or prescription claims for levodopa (26). The latter technique is problematic because not all PD patients receive dopaminergic medications; furthermore, dopaminergic medications are nonspecific and are used to treat other conditions such as Restless Leg Syndrome (26). Population surveys are one additional case-finding technique. Because individuals may report a diagnosis of parkinsonism as synonymous with PD, estimates from self-reports are higher than those from billing data (26).

Risk Factors

Overall

The three main demographic risk factors for the development of PD include age, race, and sex (3, 28). PD incidence increases with age (29). One study determined that less than four percent of individuals are diagnosed before the age of 50, and the highest

incidence is between the ages of 65 to 79 (29). An Italian study of older adults found that the incidence rate of PD increased by 10% per year of age (27). Consequently, PD is most commonly a disease of older adults. Studies in the United States and Asia suggest that Blacks and Asians have a lower prevalence of PD (3). A study with Kaiser Permanente data found that after adjusting for age and sex, the incidence rate per 100,000 person-years was 16.6 in Hispanics, 13.6 in non-Hispanic Whites, 11.3 in Asians, and 10.2 in Blacks (29). The impact of sex on disease risk will be discussed in the subsequent section.

With respect to dietary and lifestyle factors, smoking is consistently associated with a decreased risk of PD development (3). There is suggestive evidence that vitamin E, iron, and vitamin B6 intake are associated with a decreased risk of PD (3). Nonsteroidal anti-inflammatory drug use and coffee consumption may also be protective; whereas, head trauma may be a risk factor for PD (3). Further research is needed on alcohol consumption and fat/fatty acid consumption as potential risk factors (3). Occupational exposures, particularly to pesticides and herbicides, are risk factors for PD (3). The data on heavy metal exposure is inconclusive (3).

Lastly, genetics play a role in the risk for PD (30). Implicated genes include the *PARK* genes (3). Many of these genes are associated with younger onset of the disease (3). However, disease risk is likely the result of various gene-environment interactions (30).

Sex

Male sex is an additional risk factor for PD (29). Studies suggest that males have 1.37 to 3.7 times the risk of developing PD, compared to females (6, 27, 31, 32). For

example, in a Minnesota sample, females had a lifetime risk of 1.3% and males had a lifetime risk of 2.0% (32). In the same study, males had an incidence rate of 13.03 cases per 100,000 person-years and females had an incidence rate of 8.76 per 100,000 person-years (32). In a Kaiser Permanente sample, the incidence rate was 19.0 and 9.9 per 100,000 person-years in males and females, respectively (29). In all age groups, females have a decreased risk of PD (31, 32). However, the prevalence ratio is attenuated over time due to sex differences in mortality (31). Females are also typically diagnosed at a later age or have a later age of onset (6, 33, 34).

Theories behind Sex Differences in Disease Risk

Several explanations have been postulated for why there is a difference in disease risk between males and females. Theories include the effect of estrogen, the effect of androgens, genetic factors, differences in brain development, difference in brain function, and differences in environmental exposures and lifestyle factors (35, 36). However, the etiology behind sex differences is likely multi-factorial (35).

The decreased risk of PD in females and later age at onset may, in part, be due to the neuroprotective effects of estrogen; however, further study is needed (3, 37-39). In mouse studies, estrogen is neuroprotective of the NSDA system (6, 40). Estrogen is also neurotrophic (41).

Among females, several studies have been conducted examining the effect of reproductive factors and endogenous and exogenous estrogen exposure on disease risk. Although these studies consistently suggest an association between estrogen exposure and PD risk, there are some contradictory findings. One meta-analysis found an age-standardized male to female risk ratio of 1.46 (42). However, in Western populations,

compared to Asian, the ratio is exacerbated (42). The authors of this meta-analysis suggest that this lack of sex difference in risk across all populations may indicate that the estrogen theory is incorrect (42). Additionally, it is unclear whether lifetime estrogen exposure is more important or there are certain critical periods where estrogen becomes important in PD risk (31).

Several studies in females have only examined endogenous estrogen exposures. In a Minnesota study, parkinsonism risk was significantly higher among females who had undergone a unilateral or bilateral oophorectomy prior to menopause (Adjusted HR 1.75, 95% CI: 1.04, 2.95) (43). There was a trend toward a stronger association with earlier oophorectomy (43). An association between any oophorectomy and PD was also observed (Unadjusted Hazard Ratio = 1.54, 95% CI: 0.86, 2.77); however, this result was not statistically significant (43). As oophorectomies result in estrogen loss, these results support the neuroprotective effects of estrogen theory (43). In an Indian study, bivariate associations were used to study the relationship between proxies of endogeneous estrogen exposure and PD (44). Later menopause, higher parity, higher gravidity, longer length of fertile life, and longer cumulative length of pregnancies were all associated with later onset of PD; later menopause, later menarche, longer length of fertile life, and natural menopause were associated with a decreased likelihood of PD (44). Haaxma et al. (2007) found no association between age at menarche and age at onset of PD but did find an association between higher parity (among those who were not nulliparous), later age at menopause, and longer fertile lifespan and age at onset (45). Cereda et al. (2013) found that later age at onset was associated with later age at menarche, later age at menopause, longer length of fertile life, and longer duration of estrogen exposure (46).

Several additional studies have examined both endogenous and exogenous estrogen exposures simultaneously. Gatto et al. (2014) examined endogenous and exogenous estrogen exposure indicators (menarche, regular periods, pregnancy, breastfeeding, oral contraceptives, natural menopause, oophorectomy, hysterectomy, and hormone therapy) in a case control study (47). After adjustment for age, race, and smoking status, several factors were associated with a decreased risk of PD—younger and older age at menopause and higher lifetime estrogen exposure (both endogenous and exogenous) (47). However, the use of combination estrogen-progesterone or progesterone only hormone replacement therapy (HRT) was associated with an increased risk of PD (47). Martignoni et al. (2002) noted that PD patients had later menarche, similar menopause (but less HRT use), lower parity, similar breast-feeding, similar gynecological diseases, and similar menses characteristics as controls (48). Rugbjerg et al. (2013) found no associations between PD risk and parity, age at first childbirth, number of fertile years, hysterectomy, or oophorectomy (49). However, short-term contraceptive use (versus longer use) and short-term HRT (versus longer use) were associated with an increased risk of PD (49).

With respect to androgens, Rocca et al. (2008) theorized that testosterone and progesterone stemming from the ovaries may be neuroprotective (35, 43). Testosterone and progesterone drop with oophorectomy (35, 50). Consequently, the association between oophorectomies and parkinsonism could be related to testosterone. Testosterone produced by the ovary is a precursor to estrogen and testosterone produced by the ovary can be converted to estrone and estradiol (35, 41). An additional study found that testosterone levels were higher in controls than male PD patients (51). A study replicated

in a Minnesota and Rotterdam, the Netherlands sample found a trend toward increased risk of PD in males who fathered more children (52). This finding could also suggest a connection between testosterone levels, which are related to reproductive success in early life, and later PD risk (52). Interestingly, one study did document that estrogen levels were higher in male controls than male PD patients (51).

Genetics may also be a factor explaining the risk difference between males and females (36). The estrogen receptor beta gene is associated with age at onset of PD (53). X-linked susceptibility genes are theorized to be important in disease risk (36). One such example is the X-linked gene for glutamate dehydrogenase (41). Studies suggest that the *SRY* gene, a Y chromosome gene, may also be influential in PD risk (6).

Sexual dimorphisms in the brain stemming from differences in brain development or differences that occur in adulthood may also explain sex differences in PD (41). The brain develops in a different hormonal milieu for males and females (41). Hormones such as estrogens or androgens can affect the brain later in adulthood (41). As a result, there are differences in the NSDA pathway between males and females (41).

Lastly, sex differences in environmental exposures and lifestyle factors may explain sex differences in disease risk (36). Males may be more likely to have occupational exposures to pesticides or to have a history of head trauma, two risk factors for PD (36). The greater risk of PD in males is likely multifactorial and a combination of differences in exposure to risk factors as well as underlying biology (36).

C. Progression

Measurement

Clinical progression of PD is heterogeneous and can be captured with multiple disease outcome measures (30). In the literature, there has been an emphasis on motor symptoms, or impairments, due to their utility in clinical trials; however, other outcomes may be more important to patients and their care teams (30). Other progression outcomes assessed include disability, health-related quality of life, various nonmotor symptoms, and mortality (30, 54). Disease severity clinically assessed by a physician via the Unified Parkinson Disease Rating Scale (UPDRS), may not be commensurate with patient reported outcomes, such as disability and quality of life measures, due to the involvement of patient perception (38, 54, 55). Additionally, patients with declines in UPDRS total scores experience an asymmetry of change (56). One study found that individuals who declined on the UPDRS had declines in disability (measured by the Schwab & England [S&E] scale) and health-related quality of life, but those who improved on the UPDRS did not improve on disability and health-related quality of life measures (56).

In addition to the progression domains already discussed, neuroimaging is another means to track disease progression. Specifically, Positron Emission Tomography (PET) scans are used to examine presynaptic dopaminergic integrity (57) and neuroimaging of striatal dopamine-transporter density (21). Similar to what is seen with outcomes that involve patient perception, UPDRS scores do not always match neuroimaging (54). Patients may have improved symptoms due to treatment; however, imaging demonstrates further neurodegeneration (54).

Models

Studies examining progression have been criticized for extrapolating longitudinal progression from cross-sectional data (58). This technique incorrectly assumes that the rate of progression is constant and linear since time of diagnosis and assumes that the level of disease severity at diagnosis is zero (58). Others use a sparse number of data points and compare the rate of change from baseline to the end of follow-up (59-61). Again, this assumes that progression is constant and linear since study entry. The assumption that disease progression is constant and linear over time is overly simplistic (58). The rate of progression may not follow a constant linear path (61). Some studies suggest that progression, particularly with UDPRS total and UPDRS motor scores, may be fast early and slow later in the disease course (1, 54). Supporting this pattern is the finding that neuronal loss in the substantia nigra post-mortem corresponds well with UPDRS motor score patterns; drastic neuronal losses occur in the first five years of disease, which stabilize over time (62). This fast early progression and lower later progression finding may be the result of, when using cross-sectional data, not accounting for baseline UPDRS scores at diagnosis (58). In a study examining both motor scores and disability, this slowing of progression over time was seen in one study for motor symptoms but not for disability outcomes (63). Furthermore, there is a great deal of heterogeneity between patients that is lost in simplified models of progression (64).

When quantifying treatment effects, more sophisticated non-linear models of progression have been explored (65). Specifically, variations of non-constant or non-linear, longitudinal mixed-effects models have been utilized (65). Holford et al. (2006) looked at progression in UPDRS scores over eight years (66). Several hierarchical mixed

effects model functions were compared (linear, asymptotic exponential, Gompertz growth, two segment linear model) with a Gompertz function providing the best fit (66). A Gompertz function reflects a slow rate of progression followed by a faster rate of progression returning to a slower rate of progression (66). Vu et al. (2012) found a Gompertz, rather than a linear, model most appropriately described the progression of motor symptoms, UPDRS total scores, cognition, and depression and the subsequent impact of treatment (67).

Very few other studies have utilized these more advanced progression models when not assessing treatment effects. Reinoso et al. (2015) used a longitudinal, mixed-effects model with nine years of UPRDS motor score follow-up from 526 patients (68). No assumption was made that progression followed a constant, linear pattern (68). The study found that patients initially experience improvement from baseline for two to two-and-a-half years, followed by a stable seven years, and a subsequent fast progression (68). This finding suggests an improvement phase, stable phase, and a decline phase with the initial improvement phase possibly due to treatment effects (68). Evans et al. (2011) used a mixed-effects linear model of UPDRS motor scores from 132 patients incorporating patient heterogeneity with random slopes and intercepts but assuming a constant, linear progression (69). Holden et al. (2017) examined progression of Movement Disorder Society UPDRS motor scores treating time as continuous and categorical in a mixed effects model (70). In that study, linear models more appropriately described motor progression over the course of five years (70). An additional study did model PET scan neuroimaging with non-linear, random effects models (57).

Few studies look at multiple progression domains simultaneously and more advanced models are rarely applied outside of UDPRS scores. Velseboer et al. (2013) did examine motor scores, disability, and health-related quality of life over five years of follow-up (n = 129) (71). Although assuming a constant, linear rate of progression, linear mixed models were utilized (71).

Lastly, time to event models are quite common in the literature. Researchers have examined, for example, time to dementia onset and time to needing dopaminergic medication among patients diagnosed with PD (54, 72). However, time to event models can be problematic because although time to a culminating event may be similar between two patients, their disease experience to that time point may be very different (73). Essentially, the disease progression pattern is missed with this approach.

Estimates

Because a multitude of scales are used to assess progression in disability and health-related quality of life domains, estimates of disease progression primarily focus on UPDRS scores and Hoehn & Yahr staging, both commonly used outcomes (1).

In early, untreated patients, UPDRS total scores increase by 8-10 points in the first year (54). Jankovic & Kapadia (2001) found that for patients under clinical care, the annual rate of UPDRS total progression obtained from a repeated measures model was 1.43 for those assessed on medication and 1.58 in those assessed off medication (64).

Reinoso et al. (2015) found that UPDRS motor scores increased between 0.67 and 3.96 points, depending on the time since diagnosis (68). Evans et al. (2011) found a UPDRS motor score change of 2.2 units per year in newly diagnosed patients (69). Louis et al. (1999) found that among PD patients in a community registry, the annual rate of

increase in motor scores was 1.5 units (61). In early, untreated patients, progression is more rapid with a progression of 5 to 6 points on the UPDRS motor scale in the first year (64). In a clinic sample, the UPDRS motor score increased by a median of 3.3 points (range = 59.2) over the course of one year (63).

For the Hoehn & Yahr scale, time to Hoehn & Yahr stage 3 is clinically important. Study estimates for this interval have ranged from 3 years to 19.0 years (54). One study found that the time to Hoehn & Yahr stage 3 was 5 to 20 years (54). Shulman et al. (2008) found that the transition occurred in 7 years (74). A very fast estimate was found in another study—stage 3 was reached by 3 years from onset (75). The median and range of change in Hoehn & Yahr stage during one year of follow-up was 0 and 3.2 units, respectively, in clinic patients and 0.2 and 1.86, respectively, in community-dwelling PD patients (63).

D. Prognostic Factors

The etiology of PD has been thoroughly examined (30). However, much less is known about factors that influence the progression of PD (30). Risk factors for the development of PD may not be prognostic factors (30). Additionally, some factors that are beneficial early in the disease course may no longer be beneficial as the disease progresses (76). Neuroimaging studies also suggest that different factors may play a role in disease initiation versus progression (57).

Methodologic Limitations of Prognostic Models in PD

Many of these prognostic factors have been studied in the context of the methodologically limited progression models discussed previously. In general, there has been a lack of consensus among studies examining prognostic factors (68, 77). The lack

of consensus may be explained by different follow-up times (68, 78). Many studies have short follow-up (77, 79). In one review, of studies with ≥6 months of follow-up, studies have ranged in duration from one year to twelve years with the majority on the shorter end (77). Cohorts studied may also be drastically different, particularly with respect to disease duration at enrollment (79, 80). In a systematic review, the average time since diagnosis in various studies was between 23.5 months and 9.7 years (77). Prognostic studies frequently use non-inception cohorts (77). Sample sizes may vary (68, 80), and there are differences in what covariates are included in adjusted models. Lastly, different outcome measures may be used across studies (80).

General

In the literature, later age at onset, age, sex (mixed results on which sex fares worse), PIGD subtype, psychotic symptoms, cognitive problems, comorbidities, genetics, motor scores at baseline, and disability at baseline have all been associated with worse prognoses (7, 12, 30, 64, 68, 69, 81, 82).

Several systematic or evidence-based reviews have been completed examining prognostic factors in PD (10, 77, 79). Marras et al. (2002) examined 41 articles that addressed prognostic factors for UPDRS motor scores and disability (79). Thirteen of the studies reviewed were cross-sectional and only 10 examined nonmotor symptoms (79). With respect to motor scores, consistent prognostic factors included dementia and disability while mixed findings were present for disease subtype, older age, older age at onset, longer disease duration, female sex, and depression (79). For disability outcomes, consistent prognostic factors included cognitive impairment, initial lack of independence, and older age at onset; mixed findings were present for disease subtype, male sex, and

depression (79). An evidence-based review by Suchowersky et al. (2006) identified older age at onset, initial symptoms of rigidity and hypokinesia, comorbidities, PIGD subtype, and male sex as characteristics associated with a faster rate of motor progression (10). Age and initial symptoms were associated with a faster time to cognitive decline and dementia (10). Age, dementia, and less response to dopamine resulted in a faster time to nursing home placement and poorer survival (10). A systematic review by Post et al. (2007) generated a list of prognostic factors identified by high quality studies (77). Many of these studies used the UPDRS motor exam as the outcome (77). Prognostic factors for motor impairment included later age at onset and study baseline (conflicting evidence), longer time since onset at study baseline (conflicting evidence), lower baseline UDPRS motor scores (limited evidence), dementia (limited evidence), and poor S&E scores (limited evidence) (77). Strong evidence links later age at onset and PIGD subtype score with disability prognosis (77). Conflicting evidence was found for sex and disability prognosis; limited evidence was found for non-TD subtype at onset, bradykinesia score, symmetrical disease at baseline, and depression with disability prognosis (77). Reviewed studies looking at prognostic factors of quality of life were far more limited with no prognostic factors were identified (77).

One study examined factors related to prognosis in health-related quality of life outcomes (60). The study by Karlsen et al. (2000) found that age, sex, duration of dopamine therapy, levodopa dose, depression, cognitive impairment, and initial disease severity measured by UPDRS and Hoehn & Yahr stage were not associated with progression in health-related quality of life, measured by the Nottingham Health Profile, over 4 years (60). In an additional study, after adjustment for other factors, change in

physical health-related quality of life over 1.5 to 2 years was associated with baseline Short Form-36 physical health scores, depression, and intellectual impairment (59). Meanwhile, baseline Short Form-36 mental health scores, age, and disability measured by the S&E scale were associated with worse prognosis in mental health-related quality of life (59). Sex was not a prognostic factor for either health-related quality of life domain (59).

Sex and Reproductive Factors

As discussed previously, sex may be an important prognostic factor in PD progression; however, mixed results are found in the literature. For example, Marras et al. (2002) found, in a systematic literature review, that female sex may be a prognostic factor for poorer motor outcomes while male sex may be a prognostic factor for poorer disability outcomes; however, the evidence is mixed (79). Table 1 presents a summary of studies that explored sex differences in PD prognosis.

Only two studies have examined progression by sex exploring whether progression varied over time (45, 68). Haaxma et al. (2007) selected a linear progression model and no association between sex and rate of progression was seen among 253 patients (45). Meanwhile, Reinoso et al. (2015) found that females had slower initial progression followed by faster later progression, compared to males (n = 576) (68). Both studies did not isolate the causal effect of sex as other covariates were included in the models, focused only on motor symptoms (impairments), and were conducted outside of the United States (45, 68). The latter may be important given that the difference in PD risk between males and females is attenuated in Asians (42).

Haaxma et al. (2007) explored the relationship between estrogen via proxies (age at menarche, age at menopause, parity, use of postmenopausal HRT) on UPDRS motor scores. They found no association between estrogen and UPDRS motor scores, but it is unclear if these factors were incorporated into longitudinal progression models (45). No additional articles were found that explored differences in PD progression by endogenous/exogenous estrogen factors.

Table 1. Summary of articles that explored sex differences in PD progression

Author & Year	Sample	Outcomes	Model	Sex Difference
Baba et al. (2005) (83)	844 males, 420 females Baseline visit to Mayo Clinic with PD diagnosis	UPDRS motor	Correlation between UPDRS motor score and disease duration	Non-significant difference in correlation
Dahodwala et al. (2016) (80)	2,938 males, 1,741 female patients from 21 international centers	Health-related quality of life measured by 39-Item PD Questionnaire (PDQ-39)	Compared one-year change (multivariable model including sex, age, Hoehn & Yahr stage, disease duration, comorbidities)	Baseline: females older, more comorbidities, worse PDQ-39 score, worse timed up and go times, improved delayed recall No sex difference in progression
Diamond et al. (1990) (84)	47 male and 23 females seen at UCLA	Disability	Compared mean scores at each year	No sex difference in disability at any year
Haaxma et al. (2007) (45)	253 PD patients (62% male) at a Dutch medical center	UPDRS motor scores, single-photon emission computed tomography (SPECT) imaging	Random effects regression including sex, age at onset, presenting symptom, disease duration. Transformed model used for SPECT	Same rate of progression in UPDRS motor scores (0.09 points/year) Same decline in tracer binding
Hely et al. (1999) (85)	70 males and 56 females from a randomized trial (Sydney Multicentre Study of PD)	Modified Columbia and North West University disability scale	Compared rate of change in disability scores from baseline to 10 years	No sex difference in rate of change

Table 1 Continued

Author & Year	Sample	Outcomes	Model	Sex Difference
Jankovic & Kapadia (2001) (64)	181 males and 116 females seen at Baylor	UPDRS subscores (part I, II, and III)	Repeated measures mixed effects model (assumed linear)	Males faster progression in UPDRS part I and II (after adjustment)
Latourelle et al. (2017) (82)	312 patients (66.5% male) from Parkinson's Progression Markers Initiative & 317 patients (65% male) from Longitudinal and Biomarkers Study in PD	Summed Movement Disorders Society-UPDRS scores (part II + part III)	Predictive models from Bayesian machine-learning approach (assumed linear)	Females slower progression
Louis et al. (1999) (61)	Community registry of PD patients in Manhattan, NY (124 females, 113 males); in general, patients were older with longer duration of disease	UPDRS motor; tremor, bradykinesia, rigidity, gait/balance sub-scores	Repeated measures linear regression over 8 years follow-up (annual rate of progression from study entry)	Sex did not predict higher scores at all time points
Reinoso et al. (2015) (68)	328 males, 198 females with PD in the Phillippines	UPDRS motor scores	Longitudinal, mixed-effects model with 9 years of follow-up, no assumption that constant, linear progression. Sex comparison adjusted for age at diagnosis, baseline subtype, Hoehn & Yahr severity, UPDRS motor score, and cognition	Females slower initial progression followed by faster later progression, compared to males
Velseboer et al. (2013) (71)	72 males, 57 females newly diagnosed with PD in the Netherlands	UPDRS motor scores, Disability (Schwab & England, Academic Medical Center Linear Disability Scale), Health-related quality of life (Parkinson Disease Quality of Life)	Linear mixed models (assumption that progression was constant, linear) Used backward selection for variables; defined prognostic factors by whether interacted with time	Male sex was a prognostic factor for worsening motor scores but not disability and health-related quality of life

E. Women's Health & Parkinson Disease

If sex differences in disease progression do exist, a multitude of factors could explain such a difference. Hormones and underlying sex differences in biology may be one such factor. Overall, animal models suggest estrogen has a beneficial effect on disease pathogenesis (39). Estrogen interacts with the NSDA system and has antioxidant and neurotrophic effects, which may impact progression (37). The finding by Reinoso et al. (2015) that females experience slower initial progression followed by faster later progression could suggest that the benefits of estrogen dissipate over time in PD (68). Furthermore, sexual dimorphisms in the NSDA pathway may impact neurodegeneration and thus progression in PD (41).

Differences in treatment response could be an important driver of differential disease outcomes between males and females (86). The literature suggests that males and females respond differently to treatment (37, 38). There is no significant difference in the type of dopaminergic medications given to males and females (87). The pharmacokinetics of levodopa differ between males and females with levodopa being more bioavailable in females (88). Consequently, males are more likely to receive higher doses of levodopa (89). However, female PD patients have a significantly higher risk of developing dyskinesias (13, 33, 90), even after accounting for body weight (13). Females are less likely to undergo DBS (34). However, among those that do undergo DBS, males and females experience some differences in outcomes. In one study, males and females were studied before and after DBS implantation (91). Prior to surgery, females had greater levodopa-induced dyskinesias, compared to males (91). When on medication, females also had worse bradykinesia and hand-tapping scores than males. Significant sex

differences after implantation were noted for bradykinesia—females were less responsive to treatment; females also had a greater improvement in Activities of Daily Living (ADLs), although this finding was only borderline statistically significant (91). A second study that examined progression at one, three, and five years post-DBS surgery found no significant differences in ADLs and S&E scale scores (92). Females did have less UPDRS motor improvement at one year only and experienced more adverse events (92).

Differences in progression may also be largely dependent on initial disease presentation and access to care. Some studies suggest that females are more likely to develop PD at a later age (34, 45); however, other studies refute this finding (33, 93-95). As discussed previously, later age at onset may be indicative of a worse prognosis (77, 79). An additional study found that females have a similar time from symptom onset to physician visits and symptom onset to diagnosis (p-value for the latter = 0.06 with females trending toward a longer interval), but females had a significantly longer time from onset of symptoms to visiting a movement disorders specialist ($p<0.01$) (96). This delay could be the result of more mild disease presentations and symptoms, physician perceptions, and referral barriers (96). One study found no significant difference in symptoms at onset and diagnosis between males and females (95). Within females, presenting symptoms have been found to differ by some estrogen factors (age at menarche) but not others (HRT) (46). However, if females have access to care or delay in care issues, it could impact their disease prognosis (38).

Females are more likely to present with tremor or a tremor dominant (TD) disease subtype (6, 45, 93). Later age at menarche (but not number of pregnancies or HRT) is associated with an increased likelihood of presenting with tremor (46). The TD subtype

is associated with a better prognosis (77, 79). Estrogen factors (later age at menopause, longer fertile life) have been associated with lower UPDRS motor scores at baseline in at least one study (46). However, there was no association between estrogen and UPDRS motor scores in another study (47). Understanding this difference in disease severity at baseline is important because more severe disease at baseline has been associated with worse prognosis for motor and disability outcomes (79).

Other phenotypic differences over the course of the disease may impact motor scores, disability, and perceptions of quality of life over time. Symptoms and symptom severity may differ by sex (41, 97). According to a symptom inventory in one study, males experience significantly more symptoms than females (98), but females may experience more nonmotor symptoms (93, 94). In another study, males had significantly higher rigidity scores and females had significantly higher instability scores (99). Cognition is typically worse in male PD patients (33, 100); however, one study found that females scored worse on a cognitive assessment (101).

Females and males may also handle their chronic condition differently in terms of coping and disease management (38). For example, females typically have worse psychosocial consequences of PD (34). Females report more depression (98, 101). Which symptoms bother patients differs by sex (98). Females are more bothered and annoyed by anxiety and back pain (98). Males have more dissatisfaction with sexual life (102). Female perceptions of disability and health-related quality of life may differ as well. Disability and quality of life are reported to be worse by females (38, 94, 99). Although one study did document that these domains are worse in males (103). Differences in socialization and social support could also be an important factor

distinguishing male and female PD patients (38). Female PD patients are more likely to be single or widowed, have less education, and require less assistance from caregivers (103). However, this may be due to female's perceptions that they do not need a caregiver or because females are less likely to have a spousal caregiver available (34, 103).

Overall, the literature suggests that females have a lower incidence and prevalence of PD and have a later age of PD onset (34). Among PD patients, females are more likely to present with the more benign TD phenotype, more likely to present with different motor and nonmotor symptoms, less likely to have cognitive impairment, more likely to experience depression, more likely to experience greater comorbidity, more likely to report worse disability and quality of life, more likely to have a reduced mortality risk, more likely to experience a better motor response to treatment but have increased medication side-effects (dyskinesias), less likely to undergo DBS, and less likely to have a spousal caregiver (34). Consequently, many factors could lead to sex differences in PD progression.

F. Overall Gaps in the Literature

Past models of PD progression have been inconsistent and few have attempted to capture non-constant, non-linear rates of progression or inter-individual heterogeneity. Durations of follow-up and sample sizes have also been limited. Studies have rarely explored progression in multiple outcome domains and studies rarely include health-related quality of life, which may be more important to patients.

Often studies in PD have not analyzed outcomes by sex (97), and a limited number of studies have examined whether disease progression differs by sex (30). A

review article by Pavon et al. (2010) argues that there is a great need for prospective research on PD in females examining both clinical and patient-reported outcomes (34). Given that PD is a neurodegenerative disease, and the brain is particularly impacted by sex differences, it is important to study whether sex is a prognostic factor in PD (104). Studies that have explored sex differences in progression are often methodologically limited by progression models selected (68). Additionally, because they adjust for factors on the causal pathway, these studies have failed to isolate the causal effect of sex on disease progression.

Understanding prognostic factors is important given that some factors can be modified with interventions (30). No mediation analysis has been conducted to elucidate how interventions can ameliorate sex differences, if any exist, in disease presentation and progression.

Lastly, despite its impact on disease risk, very little is known about how endogenous (e.g., menopause type, parity) and exogeneous (e.g., HRT) estrogen exposure affects PD progression (34).

Addressing these limitations will help improve clinical care through improved prognostic counseling, patient management decisions, and intervention planning.

G. Significance

According to a qualitative study of PD patients, priorities for research include studies to address symptom reduction, better understand disease progression, explore the impact of PD on mental health and cognition, and improve both medical and psychological patient care (105). This study will utilize a unique, large database of PD patients. These patients have extensive follow-up data available on a multitude of

demographic, physician-assessed, and patient-reported factors. This data will help address several gaps in the literature discussed previously.

Modeling techniques will be used that will allow for a more accurate assessment of progression for males and females—specifically, by allowing for non-constant progression and accounting for inter-individual heterogeneity. Multiple outcome domains will be explored through these models.

Although hormones or underlying biology may play a major role in sex differences in PD progression, there are other potentially modifiable, mediating factors that could drive sex differences in disease progression (104). Newer, causal inference approaches to mediation analysis (106) will be used to study what sex differences, if any, remain in presentation or progression after intervening on designated factors. Lastly, this will be one of the first studies to investigate the impact of estrogen proxies on progression of PD in humans.

CHAPTER 3. STUDY DESIGN AND METHODS

A. Study Setting

The University of Maryland Parkinson Disease and Movement Disorders Center is a tertiary care center located in Baltimore, Maryland. The Center evaluates and manages patients with neurologic disorders including Parkinson disease (PD) and other movement disorders such as progressive supranuclear palsy, multiple system atrophy, and essential tremor, among others. As part of standard clinical care, at each visit, patients complete various questionnaires and undergo nurse, research assistant, and physician assessments. Clinicians routinely review patient questionnaire responses during care visits. Over time, the Center has introduced and removed questionnaires provided to patients based on clinical need and relevance. Additionally, patient sociodemographics, diagnoses, medications, and other pertinent medical information are obtained and recorded.

B. Study Design

Patients under the care of movement disorders specialists at the Center are approached to participate in a naturalistic, open cohort study (The University of Maryland Parkinson Disease and Movement Disorders Center Health Outcomes Measurement [HOME] Study). Per the University of Maryland Institutional Review Board approved protocol, patients must consent to participate in the research study. Patients are ineligible if they are attending the Center for purposes other than for evaluation of general neurologic disorders managed by the Center, if they are less than 18 years of age, or if they are a prisoner. The HOME study began in 2002 and has ongoing enrollment. Patients may withdraw from participation at any point in time. Consenting

patients have their sociodemographic, clinical, and questionnaire data from their patient visits entered into a study database. Data can be extracted from the study database for analysis purposes.

The current study ("Differences in Parkinson Disease Presentation and Progression by Sex and Reproductive Health Characteristics") was a longitudinal, secondary analysis of the parent, HOME study. Analysis was restricted to a sub-sample of parent study participants. For each aim, the "Selection of Participants" section will detail the inclusion criteria used for each respective analysis.

C. Aim 1

Selection of Participants

For this Aim, analysis was restricted to patients diagnosed with PD or patients who had their prior diagnosis of PD confirmed by one of the Center's movement disorder specialists. Diagnosis of PD is challenging given that the clinical presentation can be similar to other parkinsonisms and disorders (107). As a result, diagnoses sometimes change throughout the course of clinical care at the Center. For the purpose of this study, patients who had a PD diagnosis at at least one visit, irrespective of etiology, were considered to be diagnosed with PD. However, patients were excluded if they had a diagnosis of essential tremor alone, multiple system atrophy, progressive supranuclear palsy, or corticobasal degeneration at their last visit to the Center where diagnosis information was recorded. These aforementioned diagnoses indicate that a patient no longer had a PD diagnosis at their most recent visit to the Center. Patients who had a diagnosis of dementia with lewy bodies at their last visit were not excluded as

discrimination between the two diseases is challenging because they share a common underlying pathology (108).

The analytic sample was further restricted to patient data from visits between April 1, 2002, when data collection for the HOME study commenced, and December 31, 2016, the selected administrative censoring date for the current study. Some patients are not diagnosed with PD by the Center's specialists until after several visits. For those circumstances, data from visits prior to a patient's diagnosis were dropped from the analysis.

To ensure a consistent sample size for all sub-aims, patients were further excluded if they did not have at least one observation for each study outcome measure (n=413). Patients missing dates of birth (n=0), sex (n=0), and all key date variables (diagnosis year, symptom onset year, and levodopa start year [n=73]) were also excluded.

Variables

Independent

The independent variable, or exposure, for Aim 1 was time since diagnosis measured in years. The patient's self-reported diagnosis date or movement disorder specialist diagnosis date was set to time "zero" for subsequent analyses. Because patients only report the year of PD diagnosis, self-reported diagnosis date was assumed to be the mid-point of the diagnosis year (i.e., July 1st of the given year). If the patient had a PD diagnosis year that matched or was later than their first visit to the Center, it was assumed that a movement disorders specialist at the Center first diagnosed the patient at their first visit of the corresponding diagnosis year.

Dependent

Disease progression was assessed by three outcome domains—impairment, disability, and health-related quality of life. Although there is correlation between these three domains, a prior study at the Center determined that there is a great deal of heterogeneity in responses across domains within each score on any given domain (109). Many instruments are available to assess PD outcomes (12). The justification for the selection of the various instruments to operationalize each domain is below.

Impairment

Impairment, the primary outcome domain for this study, was captured with the Unified Parkinson's Disease Rating Scale (UPDRS) motor sub-scale score (110). The UPDRS motor sub-scale assesses motor symptoms and includes bradykinesia, tremor, rigidity, and postural instability items, among others. Other sub-scales of the UPDRS capture mentation, behavior, and mood; activities of daily living; and complications of therapy. These other sub-scales capture disability and health-related quality of life, consequently a UPDRS total score (sum of all sub-scales) was not used as an outcome measure as disability and health-related quality of life were captured with other questionnaires. Scores on the UPDRS motor range from 0 to 108 with higher scores indicating worse disease severity. The UPDRS holds the same factor structure over time suggesting it has good longitudinal properties for assessing progression (111). Importantly, the UPDRS motor score is physician assessed.

Hoehn & Yahr staging is commonly used to study disease severity and progression (1). This instrument is less impacted by treatment effects than the UPDRS;

however, it was not be used to assess progression in this study because it is not as sensitive to change (the instrument only has an eight stage range) (30).

Disability

Disability was the second outcome domain assessed in this study and was captured with two patient reported outcome measures and one physician assessed outcome measure. Patient reported disability was assessed with 1) the Older Americans Resources and Services Multidimensional Functional Assessment Questionnaire (OARS) Activities of Daily Living (ADLs) sub-section score and 2) the OARS Instrumental Activities of Daily Living (IADLs) sub-section score (112). The questionnaire asks about seven ADLs and seven IADLs. The questionnaire allows individuals to rank the amount of difficulty performing each activity in the past week as as 1 (no difficulty), 2 (slower or greater difficulty), 3 (need some help), 4 (need moderate help), and 5 (completely unable). Of note, the Likert scale of the OARS was expanded from its original design for the HOME study to allow for the patient response of "slower or greater difficulty".

Physician assessed disability was determined from the Schwab & England Scale (S&E) score (113). The S&E scale is scored as a percentile ranging from 0% (bedridden) to 100% (completely independent) with increments of 10 percentage points. Although this tool was used to determine physician assessed disability, one study of providers suggests that, frequently, other clinical professionals or staff and, occasionally, patients or caregivers help with completion of this scale (114). At the Center, subsequent to interviewing the patient and family members and/or caregivers, the physician completes the S&E scale.

Many instruments have been used to assess disability in PD for clinical and research purposes, and there is no gold standard used in the field to assess disability (115). The Parkinson Disease and Movement Disorder Society Task Force evaluated disability instruments used in PD patients (115). The UPDRS part II (Activities of Daily Living) is recommended for use in PD patients because it has undergone clinometric testing in PD patients; however, this instrument has only six ADLs represented (along with seven impairments) and does not capture IADLs (109, 115). Consequently, it was not selected for use in this study. The UPDRS part II has only four overlapping items with the OARS disability sub-scales (74). As they have not undergone clinometric testing, the OARS disability sub-scales are only suggested for use by the Task Force (115). The S&E, like the UPDRS part II, is recommended for use in PD patients. Despite the differing final recommendation ratings by the Task Force, both the OARS and S&E are deemed appropriate for use in clinical and research settings (115).

Health-Related Quality of Life

Health-related quality of life was the last domain of interest. This domain was captured with the patient-reported 12 Item Short Form Health Survey (SF-12) (116). Both 1) mental health (SF-12 MH) and 2) physical health (SF-12 PH) scale scores were used as outcomes. Responses were normalized to population T-scores (mean = 50, SD = 10) with lower T-scores indicative of poorer health-related quality of life.

Fewer studies have explored health-related quality of life in PD and a multitude of different scales have been used including the 39-item PD Questionnaire (PDQ-30) (30), Quality of Life in Neurological Disorders (Neuro-QoL) measure (30), S&E (30), Nottingham Health Profile (60), and the 36-Item Short Form Survey (SF-36) (22, 59).

Like the parent SF-36, the SF-12 allows separate mental and physical health-related quality of life components to be captured (59).

Covariates

Table 2 lists the covariates explored for use in the analysis along with details about the questionnaire used to assess each covariate and whether the covariate was time varying. As mentioned previously, questionnaires were phased in and out of use at the Center and may not have been available over the entire study time frame. Additionally, the questionnaire from which some covariates were captured changed over time. For example, cognition was originally captured by the Mini-Mental State Examination (MMSE) (117) and then by the Montreal Cognitive Assessment (MoCA) (118). Mortality status and date of death, although outcomes, were also available for a subset of individuals but are not included in Table 2.

Table 2. Description of covariates considered in analysis

Covariate	Questionnaire	Level	Scoring Range	Timing	Administration	Time Varying
Age	MD Data Form	Continuous	N/A	Current	Self Report	Yes
Apathy	AES (119)	Ordinal	18-72 (high=bad)	4 Weeks	Self Complete	Yes
BMI	N/A	Continuous	N/A	Current	Nurse Complete	Yes
Clinician	N/A	Nominal	N/A	Current	Medical Record	Yes
Cognition	MMSE & MoCA (117, 118)	Ordinal	MMSE: 0-30; MOCA: 0-30 (high=good)	Current	Nurse/Research Assistant	Yes
Comorbidities	CIRS-G (120)	Continuous & Binary	0-14 (high=more comorbidities) Yes/No Individual Items	Ever	Self-Report	Yes
Completer of Forms	OARS (112)	Nominal	Patient, Co-, Caregiver	Current	Self Complete	Yes
Disease Stage	Hoehn & Yahr (121)	Ordinal	1-5 (high=bad)	Current	MD Complete	Yes
Disease Sub-Type (Jankovic)	UPDRS (110)	Nominal	TD, PIGD, or Indeterminate (18)	Current	MD Complete	Yes
Drug Side-Effects	UDPRS Complications of Therapy (110)	Ordinal	0-23 (high=bad)	Week	MD Complete	Yes
Education	Intake	Categorical	Elementary, High, Trade, College, Graduate	Ever	Self Complete	No
Employment Status	Intake & Follow-Up	Categorical	Working, Disabled, Retired, Unemployed	Current	Self Complete	No
Falls	UPDRS Falls Question (110)	Categorical	Normal, Rare Falling, <1 per Day, 1/Day, >1/Day	Current	Self Complete	Yes
Fatigue	FSS (122)	Continuous	1-7 (high=bad)	1 Week	Self Complete	Yes
Fear of Falling	Falls Questionnaire	Ordinal	No, Mild, Moderate., Severe	4 Weeks	Self-Reported	Yes
Fluctuator Status	UPDRS (110)	Binary	Fluctuator or Non-Fluctuator	Current	MD Complete	Yes
Income	Intake	Categorical	(In Thousands) <50, 50-100, 100-150, >150	Current	Self Complete	No
Living Arrangement	Intake & Follow-Up	Categorical	Alone, w/ Spouse/Partner, w/ Other Family, Other	Current	Self Complete	No
Marital Status	Intake & Follow-Up	Categorical	Married, Single, Separated, Divorced, Widowed	Current	Self Complete	No
Medication	Dopaminergic Drug & Levodopa Drug	Binary	Yes/No	Current	Self Report	Yes
Pain	VAS (123)	Continuous	0-10 (high=bad)	Current	Self Complete	Yes
Physical Activity	IPAQ (124)	Continuous	0-Infinity (low=bad)	7 Days	Self Complete	Yes
Psychological Distress	BSI-18 (125) Sub-Scales: Somatization, Anxiety, & Depression	Continuous	0-100 T-scores (high=bad)	7 Days	Self Complete	Yes
Race/Ethnicity	Intake	Categorical	Black, White, Hispanic, Pac. Islander, Am. Indian, Asian, >1 Race	Current	Self Complete	No
Residence	Intake & Follow-Up	Categorical	Home, Retirement Community, Assisting Living, Nursing Facility	Current	Self Complete	No
Resilience	RS-15 (126)	Ordinal	7-105 (low=bad)	General	Self Complete	Yes
Self-Efficacy for Chronic Disease Management	Stanford S elf-Efficacy for Managing Chronic Disease 6-Item Scale & PROMIS (127-129)	Ordinal & Continuous	Stanford: 6-18; PROMIS 0-100 T-scores (low=bad)	Current (Both)	Self Complete	Yes
Social Activities	SAS (130)	Ordinal	0-Infinity (low=bad)	Year	Self Complete	Yes
Surgical Treatment	Deep Brain Stimulation	Binary	Yes/No	Current	MD Complete	Yes

Abbreviations: MD, Medical Doctor; AES, Apathy Evaluation Scale; BMI, Body Mass Index; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CIRS-G, Cumulative Illness Rating Scale-Geriatric; OARS, Older Americans Resources and Services Multidimensional Functional Assessment Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; TD, tremor dominant; PIGD, postural instability and gait difficulty dominant; FSS, Fatigue Severity Scale, VAS, Visual Analog Scale; IPAQ, International Physical Activity Questionnaire; BSI-18, Brief Symptom Inventory-18; RS-15, Resilience Scale 15; PROMIS, Patient Reported Outcomes Measurement Information System, SAS, Social Activities Scale

Additional time variables used in the analysis, besides diagnosis date (the independent variable of interest for this Aim), also merit brief discussion. Symptom onset and levodopa start years were recorded. These were based on self-reported information; however, prescription data was used to corroborate or impute levodopa start years. This imputation will be discussed in the data cleaning section. Throughout the methods and results, there are two other important dates—first visit to the Center ("first visit") and initial PD visit to the Center ("initial PD visit") that will be referenced. The first visit refers to the first time the patient was seen at the Center, irrespective of PD diagnosis. Initial PD visit is the first time the patient was seen at the Center with a PD diagnosis. For the majority of patients, these two dates were the same. However, some patients undergo further longitudinal follow-up, treatment, and other parkinsonism rule-out prior to receiving a PD diagnosis by one of the Center's specialists.

Analysis

All data cleaning and analysis was conducted using SAS v9.4 (Cary, NC).

Data Cleaning

Extensive data cleaning was undertaken prior to analysis. Cleaning consisted of logic and range checks of all pertinent variables. Implausible and incongruent variable entries were investigated and corrected if deemed erroneous or deemed data entry errors. For example, some visit dates were corrected due to number transpositions; meanwhile, some levodopa start years were corrected as they were listed as occurring after the year levodopa was first indicated on the patient's medications list. The Center's research staff assisted with this process, which included some chart reviews.

Missing data patterns and frequency were also assessed. Medical chart reviews were used to correct missing data for key variables, including: diagnosis year, symptom onset year, levodopa start year, zip code, deep brain stimulation (DBS) year for those who were known to have undergone DBS surgery, and death date for those who were known to have died.

Despite data cleaning efforts, some missing data remained. Reasons for missing data could be due to, but not limited to, the following reasons: a piece of information was not recorded in the patient chart, a patient did not complete a questionnaire at a given visit, a questionnaire was not administered at a given visit, a patient completed only part of a questionnaire, a patient refused to answer a specific question or complete a questionnaire, or a patient's response was illegible.

Various imputation techniques were used to address remaining missing data issues. Per standard operating procedure for the HOME study, when 75% of the Apathy Evaluation Scale (AES) items, OARS items, or Resilience Scale (RS-15) items were complete, total scores were imputed based on weighting the summary score of the completed proportion of items. Levodopa start year was also imputed for individuals who transitioned from not taking levodopa at their first visit to taking levodopa at a subsequent visit, per their medication list. The levodopa start year was assumed to be the year of the visit where this transition occurred. Common markers of socioeconomic status (SES) include income and education (131). However, these two items were missing for a large proportion of patients. Although there are limitations to using area-level markers of SES as a proxy for individual SES (132), this approach was used due to feasibility. Due to the high availability of zip codes for patients, zip code-level median

household income was used as a proxy for SES for patients. Median household income estimates (in 2015 inflation-adjusted dollars) by zip code from the United States Census Bureau, 2011-2015 American Community Survey were used to populate SES (133). Although income may be variable over time (131), median income was determined only by initial zip codes reported. If symptom and levodopa start dates were available, they were leveraged to impute missing diagnosis dates. Imputation algorithms were determined using several steps. For those with available date information, the time between symptom date and diagnosis date was calculated as well as the time between diagnosis date and levodopa start date. Those with symptom dates after diagnosis or levodopa start dates prior to symptoms were excluded from the timing calculation. Due to the variability, medians, rather than averages, were obtained. Sex differences in timing may be possible due to delays in care (96) and levodopa treatment may begin later in those under 60 years of age, who are sometimes treated with dopamine agonists prior to levodopa (134). Consequently, differences in medians for the intervals by sex and age at first visit (<60 versus ≥60 years of age) were compared with Wilcoxon rank-sum tests. There were no differences in any interval by sex; however, there was a significant difference by age at first visit for the interval between diagnosis date and levodopa start date. The following imputation algorithms were used for those missing diagnosis date information:

- <60 years of age at first visit
    - Diagnosis Date = Symptom Date + 1 Year
    - Diagnosis Date (if symptom date missing) = Levodopa Start Date – 1 Year
- ≥60 years of age at first visit

- Diagnosis Date = Symptom Date + 1 Year
- Diagnosis Date (if symptom date missing) = Levodopa Start Date

As noted in Table 2, some of the variables were treated as time invariant while others were treated as time varying. For time invariant variables, the value from the first visit with a non-missing observation was used. For all time varying variables, except the outcomes of interest, last observation carried forward was used to impute missing information at subsequent visits with missing data.

The method of assessing cognition in the parent study switched from the MMSE to the MoCA at the end of 2009. An algorithm for converting MoCA scores to MMSE scores specifically in PD patients was developed by van Steenoven et al. (2014) (135). To prevent missing cognition data due to the transition from the MMSE to the MoCA at the end of 2009, all MoCA scores were converted to MMSE scores (135). The MoCA is preferred in PD and is more sensitive to mild cognitive impairment than the MMSE (12, 30); however, conversion from the MMSE to the MoCA is not feasible since the MMSE does not overlap with the higher scores on the MoCA.

Data Exploration

Once data cleaning was complete, the distributions of all variables from Table 2 were examined to determine if any continuous variables were non-normally distributed or skewed as well as if any ordinal or nominal variables needed to be collapsed due to sparsity of data in any categories. Some categorical variables were collapsed due to sparsity and other variables were dropped completely due to limited data availability.

Highly skewed variables included complications of treatment, pain, and MMSE scores. Variables that underwent re-categorization included clinician (male versus

female), falls, education, marital status, race/ethnicity, and residence. All subsequent tables will present these variables re-categorized. Although age at visit was time-varying, static age was calculated at diagnosis. Age at diagnosis was also categorized (<50, 50-<70, 70+) based on the groupings used by Mehanna et al. (2014) (136).

Due to sparseness or lack of assessment over the entire study period, variables that were dropped from all subsequent analysis included apathy, body mass index, employment status, fatigue, fear of falling, income, physical activity, resilience, and social activities. In 2014, the Center began using PROMIS®, instead of the Stanford Self-Efficacy for Managing Chronic Disease 6-Item Scale, to assess self-efficacy. Because the Stanford Self-Efficacy Scale was used for the majority of the parent study period, only data from the Stanford Self-Efficacy Scale was used as a crosswalk between the two questionnaires does not yet exist.

Descriptive Analysis

Once data cleaning and exploration was complete, descriptive analysis was conducted. The distribution and spacing of visits to the Center were assessed. Univariate analysis was completed for all sociodemographic, clinical, treatment, and outcome variables. Univariate analysis was conducted at two time points—at diagnosis and at initial PD visit. Because information at diagnosis is only available for those diagnosed at the Center, running univariate analysis at initial PD visit provided descriptive characteristics for the full sample.

Means and standard deviations were calculated for all continuous outcomes. Counts and proportions were calculated for all nominal and ordinal outcomes adhering to any modification in categorizations based on sparsity. Medians and interquartile ranges

(IQRs) were also calculated for variables that were identified as being highly skewed during the data exploration step. Because it is an ordinal variable, medians and IQRs were also obtained for Hoehn & Yahr stage.

Aim 1.1

For Aim 1.1, impairment progression was assessed for eligible subjects using UPDRS motor sub-scale scores. Progression was assumed to be non-constant over time. To determine the optimum regression models to capture progression, multiple exploratory analysis steps were undertaken. First, spaghetti plots were constructed to visualize general disease progression patterns by time since diagnosis. Appendix A provides an example spaghetti plot for UPDRS motor scores. Second, local regression (PROC LOESS) scatterplot smoothing was used to explore the smoothed, functional form of progression (137). Results from this exploratory analysis were used to inform progression regression models. Appendix B demonstrates the results of PROC LOESS smoothing for UPDRS motor scores.

Because repeated visits to the Center did not occur at uniform, distinct time points, linear mixed effects models (PROC MIXED) were used to examine the rate of disease progression across the entire study sample while accounting for within-subject correlation (138). These models handle missing data well and allow for the incorporation of intra-individual and inter-individual heterogeneity via random effects (58, 138).

Regression splines were used to describe disease progression within PROC MIXED. Splines allowed disease progression to be modeled as non-constant over time (138). Splines were restricted to first-order polynomials (linear) to create piecewise linear models. Restricting to first-order polynomials allowed for ease of interpretation.

Furthermore, past studies suggest discrete time periods of progression (68). Higher order polynomials (e.g., quadratic splines) were deemed inappropriate based on exploratory analysis.

Other models can be used to capture non-linear disease progression. Fractional polynomials have been used to model non-linear disease progression for conditions such as multiple sclerosis (73). Fractional polynomials allow for parsimony and flexible smoothing without defining knots (73, 139). Researchers have also incorporated random intercepts and slopes into these models (73). Latent curve analysis is an additional modeling choice to examine non-linear disease progression (73). However, the decision was made to use piecewise linear models for this study due to parsimony and ease of interpretation, particularly in a clinical setting (138).

One limitation of spline models is that knots need to be defined by the researcher based on subject matter expertise (138). Consequently, several steps were used to determine knot placement. Model building in PROC MIXED began with creating knots at one year intervals of follow-up. This interval was chosen as it was, based on preliminary analysis, the smallest interval available that resulted in relatively stable estimates. A random intercept was added to the model to account for heterogeneity in disease severity score at diagnosis. Although the intention was to add random slopes at this stage to account for inter-individual differences in progression, the addition of random slopes at this stage overcomplicated the covariance structure of the models (138).

An unstructured correlation structure was used for the random effects for all repeated measures models. An unstructured correlation structure for the random effects

was chosen as it allows for exploration of the differences in the variance of progression over time.

Initially, hypothesis tests of differences in one-year spline slopes for sequential years were conducted with contrast statements. Splines were collapsed and new knot intervals with unequal spacing were created based on hypothesis testing results. However, the resultant knot placements were not clinically meaningful or resulted in one year spline intervals. Using a $p \leq 0.10$ cut-off, knots would have been placed at 1, 8, 9, and 14 years for UPDRS motor models; 14 and 15 years for S&E models; 1, 9, 10, 15, 16, and 17 years for OARS ADLs models; 9 and 10 years for OARS IADLs models; 5 and 6 years for SF-12 MH models, and 1 year for SF-12 PH models.

As a result, models were constructed with varying uniform knot placement intervals (one year, two year, three year, four year, and five year intervals) with a final knot, due to sparsity of data late in the disease course, around 20 years. The resultant progression slopes were plotted and compared across the varying intervals (Appendix C). The final model selected was the piecewise, linear spline model with five year, uniform knot placement intervals. This model was deemed the most appropriate for several reasons. First, the five year models demonstrated parsimony with a minimal loss of progression complexity and non-linearity. By simplifying the model, it prevented extensive convergence issues once random slope terms were added in subsequent steps. Additionally, smoothing in later years over a longer time frame created stability when data was more sparse.

Once the knot spacing interval of five years was selected, random slope terms were added to the model. Due to the complicated nature of random intercept and slope

models with respect to the covariance structure of random effects, there were issues with model convergence (138). Several workarounds were available to address this issue. Options included specifying starting values for parameters, increasing the number of iterations that the SAS algorithm used, relaxing the criteria for convergence, and running the analysis in a different software package such as R. Maximum likelihood estimation is used for analysis of linear mixed models (138). Within SAS, penalized quasi-likelihood and (PQL) and marginal quasi-likelihood (MQL) can be used as more efficient computational methods in PROC GLIMMIX when models have many random effects (138). PQL and MQL can potentially increase efficiency; however, these models come with drawbacks, especially with respect to handling missing data (138). In the case of convergence and memory problems, for this analysis, the HPMIXED procedure in SAS (PROC HPMIXED) was the chosen solution. PROC HPMIXED efficiently runs linear mixed effects models on large samples with many fixed and random effects (140).

Fixed and random effects were generated from PROC HPMIXED model output. These estimates determined the population mean rate of disease progression over various time intervals, defined by knots, as well as heterogeneity, as measured by between subject variance, at diagnosis and various time intervals. The analysis was unadjusted for covariates as this aim was purely to determine the functional form of progression for use in future aims. Furthermore, this study aimed to capture disease progression in the context of clinical care, irrespective of treatment regimen or other factors. However, as noted in the early progression modeling, some instability was present when smaller spline units were operationalized. Additionally, patient improvements were seen at varying time points. As this may be the result of entrance into specialty care at the Center, a term

for the first year of clinical care at the Center was entered into the model as a fixed effect. At a patient's first visit to the Center, this term took the value of zero. If that same patient returned to the clinic at 6 months and 1 year, this term took the value of 0.5 and 1, respectively. Subsequently, this term was given the value of 1 at all subsequent visits. For a patient diagnosed after 6 months of clinical care at the Center, that individual, at diagnosis, would have a value of 0.5 for the first year of clinical care term. Including a term for the first two years under clinical care at the Center, in lieu of the one year term, was explored. However, the magnitude of the beta estimate was greatly attenuated and was dropped in favor of the one year term.

The final model used to calculate disease progression and heterogeneity was as follows:

$$Y_{ij} = Bo + bo_i + B1(spline0to5_{ij}) + b1_i(spline0to5_{ij}) + B2(spline5to10_{ij}) + b2_i(spline5to10_{ij}) + B3(spline10to15_{ij}) + b3_i(spline10to15_{ij}) + B4(spline15to20_{ij}) + b4_i(spline15to20_{ij}) + B5(spline20+_{ij}) + b5_i(spline20+_{ij}) + B6(timefirstyearinclinic_{ij}) + \varepsilon_{ij}$$

Where

- Y = value of the outcome
- i = person i
- j = occasion j
- B = coefficient for fixed effects
- b = coefficient for random effects
- ε_i = the residual of each observation around its expected value, conditional on the random effects

- $b_i \sim MVN(0, \sum)$ where $\sum$ is the variance/covariance matrix of random intercepts and slopes
- $\varepsilon_{ij} \sim$ independent $N(0, \sigma_e^2)$
- $b_i \coprod \varepsilon_i$

Aim 1.2

The analytic techniques from Aim 1.1 were repeated for Aim 1.2. However, disease progression was examined with disability captured by the OARS ADLs sub-section score, the OARS IADLs sub-section score, and the S&E score. Following the same analysis plan, five-year piecewise linear spline models were deemed the most appropriate for all disability outcomes (Appendices D, E, and F) and an identical model parameterization was used.

Aim 1.3

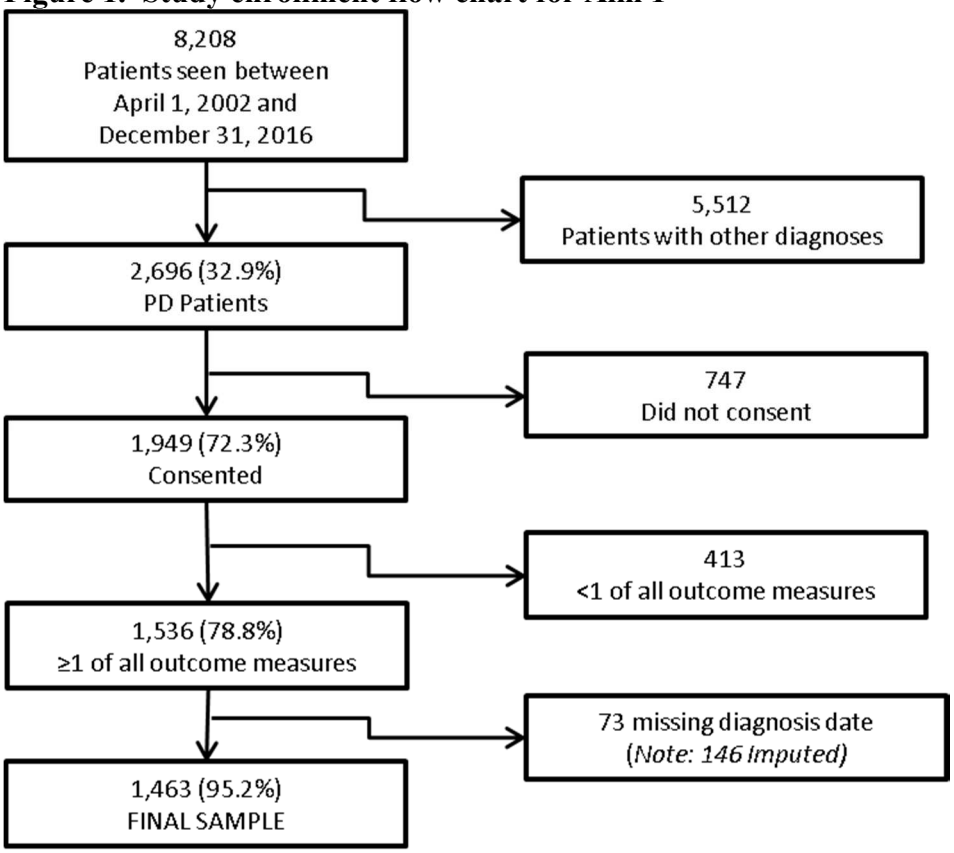
The analytic techniques from Aim 1.1 were repeated for Aim 1.3. However, disease progression was examined with health-related quality of life captured by both the SF12-MH and SF12-PH scale scores. Following the same analysis plan, five-year piecewise linear spline models were deemed the most appropriate for all health-related quality of life outcomes (Appendices G and H) and an identical model parameterization was used.

Sample Size and Power

Of all PD patients seen at the clinic (n = 8,208), 72.3% consented to participate in the parent study. Of 1,949 consented, PD patients, 1,463 (75.1%) met all inclusion criteria for Aim 1 of the current study. Figure 2 displays a flow chart of study enrollment. The 486 consented patients that were excluded were slightly older (mean =

68.2, SD = 10.82) than the final sample. Excluded individuals also had a slightly more severe disease stage (mean Hoehn & Yahr Stage = 2.5, SD = 0.97) and were slightly more likely to be male (67.0%)._ No power calculation was done for this Aim as the goal was simply to establish the heterogeneity and functional form of progression; these models were utilized in subsequent aims.

Figure 1. Study enrollment flow chart for Aim 1



Sensitivity Analyses (Aim 1)

For this Aim, several sensitivity analyses were conducted. One a priori concern was that patients with imputed diagnosis dates would be systematically different from their counterparts. To address this issue, bivariate analysis was used to explore if the patients with imputed diagnosis dates differed from those without imputed dates on sociodemographics, clinical characteristics, or treatment at diagnosis or at initial PD visit.

To explore the impact of imputation of diagnosis date on progression and heterogeneity estimates, the final models were run stratifying on those with and without an imputed diagnosis date.

Because patients under the care of specialists have improved outcomes (28), a sensitivity analysis was conducted comparing the progression patterns for those patients initially diagnosed in-clinic (incident cases) to those who sought care at the clinic after diagnosis (prevalent cases) at overlapping follow-up times. To conduct this analysis, the final models were run stratifying on whether a person was an incident or prevalent PD patient in the cohort (case status). The models were restricted to progression patterns from diagnosis to 15 years post-diagnosis, due to the limited follow-up time on patients initially diagnosed in the clinic.

There was additional interest in whether progression patterns differed by two of the described characteristics in Table 2—whether a patient, who was a fluctuator, was on or off at a given visit and whether a proxy was used to complete the questionnaires. These two factors could have resulted in biased outcome assessments and proxy responses have been documented to systematically differ from patients (141). The linear mixed effects models were re-run stratifying on on/off status for fluctuators. For self-reported outcomes, models were re-run stratifying on whether forms were completed entirely by the proxy or not.

Lastly, mortality patterns were explored with univariate analysis. Additionally, a time to event analysis was performed by constructing a Kaplan-Meier curve in SAS using PROC LIFETEST.

D. Aim 2

Selection of Participants

The same sample from Aim 1 was used for Aim 2 analysis. Details of the inclusion and exclusion criteria used can be found under the "Selection of Participants" section under Aim 1 methods.

Variables

Independent

The independent variable for Aim 1 was sex. Sex was captured via the patient medical record. It was treated as a binary variable (female versus male). For all regression models, males were the reference group.

Dependent

Aim 2 utilized the same outcome domains as Aim 1—impairment, disability, and health-related quality of life. Details of questionnaires and assessments used to operationalize each domain are detailed in the "Dependent Variables" section under Aim 1 methods.

Covariates

The same covariates explored in Aim 1 (Table 2) were used for Aim 2. Additional details can be found under the "Covariates" section under Aim 1 methods.

Mediators

From the extensive number of variables available in the dataset, a select number of variables were chosen, a priori, as mediators. The mediators selected included drug side-effects, cognition, comorbidities, psychological distress, age at diagnosis, and falls. These mediators were selected based on the literature and whether interventions are

feasible. Intervention feasibility is determined by whether an intervention could be designed or implemented to modify the mediator. For example, females are known to be less likely to have spousal caregivers, and individuals without spousal caregivers typically have more negative health outcomes (34). Consequently, marital status may be an important mediator of the relationship between sex and disease outcomes; however, this factor cannot be realistically targeted with an intervention and thus will not be assessed as a key mediator. Details of how each mediator was assessed is detailed in Table 2. A brief overview of the justification for the selection of each mediator is below, including the relationship between sex, the mediator, and PD outcomes.

Drug side-effects

The pharmacokinetics of levodopa are different between males and females (88). Female PD patients are more likely to develop dopaminergic drug side-effects, namely dyskinesias (13, 33, 90). Additionally, dyskinesias are associated with significantly worse health-related quality of life and depression (22). Improved medication management (e.g., appropriate levodopa dosing) and expanded use of dopamine agonists, which are associated with a lower risk of dyskinesias, could be intervention strategies to manage drug side-effects (90). Dopaminergic medication itself was not considered a mediator as evidence suggests that dopaminergic medication prescribing patterns are similar between males and females (87). Additionally, dopaminergic medication may be subject to confounding by severity.

Cognition

Several studies suggest that there is a sex difference, among Parkinson disease patients, in cognition and cognitive decline (33, 100, 101, 142, 143). Cognition is

associated with health-related quality of life in PD (143, 144). There are some medication options to manage dementia in PD patients, such as rivastigmine (14). Cognition was assessed with MMSE scores, including those who had their MoCA scores converted to MMSE scores, as discussed previously in the methods section.

Comorbidities

In the general population and PD patients there are sex differences in comorbidity profiles (145, 146). Additionally, comorbidities are known to predict health outcomes, particularly health-related quality of life, in PD (144). Lifestyle changes can reduce comorbidity risk and improve management.

Psychological distress

Female PD patients are more likely to experience psychological distress, particularly depression (34, 98, 101, 146). Depression without dementia in PD patients is associated with both female sex and disease severity (15). Psychological adjustment is incredibly important for health-related quality of life in PD (147) and depression is a key predictor of health-related quality of life (143). Treatments are available to PD patients, particularly for managing depression (14). There is some concern that disease symptoms can impact the evaluation of some psychological distress factors in PD (30). However, our prior study using HOME study data found that the original factor structure of the BSI-18 holds in PD patients (148).

Disease Duration at Care Milestones

There is evidence to suggest that females may experience delayed referral to PD specialists after diagnosis, and this delay could be related to physician perceptions (96). Referral delays could impact clinical treatment and thus outcomes (96). Interventions to

improve physician awareness of PD in females could prevent detrimental delays in care (38).

Falls

Females and males have differing presentations of PD with females more likely to present with the TD subtype, which is associated with improved outcomes (6, 45, 77, 79, 93). Patients with the TD subtype are less likely to experience frequent falls than those with the PIGD subtype (149). Consequently, males may be at a greater risk of falls in PD. However, one meta analysis suggests no sex difference in falls risk (150). Falls are associated with poor health outcomes in PD (151, 152). Several interventions exist to reduce falls in PD patients (153).

Self-efficacy for managing chronic conditions

The definition of self-efficacy for managing chronic conditions is, "an individual's confidence in his/her ability to successfully perform specific tasks or behaviors related to one's health in a variety of situations" (154). Individuals who are confident and knowledgeable about chronic condition management should have improved outcomes (155). The Chronic Disease Self-Management Program is an intervention that is appropriate across all chronic conditions that specifically targets self-efficacy (155). Evidence in diabetes patients suggests that self-efficacy differs between males and females (156). One limitation of using this mediator is that the instrument used in the HOME study has a modified likert scale, compared to the original Stanford Self-Efficacy Scale (127, 128). Additionally, data on self-efficacy may be more limited as the assessment instrument was recently changed to a PROMIS® instrument (129).

Analysis

Aim 2.1

Differences between males and females for all covariates and outcome measures were examined at both diagnosis and initial PD visits. Differences in covariates and outcome measures were captured with Chi-square tests for categorical variables and t-tests with Satterthwaite approximations for continuous variables. Alternatively, if the categorical variable had small cell sizes, Fisher's exact tests were used; if the continuous variable had a non-normal distribution, the Wilcoxon signed-rank tests with a t-test approximation were used. To examine care delays, differences in the time from symptom onset to diagnosis, diagnosis to first visit to the Center, diagnosis to initial PD visit at the Center, diagnosis to levodopa initiation, and diagnosis to DBS treatment were compared by sex using t-tests and Wilcoxon signed-rank tests with a t-test approximations.

Aim 2.2

Using the progression models developed in Aim 1, sex was introduced into the mixed effects models with five-year splines to determine the effect of sex on presentation at diagnosis and disease progression. A sex term was entered in the model to determine if there was a main effect of sex. If a main effect of sex was found, it would suggest that males or females had consistently higher disease severity, beginning at diagnosis. Second, sex-time interaction terms were added for each spline interval to determine if there were any differences between males and females in the change in disease severity over a given time interval. Additionally, sex-specific terms for the first year of care at the clinic were added to the models. These terms accounted for the potential differential benefit of initial care at the Center.

Differences in the variance/covariance structure by sex was also examined to determine if there was more inter-individual variation in presentation or progression for males or females with likelihood ratio Chi-square testing of nested models. The full random effects model was compared to a model that assumed the same slope random effects for males and females. This approach was repeated with separate models for all six outcomes—UPDRS Motor scores, OARS ADLs scores, OARS IADLs scores, Schwab & England scores, SF-12 MH scores, and SF-12 PH scores.

It is important to adjust for appropriate confounders in prognostic studies (78). However, all analyses was unadjusted for confounders. In order to be a confounder, a variable must be a common cause of both the independent variable (exposure) and the dependent variable (outcome) (157). As sex is determined at birth, no variables can occur before the independent variable of interest in this aim, so sex and disease severity are already d-separated (157). Thus, including any covariates in the models would constitute adjustment for factors on the causal pathway between sex and outcomes.

The final model used to calculate sex differences in disease presentation, progression, and heterogeneity was as follows:

$$Y_{ij} = B0\_male_i + b0\_male_i + B1\_female_i + b1\_female_i + B2(male\_spline0to5_{ij}) + b2_i(male\_spline0to5_{ij}) + B3(fmale\_spline0to5_{ij}) + b3_i(fmale\_spline0to5_{ij}) + B4(male\_spline5to10_{ij}) + b4_i(male\_spline5to10_{ij}) + B5(female\_spline5to10_{ij}) + b5_i(female\_spline5to10_{ij}) + B6(male\_spline10to15_{ij}) + b6_i(male\_spline10to15_{ij}) + B7(female\_spline10to15_{ij}) + b7_i(female\_spline10to15_{ij}) + B8(male\_spline15to20_{ij}) + b8_i(male\_spline15to20_{ij}) + B9(female\_spline15to20_{ij}) + b9_i(female\_spline15to20_{ij}) + B10(male\_spline20+_{ij}) + b10_i(male\_spline20+_{ij}) + B11(female\_spline20+_{ij}) +$$

$b11_i(female\_spline20+_{ij}) + B12(male\_timefirstyearinclinic_{ij}) +$

$B13(female\_timefirstyearinclinic_{ij}) + \varepsilon_{ij}$

Where

- Y = value of the outcome
- i = person i
- j = occasion j
- B = coefficient for fixed effects
- b = coefficient for random effects
- ε_i = the residual of each observation around its expected value, conditional on the random effects
- $b_i \sim MVN(0, \sum)$ where $\sum$ is a different variance/covariance matrix of random intercepts and slopes for males and females
- $\varepsilon_{ij} \sim$ independent $N(0, \sigma_e^2)$
- $b_i \coprod \varepsilon_i$

Aim 2.3

Several factors potentially lie on the causal pathway between sex and all outcome measures. For this aim, a mediation analysis was conducted to determine whether sex differences in disease presentation and progression, if any, persisted after intervening on various potential mediators. Based on the results from Aim 2.1 and 2.2, there were no substantial differences in disease progression by sex. However, sex differences in presentation were seen in self-reported outcomes at initial PD visits to the Center. Initial PD visits to the Center are an opportune time for patient interventions.

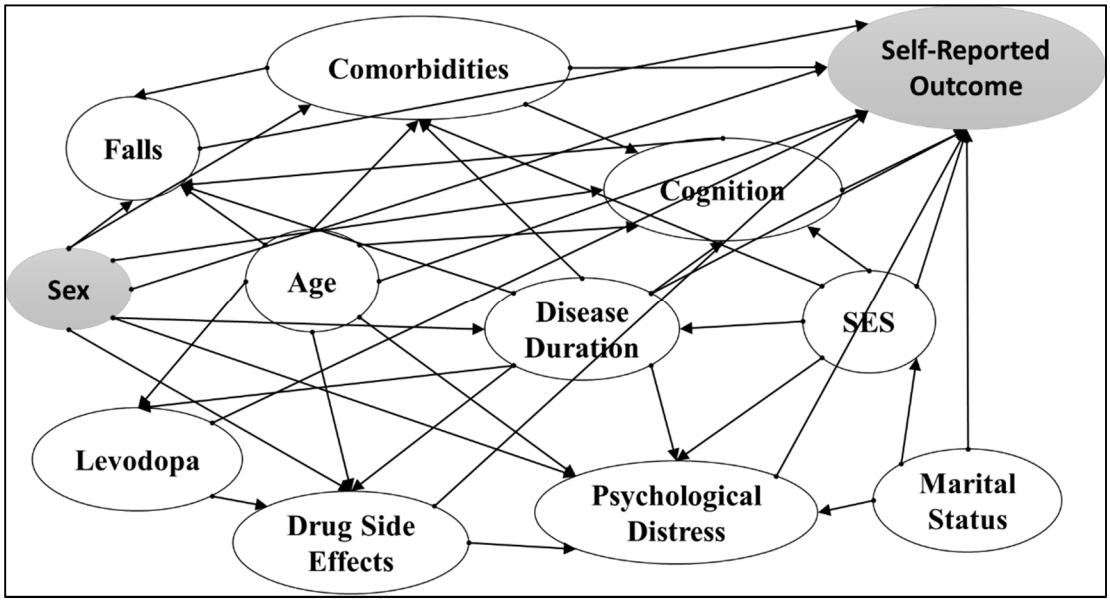
Based on these findings and logic, a mediation analysis was conducted focusing on the impact of intervening on mediators on sex differences in self-reported outcomes at initial PD visits to the Center. Prior to conducting the mediation analysis, linear regression models were constructed with PROC GLM characterizing the association between sex and all four self-reported outcomes. Males were treated as the reference group.

The assumed relationships between the independent variable (sex), the various mediators (comorbidities, falls, cognition, disease duration at initial PD visit to the Center, drug side effects, and psychological distress), dependent variables, and potential mediator-outcome confounders (age at initial PD visit to the Center, SES, and marital status) are detailed in the Directed Acyclic Graph (DAG) in Figure 2. Despite a priori selection, due to data sparsity at initial PD visits, self-efficacy was no longer considered as a mediator for this analysis. The relationships in the DAG were populated based on the previous section that discussed the a priori selection of mediators. Additional relationships were based on prior literature.

Age impacts levodopa use (134), motor complications (13), comorbidities (including mental health comorbidities and dementia) (158), and outcomes (79). Prior literature in PD suggests that age is not a risk factor for falls (150). However, age was included as a confounder of the relationships between falls and outcomes due to the association between age and falls in the general population. Disease duration at initial PD visit to the Center influences an individual's comorbidities (including health mental comorbidities and dementia) (158), falls risk (151, 152), side effects (13), and levodopa usage (13). SES, as measured by median household income of one's zip code, impacts

comorbidities (including mental health comorbidities) (159) and cognition (160). Lower SES may also have an impact on care seeking behavior (161), which could lead to delayed care and poorer outcomes (96). Comorbidities impact cognition (162) and falls (152). Lastly, marital status plays a role in SES, psychological well-being, and general health (163). The covariates displayed in the DAG stem from questionnaires that utilize various time reference stems (e.g., past four weeks, past 7 days, current) (Table 2). The difference in stems results in some ambiguity in temporality; however, the DAG displays the assumed temporal relationships based on the literature.

Figure 2. DAG showing the relationship between the independent, or exposure, variable (sex), any given self-reported outcome, mediators, and mediator-outcome confounders



Abbreviations: SES, Socioeconomic Status

A mediation analysis was conducted using the approach and SAS Macro detailed in Valeri & VanderWeele (2013) (164). This approach is a causal inference extension of the product method detailed in Baron & Kenny (1986) (164, 165). Specifically, the approach operationalizes mediation from a counterfactual framework, allows for independent variable-mediator variable interaction, and is flexible to all variables types

(i.e., continuous, dichotomous) (164). This approach was used to elucidate controlled direct effects (CDE). A CDE is defined as the effect of the independent variable, or exposure, seen if the population had the mediator been set to, or controlled to, the same value for all individuals (164, 166). A CDE exists for each possible mediator value. For this study, controlled direct effects explored the effect of sex on various outcomes after individually intervening and setting mediators to certain values. For example, the effect of sex on disability setting psychological distress on the BSI-18 to the T-score for the general population.

As all outcomes and mediators for this analysis were continuous, the equations utilized by the SAS Macro, accounting for independent variable (exposure)-mediator interaction, are detailed below (164). Standard errors were obtained from the delta method further described by Valeri & Vanderweele (2013) (164).

1) $E(M|A=a,C=c) = \beta_0 + \beta_1 a + \beta'_2 c$
2) $E(Y|A=a,M=m,C=c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a*m + \theta'_4 c$
3) Controlled Direct Effect = $E[Y_{am}-Y_{a*m}|C=c] \rightarrow$
4) $= \theta_1(a-a*) + \theta_3 m(a-a*)$

Where:

E = Expected Value

Y = Self-Reported Outcome Value at First Visit

A = Independent Variable or Exposure (Sex); a=female, a*=male

M = Mediator

C = Confounders

There are several assumptions that need to be met in order to calculate controlled direct effects. First, there must be no unmeasured independent variable (exposure)-outcome confounders, and second, there must be no unmeasured mediator-outcome confounders (106, 164, 166). For this study, only the latter was a concern. Based on the DAG in Figure 2, the minimally sufficient control set for each mediator is described in Table 3 along with the respective value the mediator was set to in order to calculate controlled direct effects.

Table 3. List of mediators, set mediator levels, and minimally sufficient adjustment set for the mediator-outcome relationship to be unconfounded

Mediator	Set Mediator Level	Confounders[a]
Drug Side-Effects	Score = 0 (No Side Effects)	Age, levodopa, disease duration
Cognition	MMSE Score = 30	Age, disease duration, comorbidities, SES[b]
Comorbidities	One Comorbidity	Age, disease duration, SES[b]
Psychological Distress Depression Anxiety Somatization	 T-Score = 50 T-Score = 50 T-Score = 50 T-Score = 40 T-Score = 40 T-Score = 40	Age, drug side effects, disease duration, marital status, SES
Disease Duration at First Visit to Center	1 year	SES[b]
Falls	Score = 0 (No Falls)	Age, disease duration, comorbidities

Abbreviations: MMSE, Mini-Mental State Examination; SES, socioeconomic status
[a]SES was captured with median household income by zip code
[b]All confounders were treated as continuous except levodopa (yes or no) and marital status (married vs. not married), which were treated as binary

Sample Size and Power

There were 1,463 PD patients that met Aim 1 and Aim 2 study inclusion criteria (Figure 1). Of those 1,463 patients, 914 were males and 549 were females.

Power calculations were based on those for a longitudinal study of change. These calculations were conducted for the primary outcome of interest, UPDRS motor scores. The power calculation was based on the final sample (914 males and 549 females). The following equation was used to calculate the variance of the difference between males and females:

$$Var(\hat{Diff}) = \frac{1}{N_M}\left(\frac{\sigma_e^2}{\sum_{Males}(t_{ij}-\bar{t}_i)^2} + \sigma_b^2\right) + \frac{1}{N_F}\left(\frac{\sigma_e^2}{\sum_{Females}(t_{ij}-\bar{t}_i)^2} + \sigma_b^2\right)$$

In the equation, σ_b represents the inter-individual standard deviation in mean change per year in UPDRS motor scores and σ_e represents the intra-individual standard deviation in UPDRS motor score for males and females. Different combinations of σ_b and σ_e values were input into the equation. Examination of prior studies suggests that the inter-individual standard deviation in mean change per year in UPDRS motor scores is greater than the intra-individual standard deviation in motor score (64, 167). Additionally, based on medians obtained from descriptive analysis, it was assumed that patients had an average of seven observations over 7.9 years of follow-up with equal spacing in between all visits.

The variance of the difference was then substituted into the following equation to solve for the detectable effect size ($\theta_M - \theta_F$) associated with 80% power (standard normal random variable=0.84).

$$\Pr\left(Standard\ \ Normal\ \ RV > 1.96 - \frac{\theta_M - \theta_F}{SE(\hat{\theta})}\right)$$

If the standard deviations in the actual data were similar to those in Table 4, this study had 80% power to detect a sex difference in slope of the UPDRS motor score of

0.061 to 0.303 points per year. Assuming a constant, linear trend and a linear mixed model, a prior study found an overall average progression rate of 0.65 points per year (58). At any given time point, a clinically meaningful UPDRS motor score difference is 2.5 points (168).

Table 4. Detectable effect size associated with 80% power and various σ_b and σ_e values

N_M	N_F	Power	σ_b	σ_e	Effect Size
914	549	80%	5.0	0.5	0.302
914	549	80%	4.0	0.5	0.242
914	549	80%	3.0	0.5	0.181
914	549	80%	2.0	0.5	0.121
914	549	80%	1.0	0.5	0.061
914	549	80%	5.0	1.0	0.302
914	549	80%	4.0	1.0	0.242
914	549	80%	3.0	1.0	0.182
914	549	80%	2.0	1.0	0.121
914	549	80%	1.0	1.0	0.061
914	549	80%	5.0	1.5	0.303
914	549	80%	4.0	1.5	0.242
914	549	80%	3.0	1.5	0.182
914	549	80%	2.0	1.5	0.122
914	549	80%	1.0	1.5	0.062
914	549	80%	5.0	2.0	0.303
914	549	80%	4.0	2.0	0.242
914	549	80%	3.0	2.0	0.182
914	549	80%	2.0	2.0	0.122
914	549	80%	1.0	2.0	0.063
914	549	80%	5.0	2.5	0.303
914	549	80%	4.0	2.5	0.243
914	549	80%	3.0	2.5	0.183
914	549	80%	2.0	2.5	0.123
914	549	80%	1.0	2.5	0.064
914	549	80%	5.0	3.0	0.303
914	549	80%	4.0	3.0	0.243
914	549	80%	3.0	3.0	0.183
914	549	80%	2.0	3.0	0.124
914	549	80%	1.0	3.0	0.066

Sensitivity Analyses (Aim 2)

Examining the timing of care milestones including those with imputed diagnoses dates could bias intervals towards the null. Consequently, the timing of care milestones were re-run excluding those with imputed diagnosis dates. Sex differences in mortality were examined with Kaplan-Meier curves.

E. Aim 3

Selection of Participants

The same inclusion and exclusion criteria for Aim 1 and Aim 2 were used for Aim 3 (see Aim 1 "Selection of Participants") with additional restrictions. Aim 3 was limited to females who were post-menopausal at their first visit to the clinic, irrespective of PD diagnosis. Many of the reproductive health characteristics of interest (e.g., menopause type and HRT use) are not relevant to pre-menopausal females. Menopause status was obtained from the reproductive health section of the patient intake questionnaire. For 56 females with unknown or pre-menopausal menopause status, menopause status was imputed or amended to post-menopausal based on two factors:

1) If the patient indicated she had had an oopherectomy, she was assumed to be post-menopausal (n = 2). As females could not indicate whether they had a unilateral or bilateral oopherectomy, all oophorectomies were assumed to be bilateral.
2) If the patient was >62 years of age at their initial PD visit, the individual was assumed to be post-menopausal (n = 52). The average age of natural menopause is between 47.3 to 50.5 years of age (169-171). Studies in the United States suggest that almost 100% of females will undergo natural

menopause by the age of 58 or 59 (169, 171). There is evidence that the age of menopause has increased over time (171). Consequently, the conservative age of 62 was selected for the sake of specificity—it would be statistically highly unlikely for an individual to be pre-menopausal after the age of 62.

The HOME study did not capture if a pre-menopausal female later undergoes menopause. Consequently, this Aim was limited to those individuals who were post-menopausal at their first visit to the Center.

Variables

Independent

Reproductive health characteristics. At intake, female patients completed the reproductive health section of the patient intake questionnaire. This questionnaire asked about the patient's menopausal status, pregnancy status, birth control use, estrogen replacement therapy use (current and history), and oopherectomy status. All patients (male and female) were asked to indicate the number of children they have. Several of these characteristics were used as proxies for both endogeneous and exogeneous estrogen exposure.

Menopause type. Menopause type was treated as a binary variable (natural versus surgical menopause). On the reproductive health section of the patient intake questionnaire, females who reported being post-menopausal were asked to report if they had ever taken estrogen therapy, and if they had had their ovaries surgically removed. Females who reported being post-menopausal and <u>had not</u> had their ovaries removed were classified as having natural menopause while those who were post menopausal and <u>have</u> had their ovaries removed were classified as having surgical menopause.

Menopause type is a proxy for endogeneous estrogen exposure with patients undergoing surgical menopause experiencing abrupt drops in endogeneous estrogen exposure. Although age of surgical menopause was not available in the database, the earlier in life an individual undergoes surgical menopause, the larger the decrease in cumulative endogeneous estrogen exposure (47).

Parity. Parity was treated as a binary variable (parous versus nulliparous) based on the number of children the patient indicated they had on the intake questionnaire. Parity was a proxy for endogenous estrogen exposure with more children indicative of greater endogenous estrogen exposure. The inability of post-menopausal females to have biological children ensures that parity was not time-varying in this sample.

Hormone replacement therapy (HRT). Postmenopausal females were asked if they were currently taking estrogen replacement therapy and if they ever had taken estrogen replacement therapy. Consequently, HRT was treated as a binary variable (current versus ever/never). HRT was a proxy for exogeneous estrogen exposure with patients reporting current or ever HRT having higher exogeneous estrogen exposure than those never receiving HRT. HRT use could also be time-varying; however, patients were only asked about HRT at intake. Collapsing ever and never users into one grouping was more reflective of the cross-sectional nature of HRT assessment in the HOME study.

Dependent

Aim 3 utilized the same outcome domains as Aim 1 and Aim 2—impairment, disability, and health-related quality of life. Details of questionnaires and assessments used to operationalize each domain are detailed in the "Dependent Variables" section under Aim 1 methods.

Covariates

The same covariates explored in Aim 1 and Aim 2 (Table 2) were used for Aim 3. Additional details can be found under the "Covariates" section under Aim 1 methods. Two covariates were selected as confounders for Aim 2.2 progression models. Those covariates included year of birth, to control for cohort effects, and median income, to control for SES.

Analysis

Aim 3.1

Differences by menopause type, parity, and HRT use for all covariates and outcome measures were examined at diagnosis and initial PD visit (first visit to the Center with a PD diagnosis) in post-menopausal females. Differences in covariates and outcome measures were captured with Chi-square tests for categorical variables and t-tests for continuous variables. Alternatively, if the categorical variable had small cell sizes, Fisher's exact tests were used. For continuous variables with non-normal distributions, Wilcoxon signed-rank tests with a t-test approximation were used.

Aim 3.2

Using the progression models developed in Aim 1, menopause type (surgical vs. natural) was introduced into the mixed-effects, five-year spline models to determine the effect of menopause type on disease presentation at diagnosis and progression. A menopause type term was entered in the models to determine if females with surgical or natural menopause had consistently worse disease severity across the entire disease course. Menopause type-spline interval interaction terms were also added to determine if

there were any differences by menopause type in change in disease severity over a time interval.

To account for potential differential benefits of initial care at the Center, menopause type-specific terms for the first year of care at the clinic, irrespective of diagnosis, were added to the models. Additionally, models were adjusted for cohort effects by adjusting for year of birth and SES by adjusting for median zip code income. Year of birth and SES were a priori selected because, based on the literature, they may affect reproductive characteristics as well as potentially impact disease progression. For example, cohort effects are seen in parity (increases over time) (171) and higher SES is associated with increased HRT usage (172). To allow for practical interpretation of estimates, the continuous confounders were mean standardized.

An unstructured correlation structure was used for the random effects. Subsequently, differences in the variance/covariance structure by menopause type were also examined to determine if there was more inter-individual variation in presentation or progression for those with surgical or natural menopause. However, convergence issues, particularly for disability outcomes, resulted in random slope terms being dropped and random intercept terms being retained to simplify the models. Consequently, inter-individual variation could only be examined at diagnosis.

The final model used to calculate menopause type differences in disease presentation, progression, and heterogeneity was as follows:

$$Y_{ij} = B0\_surgical_i + b0\_surgical_i + B1\_natural_i + b1\_natural_i +$$
$$B2(surgical\_spline0to5_{ij}) + B3(fsurgical\_spline0to5_{ij}) + B4(surgical\_spline5to10_{ij}) +$$
$$B5(natural\_spline5to10_{ij}) + B6(surgical\_spline10to15_{ij}) + B7(natural\_spline10to15_{ij}) +$$

$B8(surgical\_spline15to20_{ij}) + B9(natural\_spline15to20_{ij}) + B10(surgical\_spline20+_{ij}) + B11(natural\_spline20+_{ij}) + B12(surgical\_timefirstyearinclinic_{ij}) + B13(natural\_timefirstyearinclinic_{ij}) + B14(cohort_{ij}) + B15(SES_{ij}) + \varepsilon_{ij}$

Where

- Y = value of the outcome
- i = person i
- j = occasion j
- B = coefficient for fixed effects
- b = coefficient for random effects
- ε_i = the residual of each observation around its expected value, conditional on the random effects
- $b_i \sim MVN(0, \sum)$ where $\sum$ is a different variance/covariance matrix of random intercepts and slopes for females who underwent natural and surgical menopause
- $\varepsilon_{ij} \sim$ independent $N(0, \sigma_e^2)$
- $b_i \coprod \varepsilon_i$

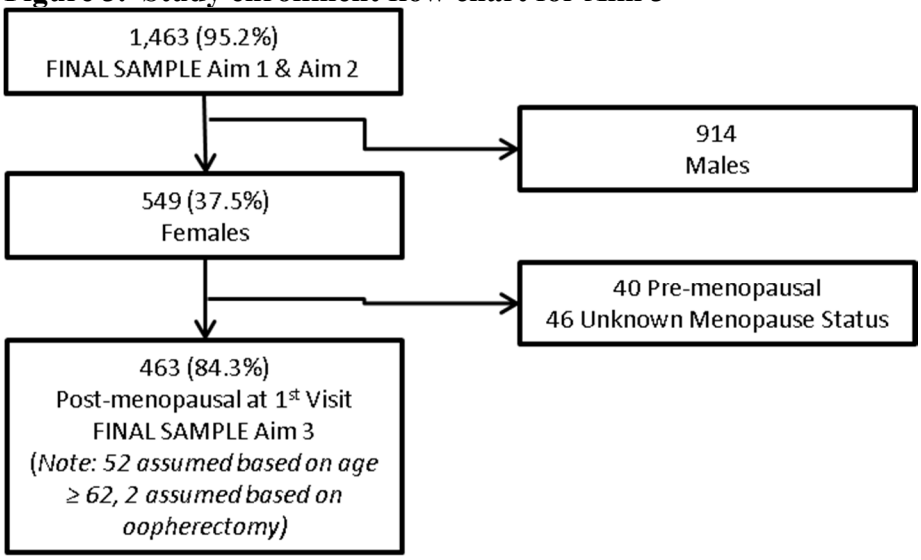
This same process was used to examine separate models for UDPRS motor, OARS ADLs, OARS IADLs, SF-12 MH, and SF-12 PH scores as the designated outcome. The identical approach was repeated to examine parity and HRT as the independent variable, or exposure, of interest.

Sample Size and Power

There were 463 female, post-menopausal PD patients that met study inclusion criteria (Figure 3). Of those, 94 had surgical menopause, 313 had natural menopause, and 56 had unknown menopause type. With respect to HRT, 216 individuals were ever

HRT users (9 current but not past users, 154 past but not current users, and 53 both current and past users), 190 were never HRT users, and 57 had unknown HRT usage. Unknown HRT users were not included in the HRT analysis. The majority of females were parous (n=358) while a small number (n=30) were nulliparous. Seventy-five females had no parity information available and were not included in the parity analysis.

Figure 3. Study enrollment flow chart for Aim 3



Identical to Aim 2, power calculations were based on those for a longitudinal study of change with UPDRS motor scores as the primary outcome of interest. The effect size calculations used the same assumptions as the power calculation for Aim 2 (except for sample size). The effect size for this study was calculated on the reproductive health characteristic with the most complete data—menopause type. Comparing the female patients that underwent surgical menopause (n = 94) to those that underwent natural menopause (n = 313), there was 80% power to detect a menopause type difference in slope of the UPDRS motor score between 0.132 to 0.661 points per year (Table 5).

Table 5. Detectable effect size associated with 80% power and various σ_b and σ_e values

N_{SM}	N_{NM}	Power	σ_b	σ_e	Effect Size
94	313	80%	0.5	5.0	0.659
94	313	80%	0.5	4.0	0.527
94	313	80%	0.5	3.0	0.395
94	313	80%	0.5	2.0	0.264
94	313	80%	0.5	1.0	0.132
94	313	80%	1.0	5.0	0.659
94	313	80%	1.0	4.0	0.527
94	313	80%	1.0	3.0	0.396
94	313	80%	1.0	2.0	0.264
94	313	80%	1.0	1.0	0.133
94	313	80%	1.0	5.0	0.659
94	313	80%	1.5	4.0	0.528
94	313	80%	1.5	3.0	0.396
94	313	80%	1.5	2.0	0.265
94	313	80%	1.5	1.0	0.135
94	313	80%	2.0	5.0	0.660
94	313	80%	2.0	4.0	0.528
94	313	80%	2.0	3.0	0.397
94	313	80%	2.0	2.0	0.266
94	313	80%	2.0	1.0	0.137
94	313	80%	2.5	5.0	0.660
94	313	80%	2.5	4.0	0.529
94	313	80%	2.5	3.0	0.398
94	313	80%	2.5	2.0	0.267
94	313	80%	2.5	1.0	0.140
94	313	80%	3.0	5.0	0.661
94	313	80%	3.0	4.0	0.530
94	313	80%	3.0	3.0	0.399
94	313	80%	3.0	2.0	0.269
94	313	80%	3.0	1.0	0.143

Abbreviations: SM, surgical menopause; NM, natural menopause

Sensitivity Analyses (Aim 3)

Three additional analyses were conducted for this Aim. First, the differences in patient characteristics were compared between those with imputed versus non-imputed menopause status. Second, exogenous estrogen exposure, in the form of HRT, was more common among those that have undergone surgical menopause (47). Because females

who have undergone surgical menopause and taken HRT may have differing outcomes than those who did not take HRT (173), characteristics were examined by menopause type-HRT groups (natural menopause with HRT, natural menopause without HRT, surgical menopause with HRT, and surgical menopause without HRT). HRT impairment progression models were re-run stratifying by menopause type—a potential effect measure modifier or confounder of any association between HRT and progression. Lastly, mortality patterns were examined by each reproductive characteristic (menopause type, HRT, parity) with time to event analysis with Kaplan-Meier curves.

CHAPTER 4. RESULTS

A. Aim 1

Descriptive

A total of 1,463 subjects met study inclusion and exclusion criteria (Figure 1). The description of patient characteristics at diagnosis (those diagnosed at the Center) and at initial PD visit (entire current study cohort) are presented in Table 6. In total, 413 (28.3%) of patients in the total cohort were initially diagnosed at the Center. At initial PD visit, the average time since diagnosis was 4.3 years (SD = 5.16) while the median time since diagnosis was 2.3 years (IQR = 6.67).

The frequency of missing data are also presented in these tables. Missing data was the most common for the Stanford Self-Efficacy Scale. The Stanford Self-Efficacy Scale was not initially collected as part of clinical care and was later replaced with a PROMIS® questionnaire. In total, 143 (9.8%) of patients included in the analysis had their diagnosis date imputed from symptom onset or levodopa start date information. Based on the imputation algorithm, it was surmised that 34 of those patients with imputed diagnosis dates were initially diagnosed at the Center.

The average patient age at initial PD visit was 64.9 years (SD = 10.61). The average age at diagnosis was 60.6 years (SD = 11.20) and the majority were diagnosed in mid-life (61.3% diagnosed between the ages of 50 and 69). The majority of patients were non-Hispanic whites (91.9%) and male (62.5%). At initial PD visits, patients were typically married (77.4%) and residing at home (95.2%) with their spouse or partner (79.2%).

Examining the clinical characteristics and treatment of those diagnosed at the Center, very few patients were fluctuators (2.3%); the majority of patients had a tremor dominant subtype (55.7%), had a mild disease stage (mean Hoehn & and Yahr Stage = 1.9, SD = 0.59), and were not experiencing falls (89.1%). Symptoms of psychological distress (somatization, depression, and anxiety) were not pronounced (T-scores close to population norms for all domains), and patients were cognitively intact (median MMSE score = 29.0, IQR = 2.00). Patients had, on average, three comorbidities (SD = 2.17) at diagnosis. The most common comorbidities, besides neurological disease, were musculoskeletal/skin disease (41.0%), psychiatric/memory problems (31.0%), upper gastrointestinal disease (27.9%), heart disease (25.5%), and genito-urinary disease (23.2%). Just over 40% of patients were on dopaminergic drugs at diagnosis; however, treatment complications were uncommon (median score = 0, IQR = 1.00).

Table 6. Descriptive characteristics of sample at diagnosis (when diagnosed at the Center) and at initial PD visit (irrespective of time since diagnosis)

	Diagnosis (n=413)		Initial PD Visit (n=1,463)	
	Value	**Missing**	**Value**	**Missing**
Sociodemographics				
Age, mean (SD)	63.2 (10.55)	0	64.9 (10.61)	0
Age at Diagnosis	N/A	N/A	60.6 (11.20)	0
Age Category at Diagnosis, n (%)		0		0
<50	47 (11.4)		255 (17.4)	
50 to <70	254 (61.5)		897 (61.3)	
70+	112 (27.1)		311 (21.3)	
Race/Ethnicity		48		144
Non-Hispanic White	325 (89.0)		1,212 (91.9)	
Other	40 (11.0)		107 (8.1)	
Male, n (%)	255 (61.7)	0	914 (62.5)	0
Education, n (%)		42		133
High School or Less	100 (27.0)		350 (26.3)	
Trade/Some College/College	151 (40.7)		515 (38.7)	
Advanced Degree	120 (32.4)		465 (35.0)	
Marital Status, n (%)		3		9
Married	324 (79.0)		1,125 (77.4)	
Single	23 (5.6)		69 (4.8)	
Divorced/Separated	38 (9.3)		129 (8.9)	
Widowed	25 (6.1)		131 (9.0)	
Completer of Forms, n (%)		85		372
Patient	265 (80.8)		786 (72.0)	
Co-Completed	63 (19.2)		303 (27.8)	
Caregiver	0 (0.0)		2 (0.2)	
Residence, n (%)		34		205
Home	371 (97.9)		1,197 (95.2)	
Retirement Community	8 (2.1)		42 (3.3)	
Assisted Living/Nursing Home	0 (0.0)		19 (1.5)	
Reside With, n (%)		34		202
Alone	45 (11.9)		167 (13.2)	
Spouse or Partner	308 (81.3)		999 (79.2)	
Other Family	18 (4.8)		68 (5.4)	
Other Family	8 (2.1)		27 (2.1)	
Median Income, mean (SD)	86,302 (32,890)	8	86,841 (34,097)	22

Table 6 Continued

	Diagnosis (n=413)		Initial PD Visit (n=1,463)	
	Value	**Missing**	**Value**	**Missing**
Clinical Characteristics				
Fluctuator, n (%)	7 (2.3)	109	258 (23.4)	362
Jankovic Subtype, n (%)		104		380
Tremor Dominant	172 (55.7)		401 (37.0)	
Postural Instability/Gait Dominant	102 (33.0)		587 (54.2)	
Indeterminate	35 (11.3)		95 (8.8)	
Falls, n (%)		66		253
No Falls	309 (89.1)		874 (72.2)	
Rare Falling	33 (9.5)		232 (19.2)	
Occasional Falls (<1/Day)	5 (1.4)		90 (7.4)	
Falls (≥1/Day)	0 (0.0)		14 (1.2)	
Treatment Complications, mean (SD)	0.4 (0.86)	28	1.4 (2.25)	85
Treatment Complications, median (IQR)	0 (1.00)	28	1.0 (2.00)	85
BSI Somatization T-Score, mean (SD)	53.4 (8.07)	89	54.1 (8.42)	531
BSI Depression T-Score, mean (SD)	51.2 (9.49)	89	51.9 (9.64)	531
BSI Anxiety T-Score, mean (SD)	49.2 (9.13)	91	50.3 (9.64)	532
CIRS Comorbidity Count, mean (SD)	3.0 (2.17)	77	3.1 (2.01)	331
Heart Disease, n (%)	84 (25.5)	83	286 (25.6)	346
Vascular Disease, n (%)	15 (4.5)	82	66 (5.9)	346
Blood Disease, n (%)	9 (2.7)	83	43 (3.9)	350
Respiratory Disease, n (%)	35 (10.6)	82	120 (10.8)	350
ENT Disease, n (%)	69 (20.9)	83	224 (20.2)	353
Upper GI Disease, n (%)	92 (27.9)	83	302 (27.0)	344
Lower GI Disease, n (%)	41 (12.5)	86	151 (13.6)	356
Liver Disease, n (%)	4 (1.2)	82	23 (2.1)	346
Renal Disease, n (%)	31 (9.3)	80	84 (7.5)	345
Genito-urinary Disease, n (%)	76 (23.2)	85	262 (23.7)	355
Musculoskeletal/Skin Disease, n (%)	135 (41.0)	84	480 (43.2)	353
Neurological Disease	252 (82.6)	108	983 (91.3)	386
Endocrine/Metabolic/Breast Disease, n (%)	42 (12.9)	88	158 (14.4)	367
Psychiatric/Memory Problems, n (%)	102 (31.0)	84	374 (34.0)	362
Stanford Self-Efficacy, mean (SD)	14.7 (2.61)	214	13.8 (2.83)	722
Pain, mean (SD)	0.9 (2.19)	88	0.9 (2.11)	373
Pain, median (IQR)	0 (0.00)	88	0 (0.00)	373
MMSE, mean (SD)	28.9 (1.38)	81	28.5 (2.10)	323
MMSE, median (IQR)	290 (2.00)	81	29.0 (2.00)	323
Hoehn & Yahr Stage, mean (SD)	1.9 (0.59)	76	2.4 (0.88)	294
Hoehn & Yahr Stage, median (IQR)	2.0 (0.00)	76	2.0 (0.50)	294

Table 6 Continued

	Diagnosis (n=413)		Initial PD Visit (n=1,463)	
	Value	**Missing**	**Value**	**Missing**
Treatment				
DBS at Current Visit, n (%)	1 (0.2)	0	34 (2.3)	4
Clinician Sex, n (%)		162		460
Male	205 (81.7)		819 (81.7)	
Female	46 (18.3)		184 (18.3)	
Carbo/Levodopa at Current Visit, n (%)	68 (28.8)	177	651 (71.2)	549
Dopaminergic at Current Visit, n (%)	112 (40.1)	134	830 (76.1)	372

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range; BSI, Brief-Symptom Inventory-18, ENT, Ear Nose and Throat, MMSE, Mini-Mental State Examination, DBS, Deep Brain Stimulation

The mean and median duration of patient follow-up care at the clinic was 8.9 years and 7.9 years, respectively. Patient data was available from diagnosis to 34.4 years post-diagnosis. Patients were seen an average of 0.5 years between any two visits to the clinic with a median time between any two visits of 0.4 years and a maximum time of 13.2 years. The average patient had 9.4 visits during the current study period (median = 7.0 visits, maximum = 69 visits). The majority of visits occurred between 0 and 10 years since diagnosis (Table 7). Much more limited visit data was available at later times.

Table 7. Frequency of visits by time interval overall and by sex

Interval	Overall	Males	Females
0 to <5 Years Since Diagnosis, n	4,586	2,871	1,715
5 to <10 Years Since Diagnosis, n	4,279	2,882	1,397
10 to <15 Years Since Diagnosis, n	2,854	1,753	1,101
15 to <20 Years Since Diagnosis, n	1,384	805	579
20 to <25 Years Since Diagnosis, n	515	293	222
≥25 Years Since Diagnosis, n	202	101	101
Total, n	13,820	8,705	5,115

Aim 1.1

The final model for PD impairment progression assessed by the UPDRS motor score is presented in Table 8. At diagnosis, the average UPDRS motor score was 21.79

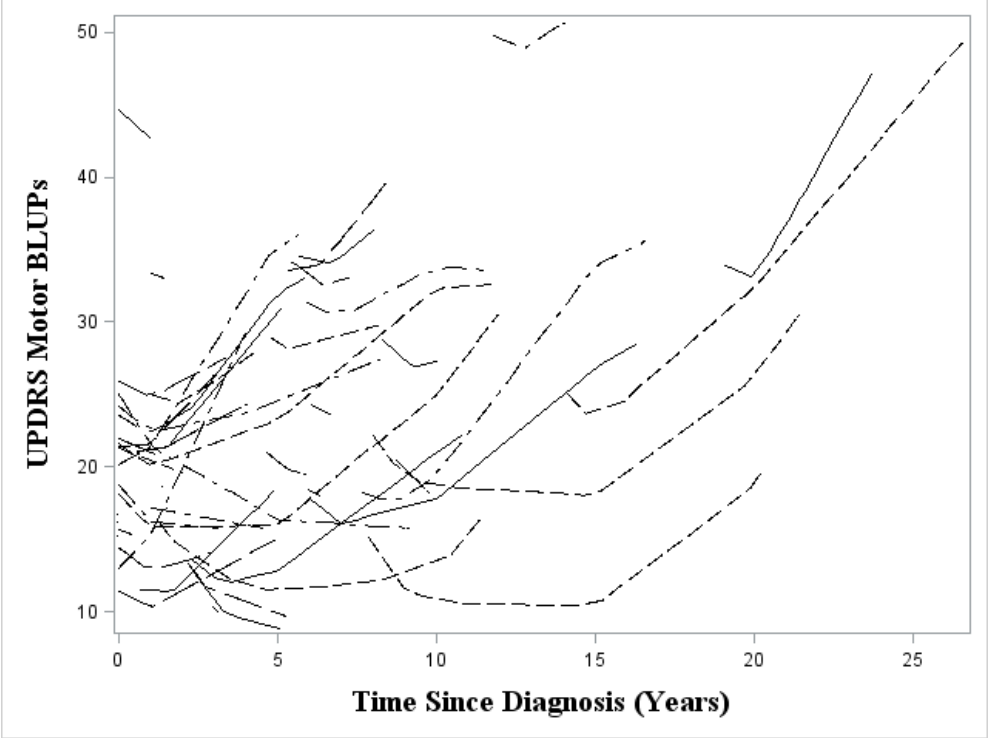
points (95% CI: 21.02, 22.56). For the population, on average, UPDRS motor scores increased between 0.68 to 1.18 points per year. All increases were significantly different from zero, and no two adjacent splines were significantly different from one another. The model suggests that at 5 years and 10 years, the marginal, or population mean, UPDRS motor score was 27.69 (21.79+[5*1.18]) and 32.69 (21.79+[5*1.18]+[5*1.00]), respectively. The random effects standard deviations (SDs), obtained by taking the square root of the variances, suggest a high amount of between-subject heterogeneity in UDPRS motor scores at diagnosis (SD = 8.03) and in change in UDPRS motor scores over time (SD = 1.84 to 2.43 points per year). There was a greater amount of heterogeneity in progression mid to late in the disease course. Random effects estimates also suggested that at any given year, some patients had much more severe increases in UPDRS motor scores while others experienced improvements in their disease. Figure 4 demonstrates this heterogeneity in the form of predicted UPDRS Motor score trajectories for a random sample of 50 patients. These predicted trajectories were determined from best linear unbiased predictors (BLUPs) obtained from the mixed effects model. Patients showed a marked, significant improvement in UDPRS motor scores (mean = -2.31 points, 95% CI: -2.94, -1.68) in the first year of care at the Center.

Table 8. Linear mixed effects model for Parkinson disease impairment progression measured with clinician-assessed, UPDRS Motor Scores

	Fixed Effects		Random Effects
Parameters	**B**	**95% CI**	**SD**
At Diagnosis[a]	21.79	21.02, 22.56	8.03
0 to <5 Years[b]	1.18	0.94, 1.41	1.84
5 to <10 Years[b]	1.00	0.76, 1.14	1.93
10 to <15 Years[b]	0.68	0.34, 1.01	2.43
15 to <20 Years[b]	0.93	0.41, 1.44	2.40
≥20 Years[b]	1.14	0.48, 1.8	2.26
First Year in Clinic[c]	-2.31	-2.94, -1.68	N/A

Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change

Figure 4. Predicted UPDRS Motor trajectories for a random sample of 50 patients



Abbreviations: BLUPs, Best Linear Unbiased Predictors

Aim 1.2

Table 9 displays the fixed and random effects estimates for disease progression as measured by disability. As was seen for UDPRS motor scores, population mean OARS ADLs and IADLs scores significantly worsened over the disease course with an annual

progression of 0.36 to 0.74 points per year and 0.43 to 1.10 points per year for ADLs and IADLs, respectively. For OARS ADLs, the slopes were significantly different between all adjacent splines, except for between the 15 to <20 years and ≥20 years splines. The same pattern was found for OARS IADLs; however, there was no significant difference between the 10 to <15 years and 15 to <20 years splines. Random effects results indicate the greatest inter-individual heterogeneity between 10 and 20 years since diagnosis. The heterogeneity, which is displayed in Figure 5 (OARS ADLs) and Figure 6 (OARS IADLs), also suggests that some individuals had more severe worsening in disability while others had improvements in disability over the course of a given year. With first year of care at the Center, patients experienced significant improvements in OARS ADLs (mean = -0.31, 95% CI: -0.51, -0.12) but not in OARS IADLs (mean = -0.15, 95% CI: -0.39, 0.09).

Mean population Schwab & England scores at baseline were 89.03 (95% CI: 88.25, 89.80). Similar to patient-reported disability, clinician assessed disability significantly worsened over time with a mean population decline in the range of -0.86 to -2.38 units per year. Significant differences in slope were present between 5 to <10 years and 10 years to <15 years as well as between 10 to <15 years and 15 to <20 years. Inter-individual heterogeneity was also the greatest between 10 and 20 years since diagnosis (Figure 7) and the first year of clinical care at the Center resulted in a significant improvement in disability (mean = 1.34, 95% CI: 0.48, 2.21).

Table 9. Linear mixed effects models for Parkinson disease disability progression measured with two patient-reported measures (OARS ADLs and OARS IADLs) and one clinician-assessed measure (Schwab & England scale)

	Fixed Effects		Random Effects
Parameters	**β**	**95% CI**	**SD**
OARS ADLs			
At Diagnosis[a]	8.56	8.36, 8.76	1.86
0 to <5 Years[b]	0.45	0.38, 0.53	0.74
5 to <10 Years[b]	0.63	0.53, 0.74	1.08
10 to <15 Years[b]	0.36	0.20, 0.52	1.37
15 to <20 Years[b]	0.74	0.44, 1.03	1.58
≥20 Years[b]	0.68	0.36, 1.01	1.19
First Year in Clinic[c]	-0.31	-0.51, -0.12	N/A
OARS IADLs			
At Diagnosis[a]	8.53	8.16, 8.69	2.75
0 to <5 Years[b]	0.51	0.41, 0.61	1.02
5 to <10 Years[b]	0.94	0.79, 1.08	1.60
10 to <15 Years[b]	0.43	0.20, 0.66	2.04
15 to <20 Years[b]	0.66	0.27, 1.06	2.37
≥20 Years[b]	1.10	0.61, 1.58	1.90
First Year in Clinic[c]	-0.15	-0.39, 0.09	N/A
Schwab & England			
At Diagnosis[a]	89.03	88.25, 89.80	4.11
0 to <5 Years[b]	-2.11	-2.41, -1.81	1.93
5 to <10 Years[b]	-2.38	-2.74, -2.01	2.42
10 to <15 Years[b]	-0.86	-1.45, -0.27	4.37
15 to <20 Years[b]	-2.21	-3.21, -1.21	4.46
≥20 Years[b]	-1.83	-2.93, -0.74	3.86
First Year in Clinic[c]	1.34	0.48, 2.21	N/A

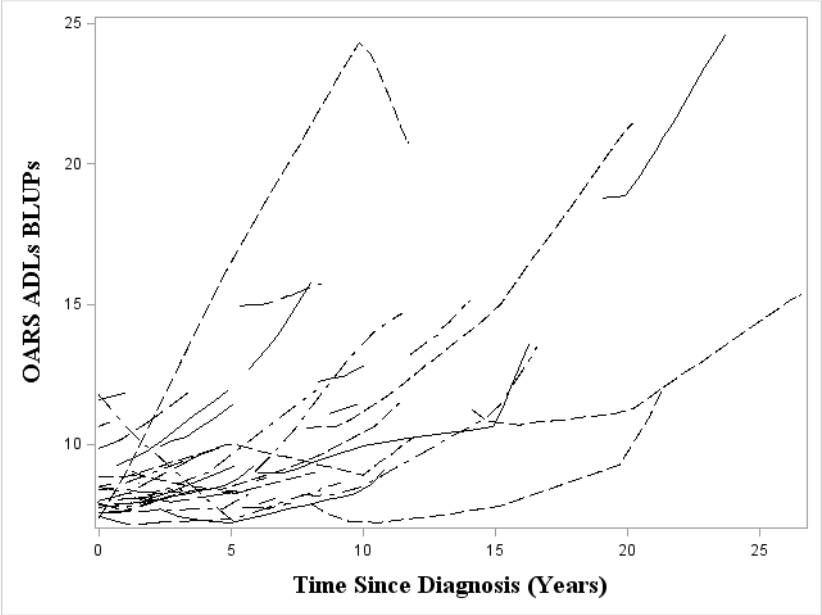
Abbreviations: CI, Confidence Interval; SD, Standard Deviation

[a]Intercept

[b]Interval represents time since diagnosis with β representing annual rate of change

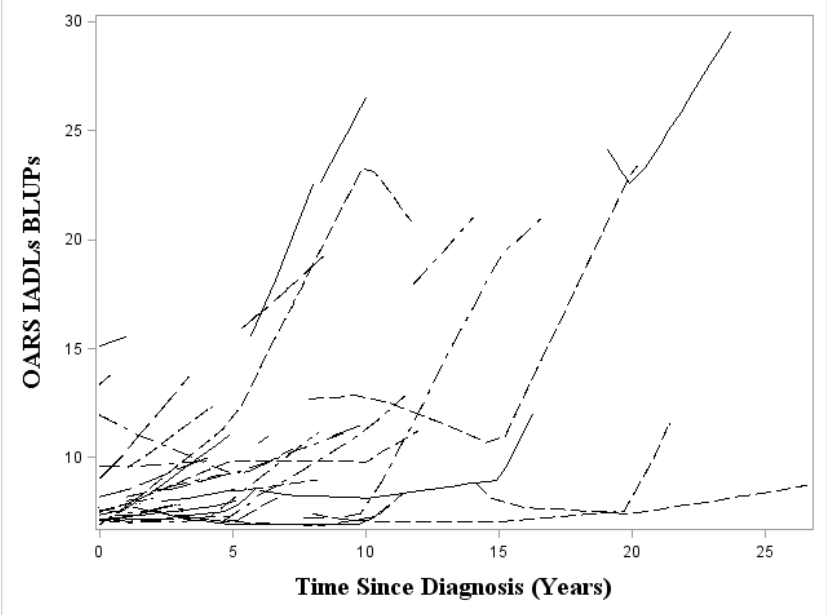
[c]One year rate of change

Figure 5. Predicted OARS ADLs trajectories for a random sample of 50 patients



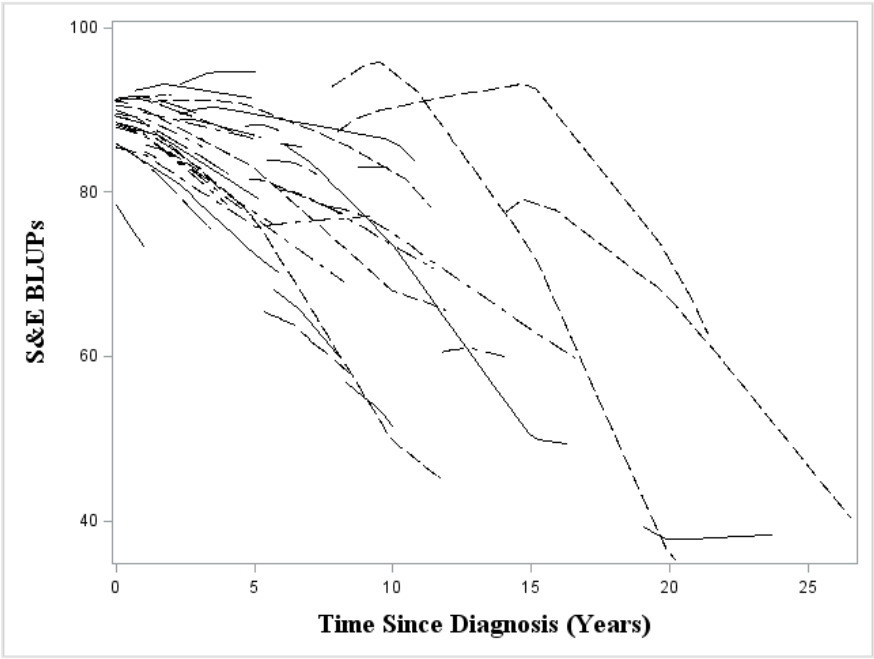
Abbreviations: BLUPs, Best Linear Unbiased Predictors

Figure 6. Predicted OARS IADLs trajectories for a random sample of 50 patients



Abbreviations: BLUPs, Best Linear Unbiased Predictors

Figure 7. Predicted Schwab & England trajectories for a random sample of 50 patients



Abbreviations: BLUPs, Best Linear Unbiased Predictors

Aim 1.3

Unlike the impairment and disability outcomes, health-related quality of life did not significantly worsen over all years since diagnosis. Population mean SF-12 Mental Health T-scores significantly worsened for all years except between 10 to 20 years after diagnosis. There were no significant differences between adjacent splines. Population mean SF-12 Physical Health T-scores significantly worsened for all years until 15 years after diagnosis. SF-12 Mental Health progression was most pronounced after 20 years post-diagnosis (mean = -0.69, 95% CI: -1.18, -0.19). The largest drop in physical health-related quality of life occurred 0 to 5 years from diagnosis (mean = -1.06, 95% CI: -1.27, -0.86). The variance between subjects was greatest 10 to 20 years after diagnosis and 5 to 15 years after diagnosis for mental (Figure 8) and physical (Figure 9) health-related quality of life, respectively. Like the other outcomes, the first year of clinical care in the

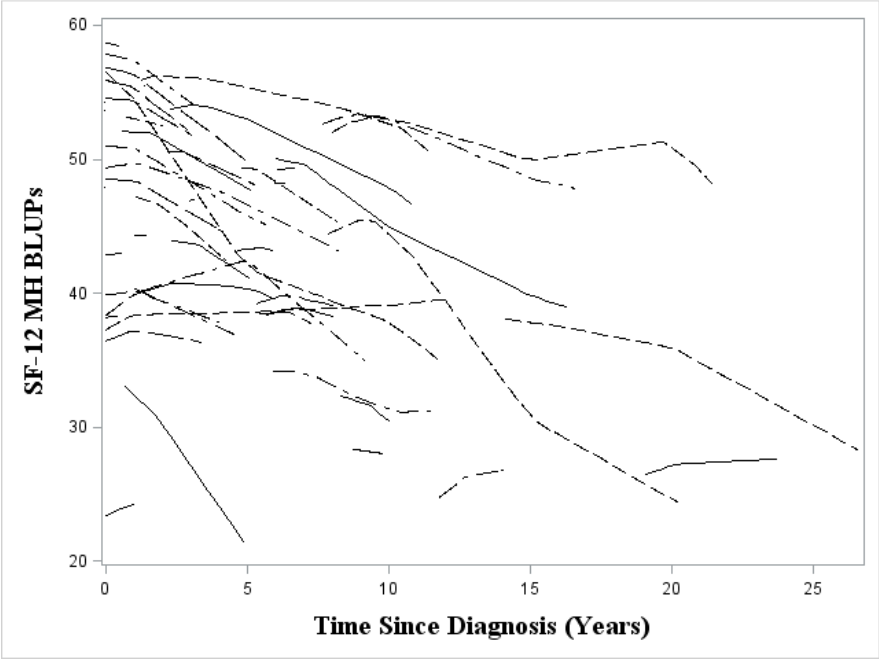
Center significantly improved both patient-reported health-related quality of life outcomes (β = 1.31, 95% CI: 0.74, 1.87; β = 1.12, 95% CI: 0.61, 1.62).

Table 10. Linear mixed effects models for Parkinson disease health-related quality of life progression measured with two patient-reported measures (SF-12 Mental Health and SF-12 Physical Health)

	Fixed Effects		Random Effects
Parameters	**β**	**95% CI**	**SD**
SF-12 Mental Health			
At Diagnosis[a]	50.51	49.80, 51.21	7.74
0 to <5 Years[b]	-0.39	-0.59, -0.20	1.05
5 to <10 Years[b]	-0.51	-0.71, -0.31	1.29
10 to <15 Years[b]	-0.21	-0.51, 0.10	2.03
15 to <20 Years[b]	-0.13	-0.60, 0.34	2.13
≥20 Years[b]	-0.69	-1.18, -0.19	1.29
First Year in Clinic[c]	1.31	0.74, 1.87	N/A
SF-12 Physical Health			
At Diagnosis[a]	45.91	45.14, 46.68	9.86
0 to <5 Years[b]	-1.06	-1.27, -0.86	1.39
5 to <10 Years[b]	-0.77	-0.97, -0.58	1.55
10 to <15 Years[b]	-0.52	-0.77, -0.28	1.53
15 to <20 Years[b]	-0.21	-0.56, 0.14	1.06
≥20 Years[b]	-0.42	-0.83, 0.00	1.17
First Year in Clinic[c]	1.12	0.61, 1.62	N/A

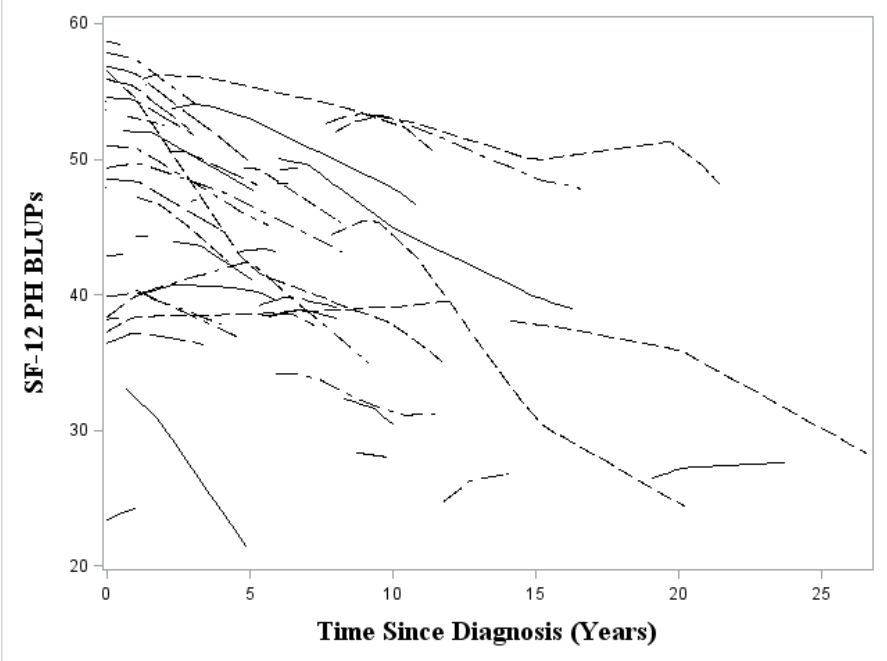
Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change

Figure 8. Predicted SF-12 Mental Health trajectories for a random sample of 50 patients



Abbreviations: BLUPs, Best Linear Unbiased Predictors

Figure 9. Predicted SF-12 Physical Health trajectories for a random sample of 50 patients



Abbreviations: BLUPs, Best Linear Unbiased Predictors

Sensitivity Analyses (Aim 1)

At diagnosis, there were minimal differences in patients by diagnosis date imputation. At diagnosis, significant differences were found for categorical age at onset (Chi-Square p-value = 0.002), mean age (t-test p-value = 0.004), and vascular disease (Fisher's Exact test p-value = 0.017). Individuals with an older age at onset, an older mean age, and vascular disease were more likely to have an imputed diagnosis date.

At initial PD visits, significant differences were present for more characteristics. Those with imputed diagnosis dates had a higher age category at diagnosis (Chi-Square p-value < 0.001); older average age at first visit (t-test p-value = 0.002); more comorbidities on average (t-test p-value = 0.010); more vascular disease (Chi-Square p-value = 0.034); more respiratory disease (Chi-Square p-value = 0.004); and more ear, nose, and throat (ENT) disease (Chi-Square p-value = 0.048). They were also more likely to live in an assisted living/nursing home (Fisher's Exact test p-value = 0.037), have an older average age at their first visit (t-test p-value=0.0013), and report more pain (Wilcoxon p-value < 0.001).

Table 11 demonstrates the estimates from the piece-wise, linear mixed effects models when stratified by whether a patient's diagnosis date was imputed. Due to the smaller number of visits from patients with an imputed diagnosis date, models with random intercept and slope terms would not converge. Consequently, the models were constructed with only a random intercept term. Although models were run with fixed and random effects, only the fixed effects are presented. In general, the mean population estimates of progression for patients with imputed diagnosis dates were more inconsistent than the patients without an imputed diagnosis date. This difference was most noticeable

late in the disease course. This difference may, in large part, be due to the smaller number of patients with imputed diagnosis dates, particularly later in the disease course. Comparing imputed versus non-imputed, for UPDRS motor scores (β = -4.55, 95% CI: -6.87, -2.24 vs. β = -1.65, 95% CI: -2.31, -0.98), OARS ADLs scores (β = -0.70, 95% CI: -1.47, 0.07 vs. β = -0.03, 95% CI: -0.27, 0.21), S&E score (β = 1.88, 95% CI: -1.82, 5.58 vs. β = 0.58, 95% CI: -.044, 1.60), and SF-12 Mental Health scores (β = 1.58, 95% CI: -0.67, 3.83 vs β = 1.14, 95% CI: 0.56, 1.73), the patients with imputed diagnosis dates experienced a larger magnitude of benefit in their first year under care at the Center than their counterparts.

Table 11. Linear mixed effects models with random intercepts for Parkinson disease progression measured with all outcomes and stratified by whether diagnosis date was imputed

	Imputed		Not Imputed	
	β	**95% CI**	**B**	**95% CI**
UPDRS Motor Score				
At Diagnosis[a]	22.90	19.94, 25.86	21.00	20.16, 21.84
0 to <5 Years[b]	1.88	1.06, 2.69	1.03	0.82, 1.24
5 to <10 Years[b]	1.39	0.57, 2.21	0.95	0.77, 1.13
10 to <15 Years[b]	0.81	-0.41, 2.02	1.15	0.93, 1.37
15 to <20 Years[b]	1.97	-0.01, 3.96	0.90	0.60, 1.20
≥20 Years[b]	-0.05	-10.93, 10.83	1.35	1.03, 1.66
First Year in Clinic[c]	-4.55	-6.87, -2.24	-1.65	-2.31, -0.98
OARS ADLs				
At Diagnosis[a]	8.48	7.43, 9.54	8.13	7.83, 8.44
0 to <5 Years[b]	0.82	0.55, 1.10	0.39	0.31, 0.47
5 to <10 Years[b]	0.24	-0.01, 0.49	0.61	0.55, 0.67
10 to <15 Years[b]	1.27	0.90, 1.64	0.59	0.51, 0.68
15 to <20 Years[b]	-0.52	-1.36, 0.31	0.47	0.35, 0.59
≥20 Years[b]	3.42	1.27, 5.58	0.79	0.65, 0.93
First Year in Clinic[c]	-0.70	-1.47, 0.07	-0.03	-0.27, 0.21
OARS IADLs				
At Diagnosis[a]	7.57	6.07, 9.06	7.87	7.46, 8.28
0 to <5 Years[b]	1.05	0.67, 1.43	0.45	0.35, 0.55
5 to <10 Years[b]	0.40	0.06, 0.75	0.83	0.74, 0.91
10 to <15 Years[b]	1.99	1.49, 2.50	0.74	0.63, 0.85
15 to <20 Years[b]	-0.30	-1.42, 0.82	0.64	0.48, 0.80
≥20 Years[b]	2.38	-0.49, 5.25	1.03	0.85, 1.21
First Year in Clinic[c]	0.07	-0.97, 1.11	0.22	-0.09, 0.54
Schwab & England				
At Diagnosis[a]	90.03	85.66, 94.41	89.56	88.34, 90.77
0 to <5 Years[b]	-3.53	-4.88, -2.19	-1.97	-2.33, -1.62
5 to <10 Years[b]	-1.49	2.87, -0.11	-1.83	-2.16, -1.51
10 to <15 Years[b]	-1.20	-3.50, 1.10	-1.76	-2.18, -1.34
15 to <20 Years[b]	-3.49	-7.90, 0.93	-2.27	-2.89, -1.65
≥20 Years[b]	-0.92	-18.97, 17.14	-1.90	-2.48, -1.32
First Year in Clinic[c]	1.88	-1.82, 5.58	0.58	-0.44, 1.60

Table 11 Continued

	Imputed		Not Imputed	
	β	**95% CI**	**B**	**95% CI**
SF-12 Mental Health				
At Diagnosis[a]	49.30	46.50, 52.10	50.60	49.91, 51.29
0 to <5 Years[b]	-0.18	-0.97, 0.61	-0.38	-0.57, -0.20
5 to <10 Years[b]	-0.44	-1.16, 0.28	-0.42	-0.58, -0.27
10 to <15 Years[b]	-0.90	-1.99, 0.19	-0.39	-0.59, -0.18
15 to <20 Years[b]	1.07	-1.55, 3.70	-0.16	-0.47, 0.15
≥20 Years[b]	-0.77	-7.32, 5.78	-0.53	-0.88, -0.19
First Year in Clinic[c]	1.58	-0.67, 3.83	1.14	0.56, 1.73
SF-12 Physical Health				
At Diagnosis[a]	46.71	44.04, 49.38	46.11	45.42, 46.80
0 to <5 Years[b]	-1.67	-2.38, -0.96	-0.99	-1.16, -0.82
5 to <10 Years[b]	-0.36	-0.98, 0.26	-0.83	-0.97, -0.69
10 to <15 Years[b]	-0.69	-1.62, 0.24	-0.82	-1.00, -0.64
15 to <20 Years[b]	0.79	-1.51, 3.09	-0.33	-0.61, -0.06
≥20 Years[b]	-1.22	-6.68, 4.24	-0.43	-0.75, -0.12
First Year in Clinic[c]	-0.34	-2.28, 1.61	1.08	0.55, 1.60

Abbreviations: CI, Confidence Interval
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change

Table 12 presents the fixed effects from the piece-wise, linear mixed effects models stratified by whether an individual was an incident or prevalent PD patient. The models were restricted to overlapping time periods—at diagnosis to 15 years post-diagnosis. Estimates were relatively similar with some exceptions. Due to the sparse amount of data for the incident group between 10 and 15 years post-diagnosis, differences in progression estimates were most pronounced in this time frame. Additionally, incident cases experienced more benefit in the first year of care, compared to prevalent cases.

Table 12. Linear mixed effects models with random slopes and intercepts for PD progression measured with all outcomes and stratified by case status in clinic

	Incident		Prevalent	
	β	**95% CI**	**β**	**95% CI**
UPDRS Motor Score				
At Diagnosis[a]	22.12	21.08, 23.16	21.80	20.40, 23.20
0 to <5 Years[b]	1.34	0.89, 1.79	1.04	0.68, 1.41
5 to <10 Years[b]	1.10	0.48, 1.72	0.93	0.66, 1.41
10 to <15 Years[b]	-0.29	-2.63, 2.04	1.12	0.80, 1.43
First Year in Clinic[c]	-2.83	-4.15, -1.52	-1.61	-2.37, -0.84
OARS ADLs				
At Diagnosis[a]	8.79	8.53, 9.04	8.39	7.98, 8.79
0 to <5 Years[b]	0.48	0.34, 0.63	0.44	0.32, 0.56
5 to <10 Years[b]	0.88	0.61, 1.15	0.52	0.40, 0.63
10 to <15 Years[b]	1.51	-0.25, 3.27	0.64	0.49, 0.80
First Year in Clinic[c]	-0.62	-0.98, -0.26	0.13	-0.13, 0.40
OARS IADLs				
At Diagnosis[a]	8.70	8.36, 9.05	8.23	7.23, 8.74
0 to <5 Years[b]	0.50	0.32, 0.68	0.48	0.33, 0.63
5 to <10 Years[b]	1.29	0.91, 1.66	0.75	0.59, 0.91
10 to <15 Years[b]	1.35	-0.99, 3.68	0.84	0.64, 1.05
First Year in Clinic[c]	-0.43	-0.88, 0.02	0.54	0.21, 0.87
Schwab & England				
At Diagnosis[a]	88.79	87.80, 89.78	88.44	87.74, 91.14
0 to <5 Years[b]	-1.99	-2.53, -1.44	-2.15	-2.67, -1.62
5 to <10 Years[b]	-3.81	-4.99, -2.63	-1.80	-2.21, -1.38
10 to <15 Years[b]	-1.51	-5.59, 2.57	-2.38	-2.92, -1.84
First Year in Clinic[c]	1.37	-0.35, 3.08	0.43	-0.74, 1.60
SF-12 Mental Health				
At Diagnosis[a]	49.35	48.37, 50.33	51.49	50.22, 52.76
0 to <5 Years[b]	-0.63	-0.96, -0.29	-0.55	-0.88, -0.22
5 to <10 Years[b]	-0.27	-0.79, 0.25	-0.47	-0.69, -0.25
10 to <15 Years[b]	-2.52	-5.35, 0.31	-0.35	-0.62, -0.08
First Year in Clinic[c]	2.91	1.71, 4.10	0.96	0.29, 1.63
SF-12 Physical Health				
At Diagnosis[a]	45.55	44.45, 46.65	46.05	44.81, 47.29
0 to <5 Years[b]	-1.10	-1.43, -0.76	-1.08	-1.39, -0.78
5 to <10 Years[b]	-1.03	-1.50, -0.56	-0.69	-0.91, -0.46
10 to <15 Years[b]	0.61	-1.92, 3.14	-0.67	-0.90, -0.43
First Year in Clinic[c]	1.97	0.84, 3.11	0.72	0.12, 1.31

Abbreviations: CI, Confidence Interval

[a]Intercept

[b]Interval represents time since diagnosis with β representing annual rate of change

[c]One year rate of change

The original intention was to examine progression differences, among fluctuators, by whether these patients were on or off at their respective visit. However, among fluctuators, on/off status was only recorded at 1,316 of the total visits. At visits where the individual was noted as being a fluctuator, patients were more likely to be on (two-sided binomial test p-value < 0.001). Overall, among fluctuators, 67.9% had their visit UPDRS exam recorded while they were on and 32.1% had their visit UPDRS exam recorded while they were off.

Progression patterns by proxy status were also not explored. Among visits where the completer of forms was recorded, forms were completed solely by proxies for only 70 visits. These visits stemmed from only 37 patients. Comparing the distribution of time from diagnosis to the use of proxies, the average time from diagnosis to proxy use was rather late in the disease course at 11.1 years (median = 10.4, minimum = 2.1, maximum = 23.4 years).

Mortality data from patients was limited. A total of 88 patients had a death date available. For those patients, the mean time from diagnosis to death was 10.9 years and the median time was 10.2 years (IQR = 6.1 years). The earliest death occurred at 3.3 years and the latest death occurred 32.8 years from diagnosis.

B. Aim 2

Aim 2.1

Table 13 displays the sociodemographics, clinical characteristics, treatment, and outcomes for those diagnosed at the Center, stratified by sex. Significant differences between males and females were present for education (t-test p-value = 0.034), marital status (Chi-square p-value < 0.001), who the individual resides with (Fisher's exact test

p-value < 0.001), anxiety T-scores (t-test p-value = 0.028), prevalence of GI disease (t-test p-value = 0.012), prevalence of genito-urinary disease (t-test p-value = 0.004), clinician sex (Fisher's exact test p-value = 0.015), dopaminergic drug use at current visit (t-test p-value = 0.048), and OARS IADLs (t-test p-value = 0.012). Females were less educated, less likely to be married, more likely to reside alone, more likely to report higher anxiety T-scores, more afflicted by GI and genito-urinary disease, more likely to see a female clinician, more likely to be taking a dopaminergic drug, and more likely to report worse IADL disability.

Table 13. Descriptive characteristics of sample at diagnosis (when diagnosed at the Center), stratified by sex

	Males (n=255)	Females (n=158)	p-value
Sociodemographics			
Age, mean (SD)	63.1 (10.19)	63.4 (11.14)	0.749[a]
Age at Diagnosis	N/A	N/A	N/A
Age Category at Diagnosis, n (%)			0.687[c]
<50	31 (12.2)	16 (10.1)	
50 to <70	158 (62.0)	96 (60.8)	
70+	66 (25.9)	46 (29.1)	
Race/Ethnicity			0.789[c]
Non-Hispanic White	196 (88.7)	129 (89.6)	
Other	25 (11.3)	15 (10.4)	
Education, n (%)			0.034[c]
High School or Less	51 (22.4)	49 (34.3)	
Trade/Some College/College	96 (42.1)	55 (38.5)	
Advanced Degree	81 (35.5)	39 (27.3)	
Marital Status, n (%)			<0.001[c]
Married	215 (85.0)	109 (69.4)	
Single	14 (5.5)	9 (5.7)	
Divorced/Separated	18 (7.1)	20 (12.7)	
Widowed	6 (2.4)	19 (12.1)	
Completer of Forms, n (%)			0.385[c]
Patient	161 (79.3)	104 (83.2)	
Co-Completed	42 (20.7)	21 (16.8)	
Caregiver	0 (0.0)	0 (0.0)	
Residence, n (%)			0.063[d]
Home	226 (99.1)	145 (96.0)	
Retirement Community	2 (0.9)	6 (4.0)	
Assisted Living/Nursing Home			
Reside With, n (%)			<0.001[d]
Alone	20 (8.8)	25 (16.6)	
Spouse or Partner	201 (88.2)	107 (70.9)	
Other Family	4 (1.8)	14 (9.3)	
Other Family	3 (1.3)	5 (3.3)	
Median Income	88,617 (35,815)	82,606 (27,290)	0.057[b]

Table 13 Continued

	Males (n=255)	Females (n=158)	p-value
Clinical Characteristics			
Fluctuator, n (%)	3 (1.6)	4 (3.3)	0.440[d]
Jankovic Subtype, n (%)			0.183[c]
Tremor Dominant	97 (51.9)	75 (61.5)	
Postural Instability/Gait Dominant	69 (36.9)	33 (27.1)	
Indeterminate	21 (11.2)	14 (11.5)	
Falls, n (%)			0.397[d]
No Falls	193 (90.6)	116 (86.6)	
Rare Falling	18 (8.5)	15 (11.2)	
Occasional Falls (<1/Day)	2 (0.9)	3 (2.2)	
Falls (1+/Day)			
Treatment Complications, mean (SD)	0.4 (0.77)	0.5 (0.98)	0.1611[a]
Treatment Complications, median (IQR)	0 (1.00)	0 (1.00)	0.238[b]
BSI Somatization T-Score, mean (SD)	53.2 (7.46)	53.7 (9.00)	0.592[a]
BSI Depression T-Score, mean (SD)	49.4 (9.20)	48.7 (9.04)	0.513[a]
BSI Anxiety T-Score, mean (SD)	50.3 (9.37)	52.7 (9.53)	0.028[a]
CIRS Comorbidity Count, mean (SD)	2.9 (2.10)	3.1 (2.27)	0.355[a]
Heart Disease, n (%)	54 (26.2)	30 (24.2)	0.683[c]
Vascular Disease, n (%)	10 (4.9)	5 (3.9)	0.682[c]
Blood Disease, n (%)	4 (2.0)	5 (4.0)	0.307[d]
Respiratory Disease, n (%)	19 (9.3)	16 (12.6)	0.345[c]
ENT Disease, n (%)	37 (18.1)	32 (25.4)	0.115[c]
Upper GI Disease, n (%)	53 (26.0)	39 (31.0)	0.328[c]
Lower GI Disease, n (%)	18 (8.9)	23 (18.4)	0.012[c]
Liver Disease, n (%)	1 (0.5)	3 (2.4)	0.160[d]
Renal Disease, n (%)	23 (11.2)	8 (6.3)	0.129[c]
Genito-urinary Disease, n (%)	58 (28.4)	18 (14.5)	0.004[c]
Musculoskeletal/Skin Disease, n (%)	76 (37.4)	59 (46.8)	0.092[c]
Neurological Disease	161 (83.9)	91 (80.5)	0.460[c]
Endocrine/Metabolic/Breast Disease, n (%)	21 (10.3)	21 (17.2)	0.074[c]
Psychiatric/Memory Problems, n (%)	60 (29.6)	42 (33.3)	0.472[c]
Lorig Self-Efficacy, mean (SD)	14.6 (2.61)	14.7 (2.63)	0.773[a]
Pain, mean (SD)	0.9 (2.11)	1.0 (2.31)	0.597[a]
Pain, median (IQR)	0 (0.00)	0 (1.00)	0.288[b]
MMSE, mean (SD)	29.0 (1.39)	28.9 (1.38)	0.639[a]
MMSE, median (IQR)	29.0 (2.00)	29.0 (2.00)	0.540[b]
Hoehn & Yahr Stage, mean (SD)	1.9 (0.54)	1.9 (0.65)	0.532[a]
Hoehn & Yahr Stage, median (IQR)	2.0 (0.00)	2.0 (0.00)	0.565[b]

Table 13 Continued

	Males (n=255)	Females (n=158)	p-value
Treatment			
DBS at Current Visit, n (%)	0 (0.0)	1 (0.63)	0.383[c]
Clinician Sex, n (%)			0.015[d]
Male	133 (86.4)	72 (74.2)	
Female	21 (13.6)	25 (25.8)	
Carbo/Levodopa at Current Visit, n (%)	37 (24.7)	31 (36.1)	0.063[c]
Dopaminergic at Current Visit, n (%)	62 (35.6)	50 (47.6)	0.048[c]
Outcomes			
Died	N/A	N/A	N/A
UPDRS Motor, mean (SD)	22.7 (10.24)	22.1 (11.13)	0.666[a]
OARS ADLs, mean (SD)	8.7 (2.42)	9.0 (2.87)	0.302[a]
OARS IADLs, mean (SD)	8.3 (2.80)	9.2 (3.40)	0.012[a]
S&E, mean (SD)	88.8 (8.64)	89.2 (9.90)	0.730[a]
SF-12 MH, mean (SD)	49.9 (10.47)	48.6 (11.01)	0.280[a]
SF-12 PH, mean (SD)	46.3 (11.11)	44.9 (11.72)	0.273[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range, N/A, Not Applicable
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 14 demonstrates the differences in characteristics between males and females at their initial PD visit to the Center. Females were older (t-test p-value = 0.038), were less educated (Chi-square p-value < 0.001), were less likely to be married (Chi-square p-value < 0.001), were less likely to live at home (Chi-square p-value < 0.001), and had a lower median household income (t-test p-value = 0.060). Clinically, females were more likely to be fluctuators (Chi-square p-value = 0.017), to fall (Chi-square p-value = 0.012), to have treatment complications (t-test p-value = 0.009), to have greater somatization (t-test p-value = 0.023), to have greater depressive symptoms (t-test p-value = 0.001), to have a blood disease (Chi-square p-value = 0.004), to have renal disease (Chi-square p-value = 0.001), to have genito-urinary disease (Chi-square p-value < 0.001), to have musculoskeletal/skin disease (Chi-square p-value = 0.005), to have

endocrine/metabolic/breast disease (Chi-square p-value < 0.001), to have pain (t-test p-value = 0.006), and to have a more advanced Hoehn & Yahr stage (t-test p-value = 0.024). Females were more likely to be seen by female clinicians (Chi-square t-test p-value < 0.001). In general, at first visit to the clinic, females were worse than males on all self-reported outcome measures. Females had worse OARS ADLs (t-test p-value = 0.021), OARS IADLs (t-test p-value=0.001), SF-12 Mental Health (t-test p-value = 0.006), and SF-12 Physical Health (t-test p-value = 0.002)

Table 14. Descriptive characteristics of sample at initial PD visit (irrespective of time since diagnosis), stratified by sex

	Males (n=914)	Females (n=549)	p-value
Sociodemographics			
Age, mean (SD)	64.5 (10.37)	65.7 (10.97)	0.038[a]
Age at Diagnosis	60.3 (11.08)	61.1 (11.39)	0.172[a]
Age Category at Diagnosis, n (%)			0.092[c]
<50	172 (18.8)	83 (15.1)	
50 to <70	560 (61.3)	337 (61.4)	
70+	182 (19.9)	129 (23.5)	
Race/Ethnicity			0.423[c]
Non-Hispanic White	761 (92.4)	451 (91.1)	
Other	63 (7.7)	44 (8.9)	
Education, n (%)			<0.001[c]
High School or Less	176 (21.1)	174 (35.0)	
Trade/Some College/College	325 (39.0)	190 (38.2)	
Advanced Degree	332 (39.9)	133 (26.8)	
Marital Status, n (%)			<0.001[c]
Married	770 (84.7)	355 (65.1)	
Single	44 (4.8)	25 (4.6)	
Divorced/Separated	66 (7.3)	63 (11.6)	
Widowed	29 (3.2)	102 (18.7)	
Completer of Forms, n (%)			0.266[d]
Patient	485 (70.5)	301 (74.7)	
Co-Completed	202 (29.4)	101 (25.1)	
Caregiver	1 (0.2)	1 (0.3)	
Residence, n (%)			0.024[c]
Home	750 (96.4)	447 (93.1)	
Retirement Community	18 (2.3)	24 (5.0)	
Assisted Living/Nursing Home	10 (1.3)	9 (1.9)	
Reside With, n (%)			<0.001[c]
Alone	64 (8.2)	103 (21.6)	
Spouse or Partner	682 (87.1)	317 (66.3)	
Other Family	24 (3.1)	44 (9.2)	
Other Family	13 (1.7)	14 (2.9)	
Median Income	88,130 (35,124)	84,717 (33,252)	0.060[a]

Table 14 Continued

	Males (n=914)	Females (n=549)	p-value
Clinical Characteristics			
Fluctuator, n (%)	146 (21.1)	112 (27.4)	0.017[c]
Jankovic Subtype, n (%)			0.752[c]
Tremor Dominant	253 (37.6)	148 (36.1)	
Postural Instability/Gait Dominant	364 (54.1)	223 (54.4)	
Indeterminate	56 (8.3)	39 (9.5)	
Falls, n (%)			0.012[c]
No Falls	567 (75.0)	307 (67.6)	
Rare Falling	127 (16.8)	105 (23.1)	
Occasional Falls (<1/Day)	51 (6.8)	39 (8.6)	
Falls (1+/Day)	11 (1.5)	3 (0.7)	
Treatment Complications, mean (SD)	1.3 (2.08)	1.7 (2.49)	0.009[a]
Treatment Complications, median (IQR)	0 (2.00)	1.0 (2.00)	<0.001[b]
BSI Somatization T-Score, mean (SD)	53.6 (8.04)	54.9 (8.95)	0.023[a]
BSI Depression T-Score, mean (SD)	51.1 (9.72)	53.2 (9.38)	0.001[a]
BSI Anxiety T-Score, mean (SD)	50.4 (9.63)	50.0 (9.65)	0.571[a]
CIRS Comorbidity Count, mean (SD)	3.1 (1.95)	3.3 (2.12)	0.165[a]
Heart Disease, n (%)	181 (25.8)	105 (25.3)	0.858[c]
Vascular Disease, n (%)	39 (5.6)	27 (6.4)	0.567[c]
Blood Disease, n (%)	28 (2.6)	25 (6.0)	0.004[c]
Respiratory Disease, n (%)	66 (9.5)	54 (12.9)	0.075[c]
ENT Disease, n (%)	130 (18.7)	94 (22.7)	0.106[c]
Upper GI Disease, n (%)	177 (25.3)	125 (29.8)	0.097[c]
Lower GI Disease, n (%)	84 (12.1)	67 (16.2)	0.057[c]
Liver Disease, n (%)	15 (2.2)	8 (1.9)	0.785[c]
Renal Disease, n (%)	67 (9.6)	17 (4.0)	0.001[c]
Genito-urinary Disease, n (%)	204 (29.4)	58 (14.0)	<0.001[c]
Musculoskeletal/Skin Disease, n (%)	277 (40.0)	203 (48.6)	0.005[c]
Neurological Disease	623 (91.6)	360 (90.7)	0.599[c]
Endocrine/Metabolic/Breast Disease, n (%)	77 (11.2)	81 (19.9)	<0.001[c]
Psychiatric/Memory Problems, n (%)	221 (32.2)	153 (37.0)	0.104[c]
Lorig Self-Efficacy, mean (SD)	13.9 (2.85)	13.7 (2.80)	0.359[a]
Pain, mean (SD)	0.8 (1.92)	1.1 (2.36)	0.006[a]
Pain, median (IQR)	0 (0.00)	0 (0.00)	<0.001[b]
MMSE, mean (SD)	28.5 (1.90)	28.4 (2.40)	0.444[a]
MMSE, median (IQR)	29.0 (2.00)	29.0 (2.00)	0.004[b]
Hoehn & Yahr Stage, mean (SD)	2.3 (0.83)	2.4 (0.96)	0.024[a]
Hoehn & Yahr Stage, median (IQR)	2.0 (0.50)	2.0 (1.00)	<0.001[b]

Table 14 Continued

	Males (n=914)	Females (n=549)	p-value
Treatment			
DBS at Current Visit, n (%)	20 (2.2)	14 (2.6)	0.660[c]
Clinician Sex, n (%)			<0.001[c]
Male	544 (86.5)	275 (73.5)	
Female	85 (13.5)	99 (26.5)	
Carbo/Levodopa at Current Visit, n (%)	406 (70.4)	245 (72.7)	0.452[c]
Dopaminergic at Current Visit, n (%)	523 (75.6)	307 (77.0)	0.611[c]
Outcomes			
Died	107 (11.7)	51 (9.3)	0.149[c]
UPDRS Motor, mean (SD)	26.4 (12.37)	26.3 (13.76)	0.974[a]
OARS ADLs, mean (SD)	10.2 (9.91)	10.8 (10.37)	0.021[a]
OARS IADLs, mean (SD)	10.2 (5.19)	11.4 (5.79)	0.001[a]
S&E, mean (SD)	81.1 (15.13)	80.0 (17.19)	0.273[a]
SF-12 MH, mean (SD)	49.5 (10.65)	47.7 (11.24)	0.006[a]
SF-12 PH, mean (SD)	42.9 (11.34)	40.6 (12.63)	0.002[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range, N/A, Not Applicable
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 15 demonstrates the spacing between various care milestones by sex. There were no significant differences by sex in the time from symptom onset to diagnosis, diagnosis to levodopa initiation, diagnosis to first visit to the Center, diagnosis to initial PD visit at the Center, or diagnosis to DBS. Although not significant at the $p<0.05$ level (t-test p-value = 0.085; Wilcoxon-Sum test p-value = 0.071), females had longer times from diagnosis to DBS (mean = 11.9 years, SD = 5.69) compared to males (mean = 10.3 years, SD = 4.84).

Table 15. Timing between care milestones in years by sex

Interval (in years)	Males	Females	p-Value
Symptom Onset to Diagnosis, mean (SD)	1.4 (1.36)	1.5 (2.17)	0.356[a]
Symptom Onset to Diagnosis, median (IQR)	1.0 (2.00)	1.0 (2.00)	0.457[b]
Diagnosis to Levodopa Initiation, mean (SD)	1.6 (2.48)	1.7 (2.76)	0.475[a]
Diagnosis to Levodopa Initiation, median (IQR)	1.0 (3.00)	1.0 (3.00)	0.771[b]
Diagnosis to First Visit to Center, mean (SD)	4.1 (4.97)	4.5 (5.54)	0.195[a]
Diagnosis to First Visit to Center, median (IQR)	2.3 (6.25)	2.3 (7.17)	0.629[b]
Diagnosis to Initial PD Visit at Center, mean (SD)	4.2 (4.94)	4.5 (5.50)	0.190[a]
Diagnosis to Initial PD Visit at Center, median (IQR)	2.3 (6.25)	2.3 (7.17)	0.645[b]
Diagnosis to DBS, mean (SD)	10.3 (4.84)	11.9 (5.69)	0.085[a]
Diagnosis to DBS, median (IQR)	9.5 (6.00)	11.0 (8.00)	0.071[b]

Abbreviations: SD, Standard Deviation, IQR, Interquartile Range; DBS, Deep Brain Stimulation
[a]t-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test

Aim 2.2

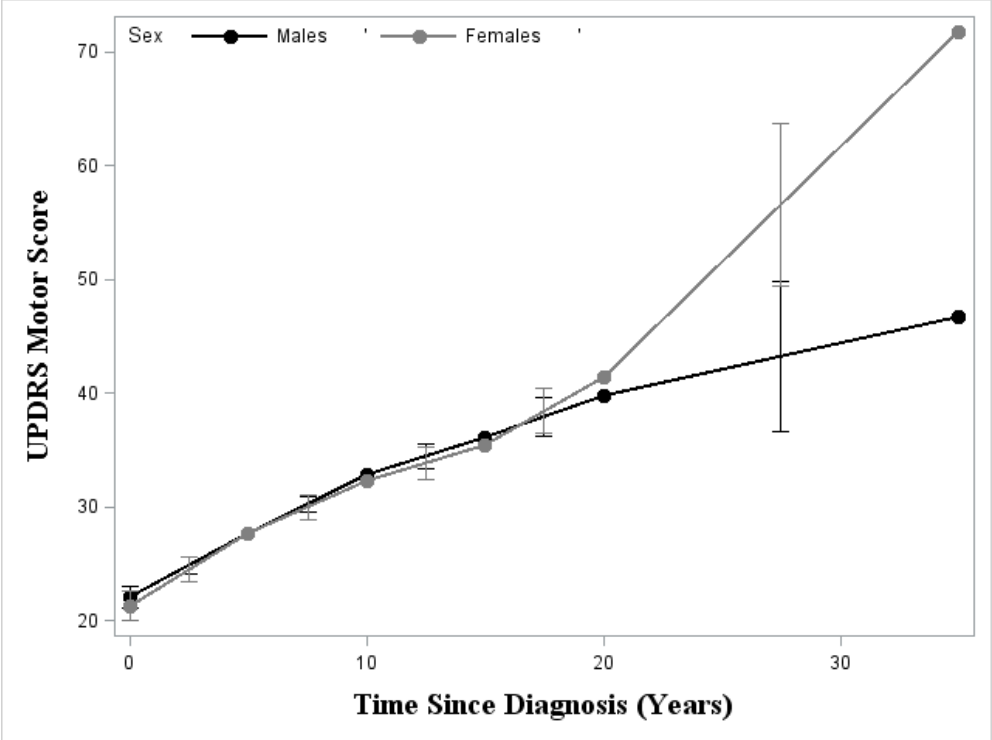
Table 16 displays the population average rate of progression for the various time intervals for males and females along with inter-individual heterogeneity for impairment progression. The resultant model is plotted in Figure 10. There were no significant differences between males and females in UPDRS scores at diagnosis (p-value = 0.343). There were no significant differences between sexes in the rate of progression until 20 years post-diagnosis (p = 0.017). Females, on average, after 20 years, had a significantly faster rate of progression (β = 2.02 points per year, 95% CI: 1.08, 2.97) compared to males (β = 0.46 points per year, 95% CI: -0.42, 1.33). Females, on average, also had a greater benefit from the first year of clinical care (β = -3.37 points, 95% CI: -4.41, -2.33), compared to males (β = -1.66, 95% CI: -2.43, -0.88). There were no sex differences in heterogeneity in progression (Likelihood ratio Chi-square test value = 20, df = 50, p = 1.000).

Table 16. Linear mixed effects model for Parkinson disease impairment progression by sex measured with the clinician-assessed, UPDRS Motor Scores

	Males			Females			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β**	**95% CI**	**SD**	**β**	**95% CI**	**SD**	**p-value[d]**
At Diagnosis[a]	22.09	21.13, 23.05	7.75	21.31	20.02, 22.60	8.45	0.343
0 to <5 Years[b]	1.12	0.83, 1.40	1.70	1.28	0.86, 1.70	2.05	0.531
5 to <10 Years[b]	1.03	0.75, 1.30	1.69	0.90	0.45, 1.35	2.45	0.650
10 to <15 Years[b]	0.65	0.22, 1.08	2.48	0.64	0.09, 1.20	2.55	0.991
15 to <20 Years[b]	0.75	0.07, 1.43	2.46	1.19	0.41, 1.98	2.35	0.405
≥20 Years[b]	0.46	-0.42, 1.33	2.59	2.02	1.08, 2.97	1.85	0.017
1st Year in Clinic[c]	-1.66	-2.43, -0.88	N/A	-3.37	-4.41, -2.33	N/A	0.010

Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change
[d]Comparison of sex differences

Figure 10. Plot of average rate of Parkinson disease UPDRS Motor progression by sex



Sex differences in the rate of disease progression, as measured by disability, are presented in Table 17 and plotted in Figures 11, 12, and 13. No sex differences at the $p<0.05$ level were noted in the average rate of progression for any measure. However, there was a borderline significant difference between males and females in the rate of OARS ADL progression 20 years post-diagnosis with males progressing faster ($\beta = 0.93$ per year, 95% CI: 0.54, 1.33) than females ($\beta = 0.26$ per year, 95% CI: -0.29, 0.81). There were, however, significant differences between males and females in the amount of disability at diagnosis and the benefit of the first year of clinical care for self-reported disability outcomes (OARS ADLs and OARS IADLs) but not physician assessed disability (Schwab & England). Females reported more ADLs disability ($p = 0.069$) and IADLs disability ($p < 0.001$) at diagnosis than their male counterparts. Males, on average, also received significantly more benefit in the first year of clinical care for both self-reported disability outcomes, compared to females. In general, there were no differences in inter-individual heterogeneity by sex (OARS ADLs Likelihood ratio Chi-square test value = 43, df = 50, $p < 0.748$; OARS IADLs Likelihood ratio Chi-square test value = 31, df = 50, $p = 0.995$). The Likelihood ratio Chi-square test could not be calculated for S&E due to convergence issues with the simplified model.

Table 17. Linear mixed effects models for Parkinson disease disability progression by sex measured with two patient-reported measures (OARS ADLs and OARS IADLs) and one clinician-assessed measure (Schwab & England scale)

	Males			Females			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β**	**95% CI**	**SD**	**β**	**95% CI**	**SD**	**p-value[d]**
OARS ADLs							
At Diagnosis[a]	8.42	8.19, 8.65	2.36	8.82	8.46, 9.18	2.29	0.069
0 to <5 Years[b]	0.46	0.37, 0.54	0.63	0.43	0.28, 0.58	0.91	0.786
5 to <10 Years[b]	0.70	0.57, 0.82	1.04	0.52	0.33, 0.71	1.25	0.131
10 to <15 Years[b]	0.24	0.01, 0.46	1.67	0.40	0.23, 0.67	1.01	0.183
15 to <20 Years[b]	0.63	0.30, 0.97	1.29	0.90	0.40, 1.39	1.91	0.390
≥20 Years[b]	0.93	0.54, 1.33	1.19	0.26	-0.29, 0.81	1.48	0.051
1st Year in Clinic[c]	-0.45	-0.69, -0.21	N/A	-0.04	-0.37, 0.29	N/A	0.046
OARS IADLs							
At Diagnosis[a]	8.04	7.74, 8.33	2.10	9.13	8.63, 9.62	3.43	<0.001
0 to <5 Years[b]	0.55	0.44, 0.67	0.99	0.43	0.25, 0.61	1.06	0.261
5 to <10 Years[b]	1.01	0.83, 1.19	1.55	0.83	0.57, 1.09	1.73	0.253
10 to <15 Years[b]	0.25	-0.07, 0.58	2.48	0.45	0.16, 0.75	1.48	0.374
15 to <20 Years[b]	1.09	0.59, 1.58	2.16	0.80	0.26, 1.34	2.29	0.445
≥20 Years[b]	1.21	0.45, 1.97	2.43	0.74	0.17, 1.31	1.58	0.332
1st Year in Clinic[c]	-0.38	-0.67, -0.08	N/A	0.30	-0.10, 0.70	N/A	0.008
Schwab & England							
At Diagnosis[a]	88.95	87.98, 89.93	3.71	88.9	87.60, 90.18	5.15	0.936
0 to <5 Years[b]	-2.07	-2.42, -1.71	1.79	-2.1	-2.61, -1.53	2.28	0.995
5 to <10 Years[b]	-2.26	-2.69, -1.84	2.11	-2.6	-3.31, -1.93	3.21	0.390
10 to <15 Years[b]	-1.20	-1.94, -0.46	4.25	-0.3	-1.33, 0.65	4.91	0.171
15 to <20 Years[b]	-1.82	-3.05, -0.60	3.73	-2.5	-4.18, -0.86	5.66	0.511
≥20 Years[b]	-2.78	-4.35, -1.21	3.89	-1.4	-3.03, 0.33	4.16	0.225
1st Year in Clinic[c]	1.93	0.89, 2.97	N/A	0.2	-1.28, 1.66	N/A	0.059

Abbreviations: CI, Confidence Interval; SD, Standard Deviation

[a]Intercept

[b]Interval represents time since diagnosis with β representing annual rate of change

[c]One year rate of change

[d]Comparison of sex differences

Figure 11. Plot of average rate of Parkinson disease OARS ADLs progression by sex

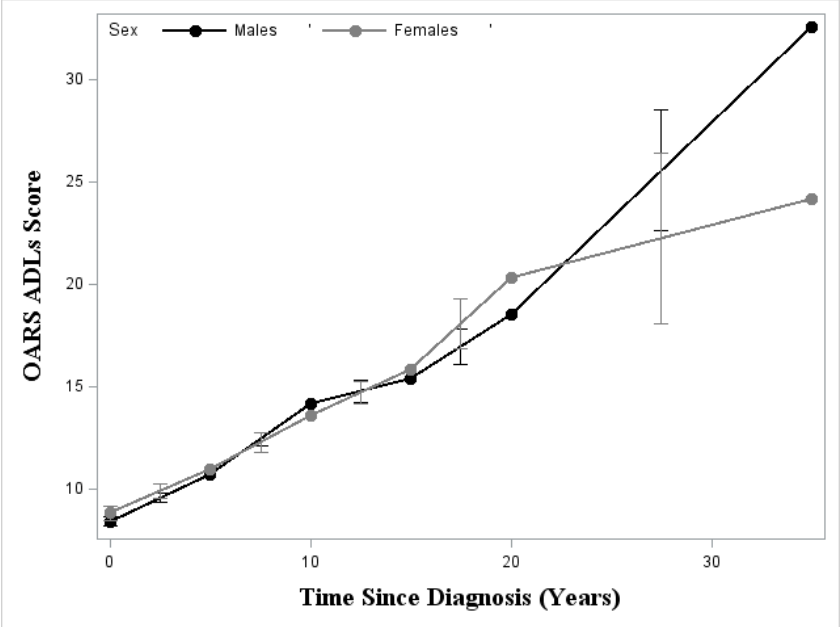


Figure 12. Plot of average rate of Parkinson disease OARS IADLs progression by sex

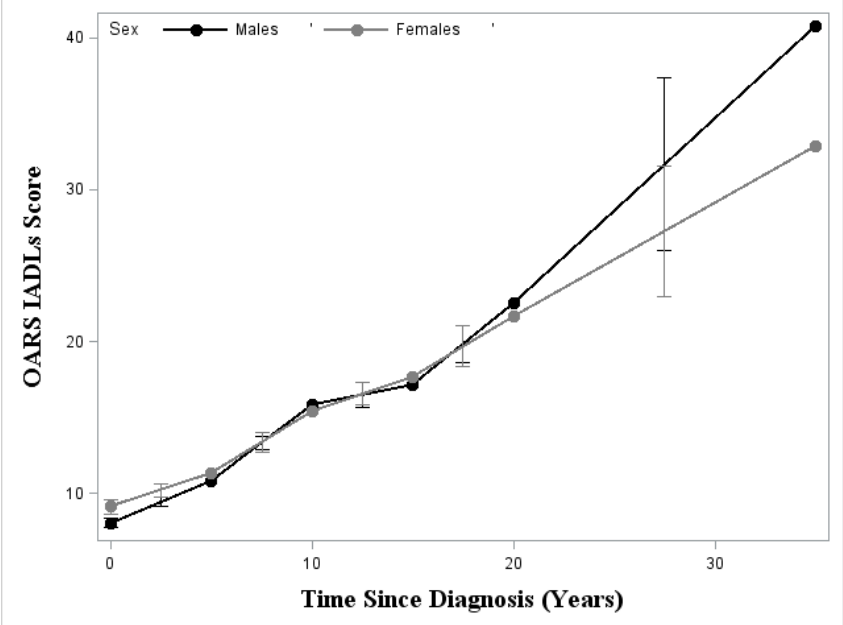
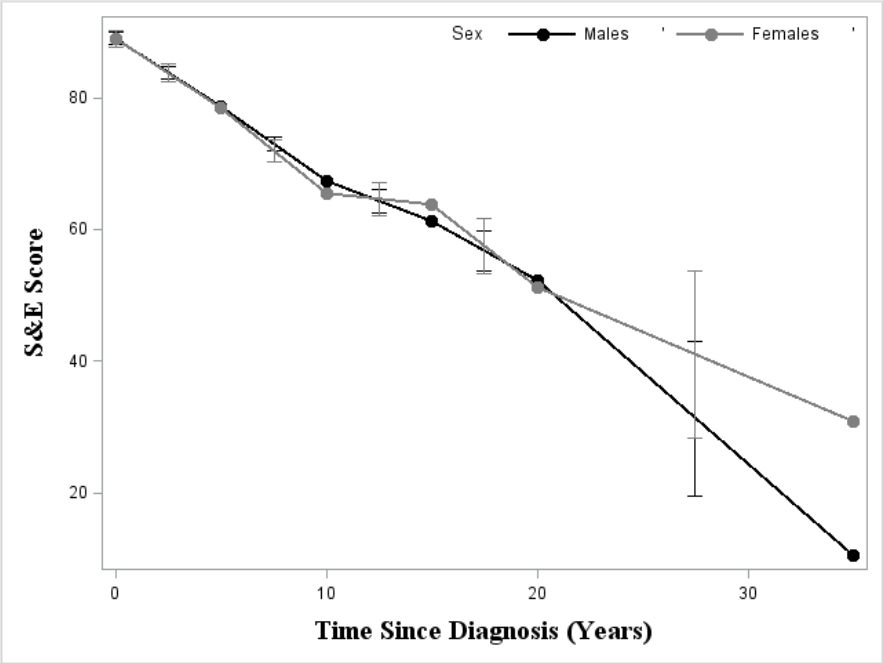


Figure 13. Plot of average rate of Parkinson disease Schwab & England progression by sex



The rate of health-related quality of life progression for males and females is displayed in Table 18 and plotted in Figures 14 and 15. Significant differences between males and females were present for mental health-related quality of life between 5 to 10 years since diagnosis ($p = 0.030$). Males progressed at a faster rate ($\beta = -0.64$, 95% CI: -0.89, -0.40) compared to females ($\beta = -0.19$, 95% CI: -0.52, 0.13). Females reported worse mental health-related quality of life ($\beta = 49.73$, 95% CI: 48.51, 50.96) than males ($\beta = 51.03$, 95% CI: 50.17, 51.89) at diagnosis; however, this finding was not statistically significant at the $p< 0.05$ level ($p = 0.091$). For physical health-related quality of life, the only significant difference between sexes was at diagnosis. Females ($\beta = 44.49$, 95% CI: 43.21, 45.77) reported worse physical health-related quality of life at diagnosis, compared to males ($\beta = 46.74$, 95% CI: 45.78, 47.69). Unlike what was seen for impairment and disability progression, although both sexes benefitted from clinical care,

there were no significant differences between sexes in the impact of the first year of clinical care at the Center. Again there were no significant differences in heterogeneity of progression by sex (SF-12 MH Likelihood ratio Chi-square test value = 9, df = 50, p = 1.000). The Likelihood ratio Chi-square test could not be calculated for SF-12 PH due to convergence issues with the simplified model.

Table 18. Linear mixed effects models for Parkinson disease health-related quality of life progression by sex measured with two patient-reported measures (SF-12 Mental Health and SF-12 Physical Health)

	Males			Females			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β**	**95% CI**	**SD**	**β**	**95% CI**	**SD**	**p-value[d]**
SF-12 Mental Health							
At Diagnosis[a]	51.03	50.17, 51.89	7.26	49.73	48.51, 50.96	8.47	0.091
0 to <5 Years[b]	-0.35	-0.59, -0.11	0.98	-0.52	-0.87, -0.18	1.23	0.428
5 to <10 Years[b]	-0.64	-0.89, -0.40	1.37	-0.19	-0.52, 0.13	1.21	0.030
10 to <15 Years[b]	-0.12	-0.49, 0.25	1.95	-0.41	-0.93, 0.10	2.14	0.368
15 to <20 Years[b]	0.15	-0.44, 0.75	2.01	-0.44	-1.22, 0.34	2.60	0.239
≥20 Years[b]	-1.05	-1.61, -0.49	1.20	-0.32	-1.18, 0.55	1.61	0.163
1st Year in Clinic[c]	1.34	0.63, 2.05	N/A	1.25	0.32, 2.18	N/A	0.883
SF-12 Physical Health							
At Diagnosis[a]	46.74	45.78, 47.69	9.53	44.49	43.21, 45.77	10.26	0.006
0 to <5 Years[b]	-1.05	-1.30, -0.80	1.45	-1.10	-1.43, -0.76	1.21	0.815
5 to <10 Years[b]	-0.75	-0.98, -0.52	1.34	-0.78	-1.14, -0.42	1.85	0.868
10 to <15 Years[b]	-0.62	-0.92, -0.32	1.48	-0.37	-0.78, 0.04	1.62	0.341
15 to <20 Years[b]	-0.14	-0.58, 0.30	0.85	-0.42	-0.95, 0.12	1.30	0.432
≥20 Years[b]	-0.14	-0.53, 0.59	1.46	-0.45	-1.02, 0.13	0.64	0.437
1st Year in Clinic[c]	0.88	0.24, 1.52	N/A	1.53	0.70, 2.36	N/A	0.225

Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change
[d]Comparison of sex differences

Figure 14. Plot of average rate of Parkinson disease SF-12 Mental Health progression by sex

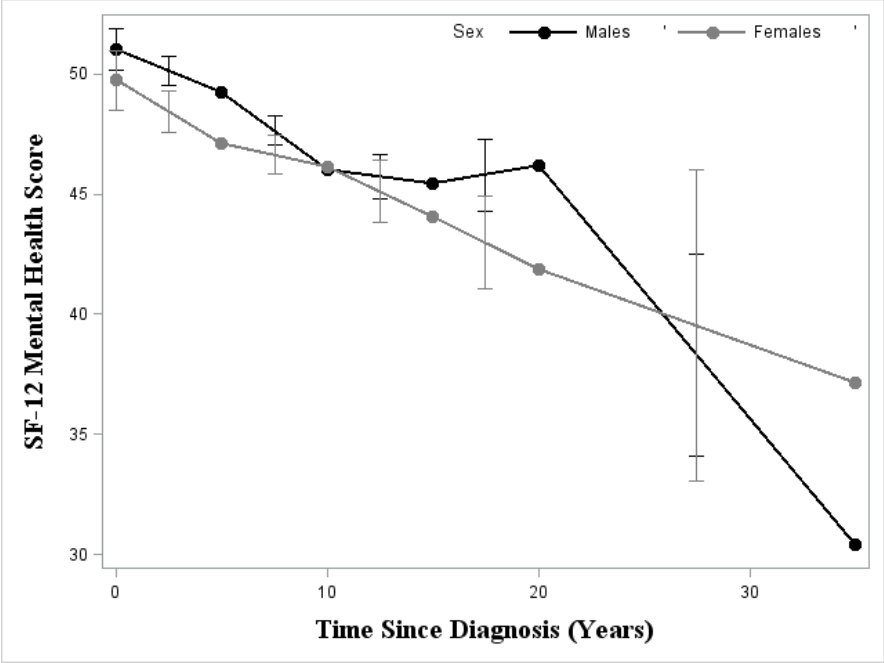
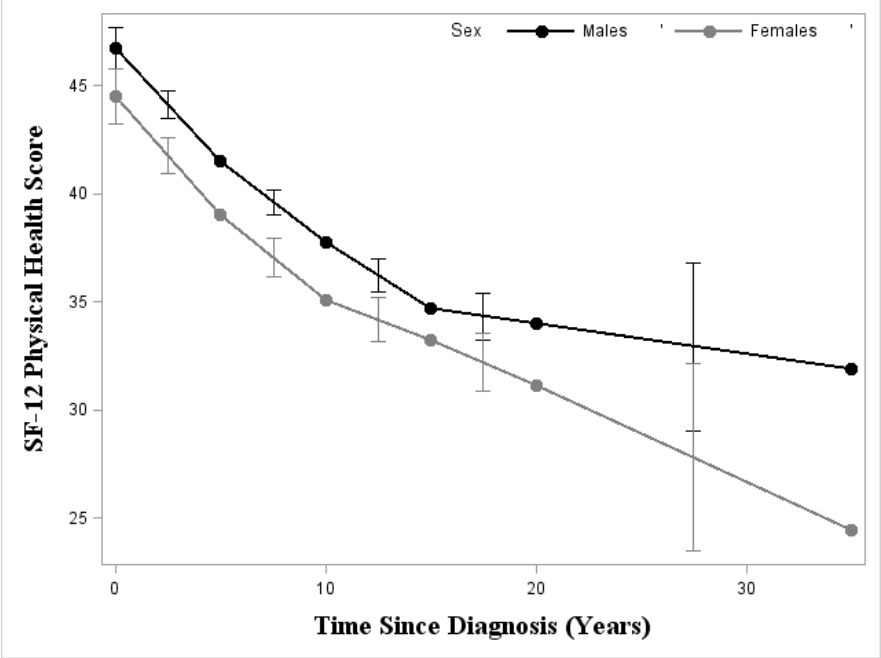


Figure 15. Plot of average rate of Parkinson disease SF-12 Physical Health progression by sex



Aim 2.3

After controlling for any mediator-outcome confounders, individually intervening on any given mediator resulted in no significant effect of sex on OARS ADLs scores (Table 19). When examining the estimates for the controlled direct of sex, setting anxiety, depression, or somatization to population normative T-scores resulted in estimates closest to the null, suggesting that intervening on psychological distress may have the largest impact on minimizing sex differences in ADLs disability.

Table 19. Results of mediation analysis demonstrating the controlled direct effect (CDE) of female sex on OARS ADLs scores

	b	95% CI	CDE	95% CI
Overall	0.62	0.12, 1.12		
Mediators				
Drug Side-Effects[a]			0.22	-0.51, 0.95
Cognition[b]			0.32	-0.27, 0.91
Comorbidities[c]			0.37	-0.31, 1.05
Psychological Distress[d]				
Anxiety			-0.22	-0.72, 0.28
Depression			0.19	-0.30, 0.67
Somatization			-0.17	-0.70, 0.36
Psychological Distress[e]				
Anxiety			-0.28	-1.06, 0.50
Depression			0.06	-0.63, 0.75
Somatization			-0.30	-1.21, 0.60
Disease Duration at First Visit to Center[f]			0.41	-0.13, 0.95
Falls[g]			2.30	-4.01, 8.62

Abbreviations: CDE, controlled direct effects
[a]Adjusted for age, levodopa use, disease duration; mediator set to score = 0
[b]Adjusted for age, disease duration, comorbidities, SES; mediator set to score = 30
[c]Adjusted for age, disease duration, SES; mediator set to 1
[d]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[e]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[f]Adjusted for SES; mediator set to 1 year
[g]Adjusted for age, disease duration, comorbidities; mediator set to 0

With respect to OARS IADLs scores, after controlling for mediator-outcome confounders and intervening on cognition or disease duration at initial PD visit, there were still a significant effects of sex. Females had worse OARS IADLs scores despite

intervening on cognition (CDE = 1.00, 95% CI: 0.28, 1.73) and despite intervening on disease duration at initial PD visit (CDE = 0.85, 95% CI: 0.15, 1.54). Interventions on all other mediators resulted in a non-significant effect of sex with point estimates attenuated the most toward the null for psychological distress interventions. If all patients were non-fallers, females would report less IADLs disability than males; however, this finding was not statistically significant (CDE = -2.82, 95% CI: -10.58, 4.94).

Table 20. Results of mediation analysis demonstrating the controlled direct effect (CDE) of female sex on OARS IADLs scores

	b	95% CI	CDE	95% CI
Overall	1.13	0.48, 1.78		
Mediators				
Drug Side-Effects[a]			0.61	-0.33, 1.54
Cognition[b]			1.00	0.28, 1.73
Comorbidities[c]			0.27	-0.58, 1.13
Psychological Distress[d]				
Anxiety			0.04	-0.59, 0.66
Depression			0.55	-0.05, 1.15
Somatization			0.26	-0.41, 0.93
Psychological Distress[e]				
Anxiety			0.14	-0.84, 1.12
Depression			0.41	-0.45, 1.27
Somatization			0.50	-0.66, 1.65
Disease Duration at First Visit to Center[f]			0.85	0.15, 1.54
Falls[g]			-2.82	-10.58, 4.94

Abbreviations: CDE, controlled direct effects
[a]Adjusted for age, levodopa use, disease duration; mediator set to score = 0
[b]Adjusted for age, disease duration, comorbidities, SES; mediator set to score = 30
[c]Adjusted for age, disease duration, SES; mediator set to 1
[d]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[e]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[f]Adjusted for SES; mediator set to 1 year
[g]Adjusted for age, disease duration, comorbidities; mediator set to 0

Table 21 displays the results of the mediation analysis examining the SF-12 Mental Health score outcome. Interventions eliminating drug side-effects (CDE = -0.58, 95% CI: -2.48, 1.32), managing anxiety to population norms (CDE = 0.01, 95% CI: -1.30, 1.33), and reducing depressive symptoms to on standard deviation below the

population mean (CDE = 0.41 , 95% CI: -0045, 1.27) would result in the most minimal sex differences. Note that different psychological distress targets have differing impacts on the effect of sex. For example, reducing anxiety to one standard deviation below population norms would result in females reporting better SF-12 MH (CDE = 0.95, 95% CI: -1.13, 3.02). Despite interventions on cognition, comorbidities, depression, and disease duration at initial PD visit, females would still report worse SF-12 MH at their initial PD visit to the Center, compared to their male counterparts. Interventions to address falls would result in males reporting worse, but not significantly worse, SF-12 Mental Health scores (CDE = 4.21, 95% CI: -14.60, 23.02).

Table 21. Results of mediation analysis demonstrating the controlled direct effect (CDE) of female sex on SF-12 Mental Health Scores

	b	95% CI	CDE	95% CI
Overall	-1.82	-3.10, -0.54		
Mediators				
Drug Side-Effects[a]			-0.58	-2.48, 1.32
Cognition[b]			-1.82	-3.57, -0.06
Comorbidities[c]			-2.27	-4.26, -0.28
Psychological Distress[d]				
Anxiety			0.01	-1.30, 1.33
Depression			-2.19	-3.36, -1.03
Somatization			-0.91	-2.49, 0.67
Psychological Distress[e]				
Anxiety			0.95	-1.13, 3.02
Depression			0.41	-0.45, 1.27
Somatization			-1.14	-3.84, 1.57
Disease Duration at First Visit to Center[f]			-1.51	-3.01, -0.00
Falls[g]			4.21	-14.60, 23.02

Abbreviations: CDE, controlled direct effects
[a]Adjusted for age, levodopa use, disease duration; mediator set to score = 0
[b]Adjusted for age, disease duration, comorbidities, SES; mediator set to score = 30
[c]Adjusted for age, disease duration, SES; mediator set to 1
[d]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[e]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[f]Adjusted for SES; mediator set to 1 year
[g]Adjusted for age, disease duration, comorbidities; mediator set to 0

Sex differences in SF-12 Physical Health at initial PD visits would be most substantially minimized by interventions addressing anxiety (CDE when set to population norms = -0.27, 95% CI: -1.82, 1.28), depression (CDE when set to population norms = -0.59, 95% CI: -2.09, 0.92), and somatization (CDE when set to population norms = -0.42, 95% CI: -1.97, 1.13) (Table 22). Females would still report significantly worse physical health if interventions targeted drug side-effects (CDE = -2.02, 95% CI: -3.99, -0.04), cognition (CDE = -2.23, 95% CI: -3.16, -0.28), or disease duration at initial PD visit (CDE = -1.62, -3.19, -0.06). Again, interventions targeting falls would, although non-significant, lead to males reporting worse physical health-related quality of life, (CDE = 6.74, 95% CI: -12.18, 25.66).

Table 22. Results of mediation analysis demonstrating the controlled direct effect (CDE) of female sex on SF-12 Physical Health Scores

	b	95% CI	CDE	95% CI
Overall	-2.25	-3.64, -0.85		
Mediator				
Drug Side-Effects[a]			-2.02	-3.99, -0.04
Cognition[b]			-2.23	-3.16, -0.28
Comorbidities[c]			-1.49	-3.46, 0.48
Psychological Distress[d]				
Anxiety			-0.27	-1.82, 1.28
Depression			-0.59	-2.09, 0.92
Somatization			-0.42	-1.97, 1.13
Psychological Distress[e]				
Anxiety			-1.40	-3.84, 1.04
Depression			-1.04	-3.19, 1.10
Somatization			-1.52	-4.17, 1.13
Disease Duration at First Visit to Center[f]			-1.62	-3.19, -0.06
Falls[g]			6.74	-12.18, 25.66

Abbreviations: CDE, controlled direct effects
[a]Adjusted for age, levodopa use, disease duration; mediator set to score = 0
[b]Adjusted for age, disease duration, comorbidities, SES; mediator set to score = 30
[c]Adjusted for age, disease duration, SES; mediator set to 1
[d]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[e]Adjusted for age, drug side effects, disease duration, marital status, SES; mediator set to T-score = 50
[f]Adjusted for SES; mediator set to 1 year
[g]Adjusted for age, disease duration, comorbidities; mediator set to 0

Sensitivity Analyses

When restricting to data from patients where diagnosis date was not imputed, there were still no significant differences between males and females with respect to any care milestone intervals (Table 23).

Table 23. Timing between care milestones in years by sex among those without imputed diagnosis dates

Interval (in years)	Males	Females	p-value
Symptom Onset to Diagnosis, mean (SD)	1.4 (2.19)	1.5 (2.29)	0.370[a]
Symptom Onset to Diagnosis, median (IQR)	1.0 (2.00)	1.0 (2.00)	0.451[b]
Diagnosis to Levodopa Initiation, mean (SD)	1.7 (2.50)	1.8 (2.80)	0.579[a]
Diagnosis to Levodopa Initiation, median (IQR)	1.0 (3.00)	1.0 (3.00)	0.969[b]
Diagnosis to First Visit to Center, mean (SD)	4.1 (4.98)	4.5 (5.64)	0.191[a]
Diagnosis to First Visit to Center, median (IQR)	2.3 (6.25)	2.2 (7.41)	0.709[b]
Diagnosis to Initial PD Visit at Center, mean (SD)	4.2 (4.96)	4.6 (5.60)	0.168[a]
Diagnosis to Initial PD Visit at Center, median (IQR)	2.3 (6.25)	2.2 (7.41)	0.659[b]
Diagnosis to DBS, mean (SD)	10.3 (4.90)	11.8 (5.79)	0.126[a]
Diagnosis to DBS, median (IQR)	10.0 (6.00)	11.0 (8.00)	0.112[b]

Abbreviations: SD, Standard Deviation, IQR, Interquartile Range; DBS, Deep Brain Stimulation
[a]t-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test

When examining mortality outcomes, there were no significant difference in time to death by sex (Log-rank p-value = 0.068, Wilcoxon p-value = 0.295, -2Log(LR) p-value = 0.386). A larger proportion of males died during the study period (n = 63, 6.9%), compared to females (n = 25, 4.6%). Although not significant, when data was available, females, in general, died sooner after diagnosis, compared to their male counterparts. Females had a mean time to death of 10.28 years and a median time to death of 10.10 years, compared to 12.58 years and 12.16 years for males.

C. Aim 3

Aim 3.1

Table 24, 25, and 26 display the sociodemographics, clinical characteristics, treatment, and outcomes at diagnosis (for those diagnosed at the Center), stratified by menopause type, HRT, and parity, respectively.

With respect to menopause type, there was only one significant difference between the two groups (Table 24). Females with surgical menopause were significantly more likely to have musculoskeletal/skin disease (t-test p-value = 0.002). Although not statistically significant, females who underwent surgical menopause were older, were less likely to live at home, had worse psychological distress (somatization, depression, and anxiety), had less heart disease, had less endocrine/metabolic/breast disease, were more likely to see a male physician, had worse UPDRS motor scores, and worse OARS ADLs scores.

Examining HRT, females who ever had HRT had significantly more endocrine/metabolic/breast disease (t-test p-value = 0.012) (Table 25). There was a significant difference in pain levels based on the Wilcoxon rank-sum test (p = 0.046); however, median pain scores were the same. Females who had ever used HRT were more likely to self-complete forms, were more likely to live alone, had more comorbidities, and were more likely to see a female clinician. However, all of these relationships were not significantly different between the two groups.

For parity (Table 26), at diagnosis, significant differences were present for self-efficacy (t-test p-value <0.001), mean pain (t-test p-value <0.001), median Hoehn & Yahr stage (Wilcoxon p-value = 0.035), OARS IADLs (t-test p-value = 0.013), and SF-12

physical health (t-test p-value = 0.023). Parous women had significantly higher self-efficacy, higher mean pain, less severe Hoehn & Yahr stage, worse OARS IADL disability, and better SF-12 physical health. Although non-significant, nulliparous females were more educated, were more likely to live alone, had more lower GI disease, and were more likely to be on dopaminergic drugs.

Table 24. Descriptive characteristics of sample at diagnosis (when diagnosed at the Center), stratified by menopause type

	Surgical (n=26)	Natural (n=80)	p-value
Sociodemographics			
Age, mean (SD)	69.5 (10.32)	66.6 (8.80)	0.211[a]
Age at Diagnosis	N/A	N/A	N/A
Age Category at Diagnosis, n (%)			0.729[d]
<50	0 (0.0)	1 (1.3)	
50 to <70	15 (57.7)	51 (63.8)	
70+	11 (42.3)	28 (35.0)	
Race/Ethnicity			1.000[d]
Non-Hispanic White	22 (91.7)	70 (89.7)	
Other	2 (8.3)	8 (10.3)	
Education, n (%)			0.387[d]
High School or Less	11 (50.0)	27 (36.0)	
Trade/Some College/College	8 (36.4)	29 (38.7)	
Advanced Degree	3 (13.6)	19 (25.3)	
Marital Status, n (%)			0.756[d]
Married	17 (65.4)	54 (67.5)	
Single	0 (0.0)	4 (5.0)	
Divorced/Separated	4 (15.4)	11 (13.8)	
Widowed	5 (19.2)	11 (13.8)	
Completer of Forms, n (%)			0.755[d]
Patient	16 (76.2)	51 (81.0)	
Co-Completed	5 (23.8)	12 (19.1)	
Caregiver			
Residence, n (%)			0.089[d]
Home	22 (88.0)	77 (97.5)	
Retirement Community	3 (12.0)	2 (2.5)	
Assisted Living/Nursing Home	0 (0.0)	0 (0.0)	
Reside With, n (%)			0.804[d]
Alone	5 (20.0)	16 (20.3)	
Spouse or Partner	17 (68.0)	54 (68.4)	
Other Family	2 (8.0)	8 (10.1)	
Other Family	1 (4.0)	1 (1.3)	
Median Income	79,334 (20,039)	81,053 (26,622)	0.729[a]

Table 24 Continued

	Surgical (n=26)	Natural (n=80)	p-value
Clinical Characteristics			
Fluctuator, n (%)	18 (94.7)	60 (100.0)	0.241[d]
Jankovic Subtype, n (%)			0.833[c]
Tremor Dominant	12 (60.0)	32 (52.5)	
Postural Instability/Gait Dominant	6 (30.0)	21 (34.4)	
Indeterminate	2 (10.0)	8 (13.1)	
Falls, n (%)			1.000[d]
No Falls	19 (86.4)	58 (85.3)	
Rare Falling	3 (13.6)	8 (11.8)	
Occasional Falls (<1/Day)	0 (0.0)	2 (2.9)	
Falls (1+/Day)	0 (0.0)	0 (0.0)	
Treatment Complications, mean (SD)	0.5 (0.71)	0.5 (0.93)	0.944[a]
Treatment Complications, median (IQR)	0 (1.00)	0 (1.00)	0.578[b]
BSI Somatization T-Score, mean (SD)	55.8 (8.69)	51.6 (8.28)	0.055[a]
BSI Depression T-Score, mean (SD)	51.4 (8.64)	47.3 (8.16)	0.067[a]
BSI Anxiety T-Score, mean (SD)	54.5 (10.53)	50.9 (9.47)	0.170[a]
CIRS Comorbidity Count, mean (SD)	3.6 (2.15)	3.2 (2.42)	0.509[a]
Heart Disease, n (%)	9 (40.9)	16 (73.5)	0.198[c]
Vascular Disease, n (%)	2 (9.1)	2 (3.2)	0.274[d]
Blood Disease, n (%)	1 (4.8)	2 (3.2)	1.000[d]
Respiratory Disease, n (%)	2 (9.1)	9 (14.3)	0.720[d]
ENT Disease, n (%)	6 (27.3)	17 (27.4)	1.000[d]
Upper GI Disease, n (%)	6 (27.3)	23 (32.1)	0.405[c]
Lower GI Disease, n (%)	5 (23.8)	13 (20.6)	0.765[d]
Liver Disease, n (%)	0 (0.0)	2 (3.1)	1.000[d]
Renal Disease, n (%)	2 (9.1)	5 (7.8)	1.000[d]
Genito-urinary Disease, n (%)	4 (19.1)	8 (12.5)	0.480[d]
Musculoskeletal/Skin Disease, n (%)	17 (77.3)	25 (39.7)	0.002[c]
Neurological Disease	16 (76.2)	46 (85.2)	0.497[d]
Endocrine/Metabolic/Breast Disease, n (%)	1 (4.8)	16 (26.2)	0.058[d]
Psychiatric/Memory Problems, n (%)	7 (31.8)	20 (31.8)	0.995[c]
Lorig Self-Efficacy, mean (SD)	14.2 (2.32)	14.7 (2.95)	0.499[a]
Pain, mean (SD)	0.8 (2.06)	0.9 (2.24)	0.822[a]
Pain, median (IQR)	0 (0.00)	0 (1.00)	0.878[b]
MMSE, mean (SD)	29.0 (1.05)	28.7 (1.58)	0.393[a]
MMSE, median (IQR)	29.0 (2.00)	29.0 (2.00)	0.840[b]
Hoehn & Yahr Stage, mean (SD)	2.1 (0.59)	2.0 (0.63)	0.396[a]
Hoehn & Yahr Stage, median (IQR)	2.0 (0.50)	2.0 (0.00)	0.275[b]

Table 24 Continued

	Surgical (n=26)	Natural (n=80)	p-value
Treatment			
DBS at Current Visit, n (%)	0 (0)	0 (0.0)	N/A
Clinician Sex, n (%)			0.058[c]
Male	11 (78.6)	35 (70.0)	
Female	3 (21.4)	15 (30.0)	
Carbo/Levodopa at Current Visit, n (%)	5 (35.7)	18 (40.0)	0.774[c]
Dopaminergic at Current Visit, n (%)	7 (43.8)	25 (48.1)	0.762[c]
Outcomes			
Died	N/A	N/A	N/A
UPDRS Motor, mean (SD)	26.3 (11.43)	22.8 (10.51)	0.200[a]
OARS ADLs, mean (SD)	9.8 (2.31)	8.9 (2.51)	0.130[a]
OARS IADLs, mean (SD)	9.9 (3.13)	9.4 (3.59)	0.573[a]
S&E, mean (SD)	87.5 (8.51)	89.2 (9.58)	0.438[a]
SF-12 MH, mean (SD)	47.6 (13.08)	50.1 (9.36)	0.413[a]
SF-12 PH, mean (SD)	40.4 (13.76)	44.1 (10.85)	0.279[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range, N/A, Not Applicable
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 25. Descriptive characteristics of sample at diagnosis (when diagnosed at the Center), stratified by HRT

	Ever HRT (n=55)	Never HRT (n=51)	p-value
Sociodemographics			
Age, mean (SD)	67.8 (8.66)	66.7 (10.06)	0.559[c]
Age at Diagnosis	N/A	N/A	N/A
Age Category at Diagnosis, n (%)			0.688[d]
<50	0 (0.0)	1 (2.0)	
50 to <70	34 (61.8)	32 (62.8)	
70+	21 (38.2)	18 (35.3)	
Race/Ethnicity			0.244[c]
Non-Hispanic White	50 (92.6)	41 (85.4)	
Other	4 (7.4)	7 (14.6)	
Education, n (%)			0.371[c]
High School or Less	18 (35.3)	20 (43.5)	
Trade/Some College/College	18 (35.3)	18(39.1)	
Advanced Degree	15 (29.4)	8 (17.4)	
Marital Status, n (%)			0.786[d]
Married	38 (69.1)	33 (64.7)	
Single	1 (1.8)	3 (5.9)	
Divorced/Separated	8 (14.6)	7 (13.7)	
Widowed	8 (14.6)	8 (15.7)	
Completer of Forms, n (%)			0.061[c]
Patient	40 (87.0)	26 (70.3)	
Co-Completed	6 (13.0)	11 (29.7)	
Caregiver	0 (0.0)	0 (0.0)	
Residence, n (%)			0.744[c]
Home	52 (94.6)	47 (95.9)	
Retirement Community	3 (5.5)	2 (4.1)	
Assisted Living/Nursing Home			
Reside With, n (%)			0.073[d]
Alone	13 (23.6)	8 (16.3)	
Spouse or Partner	38 (69.1)	33 (67.4)	
Other Family	2 (3.6)	8 (16.3)	
Other Family	2 (3.6)	0 (0.0)	
Median Income	82,738 (25,727)	78,728 (24,886)	0.419[c]

Table 25 Continued

	Ever HRT (n=55)	Never HRT (n=51)	p-value
Clinical Characteristics			
Fluctuator, n (%)	0 (0.0)	1 (2.8)	0.462[d]
Jankovic Subtype, n (%)			0.811[c]
Tremor Dominant	24 (57.1)	19 (50.0)	
Postural Instability/Gait Dominant	13 (31.0)	14 (36.8)	
Indeterminate	5 (11.9)	5 (13.2)	
Falls, n (%)			0.990[c]
No Falls	40 (85.1)	36 (85.7)	
Rare Falling	6 (12.8)	5 (11.9)	
Occasional Falls (<1/Day)	1 (2.1)	1 (2.4)	
Falls (1+/Day)	0 (0.0)	0 (0.0)	
Treatment Complications, mean (SD)	0.4 (0.82)	0.5 (0.95)	0.844[c]
Treatment Complications, median (IQR)	0 (1.00)	0 (1.00)	0.898[b]
BSI Somatization T-Score, mean (SD)	53.3 (8.11)	51.7 (9.00)	0.378[c]
BSI Depression T-Score, mean (SD)	48.2 (7.55)	48.5 (9.54)	0.849[c]
BSI Anxiety T-Score, mean (SD)	52.8 (9.05)	51.2 (10.56)	0.455[c]
CIRS Comorbidity Count, mean (SD)	3.5 (2.30)	2.9 (2.30)	0.201[c]
Heart Disease, n (%)	13 (28.9)	11 (29.7)	0.934[c]
Vascular Disease, n (%)	3 (6.5)	1 (2.6)	0.623[d]
Blood Disease, n (%)	2 (4.4)	1 (2.7)	1.000[d]
Respiratory Disease, n (%)	5 (10.9)	5 (13.2)	0.750[d]
ENT Disease, n (%)	10 (22.2)	13 (34.2)	0.224[c]
Upper GI Disease, n (%)	18 (39.1)	10 (27.0)	0.246[c]
Lower GI Disease, n (%)	10 (22.7)	7 (18.0)	0.590[c]
Liver Disease, n (%)	1 (2.2)	1 (2.6)	1.000[d]
Renal Disease, n (%)	6 (13.0)	1 (2.6)	0.118[d]
Genito-urinary Disease, n (%)	5 (10.9)	6 (15.8)	0.534[d]
Musculoskeletal/Skin Disease, n (%)	26 (57.8)	16 (41.0)	0.126[c]
Neurological Disease	35 (85.4)	26 (78.8)	0.460[c]
Endocrine/Metabolic/Breast Disease, n (%)	13 (30.2)	3 (7.9)	0.012[c]
Psychiatric/Memory Problems, n (%)	15 (33.3)	11 (28.2)	0.612[c]
Lorig Self-Efficacy, mean (SD)	14.3 (2.83)	14.8 (2.65)	0.556[c]
Pain, mean (SD)	1.3 (2.66)	0.5 (1.45)	0.058[c]
Pain, median (IQR)	0 (1.00)	0 (0.00)	0.046[b]
MMSE, mean (SD)	28.8 (1.49)	28.8 (1.46)	0.803[c]
MMSE, median (IQR)	29.0 (2.00)	29.0 (2.00)	0.750[b]
Hoehn & Yahr Stage, mean (SD)	2.1 (0.62)	2.0 (0.61)	0.587[c]
Hoehn & Yahr Stage, median (IQR)	2.0 (0.50)	2.0 (0.00)	0.626[b]

Table 25 Continued

	Ever HRT (n=55)	Never HRT (n=51)	p-value
Treatment			
DBS at Current Visit, n (%)	0 (0.0)	0 (0.0)	N/A
Clinician Sex, n (%)			0.199[c]
Male	23 (65.7)	24 (80.0)	
Female	12 (34.3)	6 (20.0)	
Carbo/Levodopa at Current Visit, n (%)	14 (40.0)	9 (37.5)	0.847[c]
Dopaminergic at Current Visit, n (%)	19 (47.5)	13 (41.2)	0.931[c]
Outcomes			
Died	N/A	N/A	N/A
UPDRS Motor, mean (SD)	24.3 (11.60)	23.1 (9.95)	0.597[c]
OARS ADLs, mean (SD)	9.2 (2.53)	8.9 (2.48)	0.577[c]
OARS IADLs, mean (SD)	9.3 (2.93)	9.7 (4.05)	0.633[c]
S&E, mean (SD)	88.5 (9.45)	88.9 (9.24)	0.842[c]
SF-12 MH, mean (SD)	49.1 (10.93)	50.0 (9.74)	0.649[c]
SF-12 PH, mean (SD)	42.3 (11.33)	44.3 (12.06)	0.426[c]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range, N/A, Not Applicable
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 26. Descriptive characteristics of sample at diagnosis (when diagnosed at the Center), stratified by parity

	Parous (n=96)	Nulliparous (n=6)	p-value
Sociodemographics			
Age, mean (SD)	67.0 (9.20)	65.6 (9.99)	0.754[a]
Age at Diagnosis	N/A	N/A	N/A
Age Category at Diagnosis, n (%)			0.709[d]
<50	2 (2.1)	0 (0.0)	
50 to <70	59 (61.5)	3 (50.0)	
70+	35 (36.5)	3 (50.0)	
Race/Ethnicity			1.000[d]
Non-Hispanic White	81 (89.0)	6 (100.0)	
Other	10 (11.0)	0 (0.0)	
Education, n (%)			0.137[d]
High School or Less	36 (40.5)	2 (40.0)	
Trade/Some College/College	32 (36.0)	0 (0.0)	
Advanced Degree	21 (23.6)	3 (60.0)	
Marital Status, n (%)			0.171[d]
Married	65 (68.4)	3 (50.0)	
Single	4 (4.2)	1 (16.7)	
Divorced/Separated	13 (13.7)	0 (0.0)	
Widowed	13 (13.7)	2 (33.3)	
Completer of Forms, n (%)			
Patient	61 (80.3)	3 (75.0)	
Co-Completed	15 (19.7)	1 (25.0)	
Caregiver	0 (0.0)	0 (0.0)	0.798[c]
Residence, n (%)			0.273[d]
Home	89 (95.7)	5 (83.3)	
Retirement Community	4 (4.3)	1 (16.7)	
Assisted Living/Nursing Home	0 (0.0)	0 (0.0)	
Reside With, n (%)			0.218[d]
Alone	15 (16.1)	3 (50.0)	
Spouse or Partner	65 (69.9)	3 (50.0)	
Other Family	11 (11.8)	0 (0.0)	
Other Family	2 (2.2)	0 (0.0)	
Median Income	82,277 (23,181)	80,807 (40,467)	0.933[a]

Table 26 Continued

	Parous (n=96)	Nulliparous (n=6)	p-value
Clinical Characteristics			
Fluctuator, n (%)	1 (1.5)	0 (0.0)	1.000[d]
Jankovic Subtype, n (%)			0.529[d]
Tremor Dominant	42 (57.5)	1 (33.3)	
Postural Instability/Gait Dominant	21 (28.8)	2 (66.7)	
Indeterminate	10 (13.7)	0 (0.0)	
Falls, n (%)			1.000[d]
No Falls	69 (87.3)	6 (100.0)	
Rare Falling	9 (11.4)	0 (0.0)	
Occasional Falls (<1/Day)	1 (1.3)	0 (0.0)	
Falls (1+/Day)	0 (0.0)	0 (0.0)	
Treatment Complications, mean (SD)	0.5 (0.87)	0.3 (0.82)	0.724[a]
Treatment Complications, median (IQR)	0 (1.00)	0 (0.00)	0.570[b]
BSI Somatization T-Score, mean (SD)	52.8 (8.90)	52.8 (5.72)	0.994[a]
BSI Depression T-Score, mean (SD)	48.4 (8.58)	51.4 (9.56)	0.521[a]
BSI Anxiety T-Score, mean (SD)	51.9 (9.49)	54.2 (12.03)	0.696[a]
CIRS Comorbidity Count, mean (SD)	3.4 (2.33)	3.3 (3.06)	0.963[a]
Heart Disease, n (%)	23 (30.7)	1 (33.3)	1.000[d]
Vascular Disease, n (%)	4 (5.3)	0 (0.0)	1.000[d]
Blood Disease, n (%)	3 (4.0)	0 (0.0)	1.000[d]
Respiratory Disease, n (%)	10 (13.2)	0 (0.0)	1.000[d]
ENT Disease, n (%)	22 (29.3)	0 (0.0)	0.555[d]
Upper GI Disease, n (%)	24 (32.0)	2 (66.7)	0.256[d]
Lower GI Disease, n (%)	14 (18.7)	2 (66.7)	0.105[d]
Liver Disease, n (%)	2 (2.6)	0 (0.0)	1.000[d]
Renal Disease, n (%)	8 (10.4)	0 (0.0)	1.000[d]
Genito-urinary Disease, n (%)	12 (16.0)	0 (0.0)	1.000[d]
Musculoskeletal/Skin Disease, n (%)	40 (52.6)	1 (33.3)	0.606[d]
Neurological Disease	58 (84.1)	2 (100.0)	1.000[d]
Endocrine/Metabolic/Breast Disease, n (%)	15 (20.3)	0 (0.0)	1.000[d]
Psychiatric/Memory Problems, n (%)	26 (34.2)	2 (66.7)	0.285[d]
Lorig Self-Efficacy, mean (SD)	15.0 (2.56)	12.0 (0.00)	<0.001[a]
Pain, mean (SD)	1.0 (2.27)	0 (0.00)	<0.001[a]
Pain, median (IQR)	0 (1.00)	0 (0.00)	0.190[b]
MMSE, mean (SD)	28.8 (1.35)	29.8 (0.45)	0.003[a]
MMSE, median (IQR)	29.0 (2.00)	30.0 (0.00)	0.087[b]
Hoehn & Yahr Stage, mean (SD)	2.0 (0.53)	2.4 (0.42)	0.076[a]
Hoehn & Yahr Stage, median (IQR)	2.0 (0.00)	2.5 (0.50)	0.035[b]

Table 26 Continued

	Parous (n=96)	Nulliparous (n=6)	p-value
Treatment			
DBS at Current Visit, n (%)	0 (0.0)	0 (0.0)	N/A
Clinician Sex, n (%)			0.585[d]
Male	41 (77.4)	3 (60.0)	
Female	12 (22.6)	2 (40.0)	
Carbo/Levodopa at Current Visit, n (%)	21 (38.2)	1 (100.0)	0.393[d]
Dopaminergic at Current Visit, n (%)	28 (45.2)	3 (100.0)	0.103[d]
Outcomes			
Died	N/A	N/A	N/A
UPDRS Motor, mean (SD)	22.8 (9.25)	24.2 (8.51)	0.705[a]
OARS ADLs, mean (SD)	9.1 (2.78)	8.2 (1.15)	0.157[a]
OARS IADLs, mean (SD)	9.7 (3.61)	7.9 (1.02)	0.013[a]
S&E, mean (SD)	89.4 (8.90)	90.0 (6.32)	0.841[a]
SF-12 MH, mean (SD)	49.7 (10.51)	50.4 (6.74)	0.822[a]
SF-12 PH, mean (SD)	42.9 (11.75)	53.4 (6.93)	0.023[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range, N/A, Not Applicable
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 27, 28, and 29 display the sociodemographics, clinical characteristics, treatment, and outcomes at initial PD visit, stratified by menopause type, HRT, and parity, respectively.

Significant differences by menopause type were present for falls (Chi-square p-value = 0.042), depressive symptoms (t-test p-value = 0.011), anxiety symptoms (t-test p-value = 0.016), vascular disease (Fisher's p-value = 0.011), mortality (Chi-square p-value = 0.005), OARS IADLs (t-test p-value = 0.043), and SF-12 PH (t-test p-value = 0.022) (Table 27). Those with surgical menopause had more falls, worse depressive symptoms, worse anxiety symptoms, more vascular disease, higher mortality, worse IADL disability, and worse physical health-related quality of life.

Table 28 demonstrates that there were significant differences by HRT usage for comorbidity count (t-test p-value = 0.043) and average pain (t-test p-value = 0.047). Those who have ever used HRT had more comorbidities and more pain.

There were three sociodemographic differences between parous and nulliparous females (Table 29). Nulliparous females had significantly greater education (Chi-square p-value = 0.013), were significantly less likely to be married (Fisher's exact test p-value <0.001), and were significantly more likely to live alone (Fisher's exact test p-value = 0.024).

Table 27. Descriptive characteristics of sample at initial PD visit to the Center, stratified by menopause type

	Surgical (n=94)	Natural (n=313)	p-value
Sociodemographics			
Age, mean (SD)	69.7 (9.35)	67.8 (8.88)	0.079[a]
Age at Diagnosis	64.2 (10.58)	63.1 (9.99)	0.367[a]
Age Category at Diagnosis, n (%)			0.913[c]
<50	8 (8.5)	24 (7.7)	
50 to <70	60 (63.8)	207 (66.1)	
70+	26 (27.7)	82 (26.2)	
Race/Ethnicity			0.281[c]
Non-Hispanic White	81 (89.0)	274 (92.6)	
Other	10 (11.0)	22 (7.4)	
Education, n (%)			0.419[c]
High School or Less	39 (44.3)	106 (36.6)	
Trade/Some College/College	29 (33.0)	111 (38.3)	
Advanced Degree	20 (22.7)	73 (25.2)	
Marital Status, n (%)			0.252[c]
Married	65 (69.2)	190 (60.9)	
Single	1 (1.1)	14 (4.5)	
Divorced/Separated	8 (8.5)	39 (12.5)	
Widowed	20 (21.3)	69 (22.1)	
Completer of Forms, n (%)			0.571[d]
Patient	48 (69.6)	170 (73.9)	
Co-Completed	21 (30.4)	59 (25.7)	
Caregiver	0 (0.0)	1 (0.4)	
Residence, n (%)			0.616[d]
Home	80 (90.9)	262 (93.6)	
Retirement Community	6 (6.8)	14 (5.0)	
Assisted Living/Nursing Home	2 (2.3)	4 (1.4)	
Reside With, n (%)			0.565[c]
Alone	18 (20.5)	70 (25.1)	
Spouse or Partner	58 (65.9)	178 (63.8)	
Other Family	9 (10.2)	27 (9.7)	
Other Family	3 (3.4)	4 (1.4)	
Median Income	80,608 (34,541)	83,674 (30,325)	0.440[a]

Table 27 Continued

	Surgical (n=94)	Natural (n=313)	p-value
Clinical Characteristics			
Fluctuator, n (%)	48 (61.5)	168 (73.0)	0.055[c]
Jankovic Subtype, n (%)			0.793[c]
Tremor Dominant	23 (29.5)	77 (33.5)	
Postural Instability/Gait Dominant	47 (60.3)	129 (56.1)	
Indeterminate	8 (10.3)	24 (10.4)	
Falls, n (%)			0.042[d]
No Falls	48 (57.8)	179 (69.1)	
Rare Falling	24 (28.9)	59 (22.8)	
Occasional Falls (<1/Day)	9 (10.8)	21 (8.1)	
Falls (1+/Day)	2 (2.4)	0 (0.0)	
Treatment Complications, mean (SD)	2.0 (3.01)	1.7 (2.40)	0.347[a]
Treatment Complications, median (IQR)	1.0 (3.00)	1.0 (2.00)	0.415[b]
BSI Somatization T-Score, mean (SD)	56.5 (9.01)	54.1 (8.82)	0.075[a]
BSI Depression T-Score, mean (SD)	52.8 (9.58)	49.2 (9.24)	0.011[a]
BSI Anxiety T-Score, mean (SD)	55.2 (9.36)	51.9 (9.21)	0.016[a]
CIRS Comorbidity Count, mean (SD)	3.7 (2.25)	3.2 (3.24)	0.094[a]
Heart Disease, n (%)	24 (32.9)	62 (26.2)	0.262[d]
Vascular Disease, n (%)	10 (13.3)	10 (4.2)	0.011[d]
Blood Disease, n (%)	4 (5.4)	14 (5.9)	1.000[c]
Respiratory Disease, n (%)	11 (14.7)	29 (12.2)	0.583[c]
ENT Disease, n (%)	15 (20.8)	54 (22.9)	0.715[c]
Upper GI Disease, n (%)	26 (35.1)	78 (32.5)	0.674[c]
Lower GI Disease, n (%)	14 (19.7)	40 (16.8)	0.571[c]
Liver Disease, n (%)	1 (1.4)	6 (2.5)	1.000[d]
Renal Disease, n (%)	3 (4.0)	12 (5.0)	1.000[d]
Genito-urinary Disease, n (%)	13 (18.1)	24 (10.0)	0.094[d]
Musculoskeletal/Skin Disease, n (%)	45 (60.8)	116 (48.3)	0.061[c]
Neurological Disease	66 (90.4)	207 (92.8)	0.504[c]
Endocrine/Metabolic/Breast Disease, n (%)	15 (21.1)	50 (21.4)	0.965[c]
Psychiatric/Memory Problems, n (%)	30 (41.7)	89 (37.1)	0.483[c]
Lorig Self-Efficacy, mean (SD)	13.4 (2.46)	13.6 (2.82)	0.751[a]
Pain, mean (SD)	1.5 (2.88)	1.1 (2.23)	0.244[a]
Pain, median (IQR)	0 (1.00)	0 (0.00)	0.614[b]
MMSE, mean (SD)	28.0 (3.33)	28.4 (2.33)	0.307[a]
MMSE, median (IQR)	29.0 (3.00)	29.0 (2.00)	0.535[b]
Hoehn & Yahr Stage, mean (SD)	2.7 (0.98)	2.5 (0.96)	0.176[a]
Hoehn & Yahr Stage, median (IQR)	2.5 (1.00)	2.0 (1.00)	0.134[b]

Table 27 Continued

	Surgical (n=94)	Natural (n=313)	p-value
Treatment			
DBS at Current Visit, n (%)	2 (2.1)	7 (2.2)	1.000[d]
Clinician Sex, n (%)			0.071[c]
Male	54 (79.4)	151 (68.0)	
Female	14 (20.6)	71 (32.0)	
Carbo/Levodopa at Current Visit, n (%)	47 (73.4)	148 (75.1)	0.787[c]
Dopaminergic at Current Visit, n (%)	61 (78.2)	174 (78.0)	0.974[c]
Outcomes			
Died	16 (17.0)	23 (7.4)	0.005[c]
UPDRS Motor, mean (SD)	28.9 (14.84)	26.5 (13.55)	0.189[a]
OARS ADLs, mean (SD)	12.1 (5.36)	10.8 (4.70)	0.059[a]
OARS IADLs, mean (SD)	13.0 (6.14)	11.4 (5.87)	0.043[a]
S&E, mean (SD)	76.4 (18.31)	79.9 (17.8)	0.131[a]
SF-12 MH, mean (SD)	47.0 (11.45)	48.6 (10.83)	0.295[a]
SF-12 PH, mean (SD)	36.2 (12.67)	40.0 (12.03)	0.022[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 28. Descriptive characteristics of sample at initial PD visit to the Center, stratified by HRT

	Ever HRT (n=216)	Never HRT (n=190)	p-value
Sociodemographics			
Age, mean (SD)	68.3 (8.53)	67.9 (9.62)	0.655[a]
Age at Diagnosis	63.4 (9.79)	63.0 (10.65)	0.720[a]
Age Category at Diagnosis, n (%)			0.794[c]
<50	16 (7.4)	17 (9.0)	
50 to <70	141 (65.3)	125 (65.8)	
70+	59 (27.3)	48 (25.3)	
Race/Ethnicity			0.144[c]
Non-Hispanic White	191 (93.2)	161 (89.0)	
Other	14 (6.8)	20 (11.1)	
Education, n (%)			0.194[c]
High School or Less	69 (34.5)	76 (42.9)	
Trade/Some College/College	81 (40.5)	58 (32.8)	
Advanced Degree	50 (25.0)	43 (24.3)	
Marital Status, n (%)			0.396[c]
Married	143 (66.2)	110 (58.2)	
Single	7 (3.2)	9 (4.8)	
Divorced/Separated	22 (10.2)	25 (13.2)	
Widowed	44 (20.4)	45 (23.8)	
Completer of Forms, n (%)			0.101[d]
Patient	123 (74.9)	93 (67.9)	
Co-Completed	37 (23.1)	43 (31.4)	
Caregiver	0 (0.0)	1 (0.7)	
Residence, n (%)			1.000[d]
Home	186 (92.5)	154 (92.2)	
Retirement Community	11 (5.5)	9 (5.4)	
Assisted Living/Nursing Home	4 (2.0)	4 (2.4)	
Reside With, n (%)			0.573[d]
Alone	46 (23.0)	43 (25.8)	
Spouse or Partner	133 (66.5)	102 (61.1)	
Other Family	16 (8.0)	19 (11.4)	
Other Family	5 (2.5)	3 (1.8)	
Median Income	84,326 (30,606)	82,067 (32,271)	0.473[a]

Table 28 Continued

	Ever HRT (n=216)	Never HRT (n=190)	p-value
Clinical Characteristics			
Fluctuator, n (%)	46 (28.2)	45 (31.9)	0.483[c]
Jankovic Subtype, n (%)			0.337[c]
Tremor Dominant	57 (35.2)	41 (28.9)	
Postural Instability/Gait Dominant	91 (56.2)	83 (58.5)	
Indeterminate	14 (8.6)	18 (12.7)	
Falls, n (%)			0.761[d]
No Falls	117 (65.4)	107 (66.9)	
Rare Falling	44 (24.6)	38 (23.8)	
Occasional Falls (<1/Day)	16 (8.9)	15 (9.4)	
Falls (1+/Day)	2 (1.1)	0 (0.0)	
Treatment Complications, mean (SD)	1.6 (2.47)	1.9 (2.70)	0.235[a]
Treatment Complications, median (IQR)	1.0 (2.00)	1.0 (3.00)	0.203[b]
BSI Somatization T-Score, mean (SD)	55.0 (8.59)	54.2 (9.30)	0.473[a]
BSI Depression T-Score, mean (SD)	50.4 (9.24)	49.6 (9.73)	0.482[a]
BSI Anxiety T-Score, mean (SD)	53.4 (9.26)	52.0 (9.39)	0.198[a]
CIRS Comorbidity Count, mean (SD)	3.6 (2.21)	3.1 (1.98)	0.043[a]
Heart Disease, n (%)	47 (28.5)	36 (25.2)	0.514[c]
Vascular Disease, n (%)	11 (6.6)	8 (5.5)	0.694[c]
Blood Disease, n (%)	12 (7.2)	7 (4.9)	0.395[c]
Respiratory Disease, n (%)	24 (14.5)	15 (10.4)	0.285[c]
ENT Disease, n (%)	32 (19.9)	38 (26.2)	0.188[c]
Upper GI Disease, n (%)	59 (35.3)	43 (29.7)	0.287[c]
Lower GI Disease, n (%)	30 (18.4)	22 (15.3)	0.466[c]
Liver Disease, n (%)	4 (2.4)	3 (2.1)	1.000[d]
Renal Disease, n (%)	7 (4.2)	8 (5.4)	0.596[c]
Genito-urinary Disease, n (%)	23 (14.0)	14 (9.7)	0.238[c]
Musculoskeletal/Skin Disease, n (%)	93 (56.4)	68 (46.3)	0.075[c]
Neurological Disease	146 (92.4)	125 (91.9)	0.875[c]
Endocrine/Metabolic/Breast Disease, n (%)	40 (24.5)	24 (17.1)	0.116[c]
Psychiatric/Memory Problems, n (%)	71 (43.3)	48 (32.9)	0.060[c]
Lorig Self-Efficacy, mean (SD)	13.5 (2.67)	13.6 (2.88)	0.901[a]
Pain, mean (SD)	1.4 (2.66)	0.9 (2.03)	0.047[a]
Pain, median (IQR)	0 (2.00)	0 (0.00)	0.069[b]
MMSE, mean (SD)	28.3 (2.64)	28.2 (2.62)	0.613[a]
MMSE, median (IQR)	29.0 (2.00)	29.0 (3.00)	0.348[b]
Hoehn & Yahr Stage, mean (SD)	2.5 (0.88)	2.5 (1.04)	0.994[a]
Hoehn & Yahr Stage, median (IQR)	2.0 (1.00)	2.0 (1.00)	0.511[b]

Table 28 Continued

	Ever HRT (n=216)	Never HRT (n=190)	p-value
Treatment			
DBS at Current Visit, n (%)	3 (1.4)	7 (3.7)	0.200[d]
Clinician Sex, n (%)			0.342[c]
Male	107 (68.6)	98 (73.7)	
Female	49 (31.4)	35 (26.3)	
Carbo/Levodopa at Current Visit, n (%)	103 (74.6)	90 (74.4)	0.962[c]
Dopaminergic at Current Visit, n (%)	127 (78.4)	106 (77.4)	0.832[c]
Outcomes			
Died	25 (11.6)	14 (7.4)	0.151[c]
UPDRS Motor, mean (SD)	26.9 (13.97)	27.3 (13.94)	0.798[a]
OARS ADLs, mean (SD)	11.1 (4.72)	11.1 (5.04)	0.933[a]
OARS IADLs, mean (SD)	11.8 (5.64)	11.6 (6.23)	0.821[a]
S&E, mean (SD)	79.8 (17.28)	78.6 (18.47)	0.561[a]
SF-12 MH, mean (SD)	47.7 (11.35)	48.7 (10.65)	0.403[a]
SF-12 PH, mean (SD)	38.6 (12.12)	40.0 (12.42)	0.324[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Table 29. Descriptive characteristics of sample at initial PD visit to the Center, stratified by parity

	Parous (n=358)	Nulliparous (n=30)	p-value
Sociodemographics			
Age, mean (SD)	68.2 (8.74)	68.1 (10.50)	0.983[a]
Age at Diagnosis	63.4 (10.03)	64.0 (10.05)	0.771[a]
Age Category at Diagnosis, n (%)			0.446[c]
<50	27 (7.5)	2 (6.7)	
50 to <70	238 (66.5)	17 (56.7)	
70+	93 (26.0)	11 (36.7)	
Race/Ethnicity			0.468[d]
Non-Hispanic White	306 (93.0)	27 (90.0)	
Other	23 (7.0)	3 (10.0)	
Education, n (%)			0.013[c]
High School or Less	126 (38.4)	6 (21.4)	
Trade/Some College/College	121 (36.9)	8 (28.6)	
Advanced Degree	81 (24.7)	14 (50.0)	
Marital Status, n (%)			<0.001[d]
Married	227 (63.8)	11 (36.7)	
Single	7 (2.0)	9 (30.0)	
Divorced/Separated	49 (13.8)	1 (3.3)	
Widowed	73 (20.5)	9 (30.0)	
Completer of Forms, n (%)			0.265[d]
Patient	188 (70.2)	18 (85.7)	
Co-Completed	79 (29.5)	3 (14.3)	
Caregiver	1 (0.4)	0 (0.0)	
Residence, n (%)			0.263[d]
Home	299 (92.6)	23 (88.5)	
Retirement Community	15 (4.6)	3 (11.5)	
Assisted Living/Nursing Home	9 (2.8)	0 (0.0)	
Reside With, n (%)			0.024[d]
Alone	71 (22.0)	12 (48.0)	
Spouse or Partner	207 (64.1)	11 (44.0)	
Other Family	37 (11.5)	1 (4.0)	
Other Family	8 (2.5)	1 (4.0)	
Median Income	84,315 (31,840)	91,261 (34,576)	0.295[a]

Table 29 Continued

	Parous (n=358)	Nulliparous (n=30)	p-value
Clinical Characteristics			
Fluctuator, n (%)	73 (27.8)	7 (28.0)	0.979[c]
Jankovic Subtype, n (%)			0.145[c]
Tremor Dominant	91 (34.3)	7 (30.4)	
Postural Instability/Gait Dominant	142 (53.6)	16 (69.6)	
Indeterminate	32 (12.1)	0 (0.0)	
Falls, n (%)			0.627[d]
No Falls	193 (66.1)	16 (57.1)	
Rare Falling	72 (24.7)	9 (32.1)	
Occasional Falls (<1/Day)	24 (8.2)	3 (10.7)	
Falls (1+/Day)	3 (1.0)	0 (0.0)	
Treatment Complications, mean (SD)	1.6 (2.54)	2.0 (2.74)	0.442[a]
Treatment Complications, median (IQR)	1.0 (2.00)	0.5 (3.00)	0.572[b]
BSI Somatization T-Score, mean (SD)	54.6 (8.86)	57.1 (9.79)	0.255[a]
BSI Depression T-Score, mean (SD)	50.3 (9.73)	49.8 (9.39)	0.809[a]
BSI Anxiety T-Score, mean (SD)	53.0 (9.43)	53.5 (9.04)	0.815[a]
CIRS Comorbidity Count, mean (SD)	3.4 (2.17)	3.9 (2.35)	0.408[a]
Heart Disease, n (%)	72 (26.5)	8 (40.0)	0.190[c]
Vascular Disease, n (%)	23 (8.4)	0 (0.0)	0.383[d]
Blood Disease, n (%)	15 (5.5)	1 (5.3)	1.000[d]
Respiratory Disease, n (%)	37 (13.5)	4 (20.0)	0.498[d]
ENT Disease, n (%)	64 (23.8)	5 (25.0)	1.000[d]
Upper GI Disease, n (%)	84 (30.6)	10 (50.0)	0.071[c]
Lower GI Disease, n (%)	45 (16.6)	5 (25.0)	0.356[d]
Liver Disease, n (%)	7 (2.5)	0 (0.0)	1.000[d]
Renal Disease, n (%)	13 (4.7)	1 (5.0)	1.000[d]
Genito-urinary Disease, n (%)	40 (14.8)	2 (10.0)	0.749[d]
Musculoskeletal/Skin Disease, n (%)	142 (51.6)	10 (50.0)	0.888[c]
Neurological Disease	244 (93.1)	16 (84.2)	0.160[d]
Endocrine/Metabolic/Breast Disease, n (%)	55 (20.5)	7 (36.8)	0.143[d]
Psychiatric/Memory Problems, n (%)	105 (38.8)	8 (40.0)	1.000[d]
Lorig Self-Efficacy, mean (SD)	13.7 (2.77)	12.6 (3.09)	0.233[a]
Pain, mean (SD)	1.3 (2.48)	0.9 (2.26)	0.421[a]
Pain, median (IQR)	0 (1.00)	0 (0.00)	0.310[b]
MMSE, mean (SD)	28.4 (2.26)	28.6 (2.00)	0.559[a]
MMSE, median (IQR)	29.0 (2.00)	29.5 (2.00)	0.333[b]
Hoehn & Yahr Stage, mean (SD)	2.4 90.95)	2.6 (0.89)	0.710[a]
Hoehn & Yahr Stage, median (IQR)	2.0 (1.00)	2.0 (1.00)	0.585[b]

Table 29 Continued

	Parous (n=358)	Nulliparous (n=30)	p-value
Treatment			
DBS at Current Visit, n (%)	10 (2.8)	0 (0.0)	1.000[d]
Clinician Sex, n (%)			0.915[c]
Male	172 (72.9)	17 (73.9)	
Female	64 (27.1)	6 (26.1)	
Carbo/Levodopa at Current Visit, n (%)	167 (73.6)	12 (80.0)	0.765[d]
Dopaminergic at Current Visit, n (%)	200 (76.9)	19 (86.4)	0.427[d]
Outcomes			
Died	31 (8.7)	4 (13.3)	0.332[d]
UPDRS Motor, mean (SD)	27.3 (13.64)	25.6 (12.78)	0.495[a]
OARS ADLs, mean (SD)	11.1 (4.96)	11.2 (4.17)	0.939[a]
OARS IADLs, mean (SD)	11.7 (5.93)	12.1 (5.77)	0.786[a]
S&E, mean (SD)	79.6 (17.06)	80.4 (17.43)	0.828[a]
SF-12 MH, mean (SD)	47.6 (11.42)	47.9 (9.98)	0.889[a]
SF-12 PH, mean (SD)	39.8 (12.04)	40.0 (14.01)	0.936[a]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range
[a]T-test with Satterthwaite Approximation
[b]Wilcoxon Rank-Sum Test
[c]Chi-Square Test
[d]Fisher's Exact Test

Aim 3.2

Table 30 displays the population average severity at diagnosis, average rate of progression, and inter-individual heterogeneity at diagnosis by menopause type, HRT, and parity. Figure 16, 17, and 18 show plots of the progression patterns by menopause type, HRT, and parity, respectively.

Examining menopause type, there were no significant differences at diagnosis; however, individuals with surgical menopause had significantly faster progression between 5 and 10 years since diagnosis ($\beta = 2.17$, 95% CI: 1.36, 2.98), compared to those with natural menopause ($\beta = 0.62$, 95% CI: 0.23, 1.01), and significantly slower progression from 20 years since diagnosis onward ($\beta = 0.30$, 95% CI: -0.78, 1.39), compared to those with natural menopause ($\beta = 2.28$, 95% CI: 1.63, 2.92). The natural

menopause group demonstrated significant worsening over all time intervals; however, the surgical menopause group had non-significant worsening from 0 to 5 years, significant worsening from 5 to 15 years, and non-significant worsening from 15 years and beyond.

For HRT, there were no significant differences between the groups at diagnosis. The ever HRT group fared significantly worse than the never HRT group between 5 and 10 years ($\beta = 1.32$, 95% CI: 0.86, 1.77 versus $\beta = 0.21$, 95% CI: -0.36, 0.78) and between 15 and 20 years ($\beta = 2.02$, 95% CI: 1.30, 2.75 versus $\beta = 0.36$, 95% CI: -0.39, 1.11).

No significant differences were present for UPDRS motor scores at diagnosis nor impairment progression by parity. The parous group demonstrated significant progression at all time intervals; whereas, significant progression for the nulliparous group was limited to 10 to 15 years from diagnosis.

Table 30. Linear mixed effects model for Parkinson disease impairment progression by menopause type, HRT, and parity measured with the clinician-assessed, UPDRS Motor Scores

	Surgical Menopause			Natural Menopause			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
At Diagnosis[a]	21.15	17.45, 24.84	11.84	20.83	18.99, 22.67	10.06	0.879
0 to <5 Years[b]	0.36	-0.54, 1.26		1.25	0.78, 1.72		0.087
5 to <10 Years[b]	2.17	1.36, 2.98		0.62	0.23, 1.01		0.001
10 to <15 Years[b]	1.64	0.23, 1.01		1.12	0.71, 1.53		0.347
15 to <20 Years[b]	1.09	-0.29, 2.46		1.24	0.68, 1.81		0.836
≥20 Years[b]	0.30	-0.78, 1.38		2.28	1.63, 2.92		0.002
1st Year in Clinic[c]	-0.85	-3.41, 1.70		-3.27	-4.63, -1.90		0.102
	Ever HRT			**Never HRT**			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
At Diagnosis[a]	19.77	17.52, 22.03	10.83	22.27	19.87, 24.66	9.93	0.137
0 to <5 Years[b]	1.00	0.45, 1.55		1.27	0.64, 1.90		0.529
5 to <10 Years[b]	1.32	0.86, 1.77		0.21	-0.36, 0.78		0.003
10 to <15 Years[b]	1.17	0.67, 1.68		0.95	0.37, 1.54		0.578
15 to <20 Years[b]	2.02	1.30, 2.75		0.36	-0.39, 1.11		0.002
≥20 Years[b]	1.23	0.42, 2.03		2.11	1.43, 2.78		0.101
1st Year in Clinic[c]	-2.71	-4.37, -1.06		-2.76	-4.51, -1.02		0.966
	Parous			**Nulliparous**			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
At Diagnosis[a]	21.66	19.90, 23.42	10.77	20.62	15.18, 26.05	7.55	0.720
0 to <5 Years[b]	1.15	0.71, 1.59		0.54	-0.87, 1.95		0.418
5 to <10 Years[b]	0.82	0.45, 1.20		1.06	-0.09, 2.21		0.708
10 to <15 Years[b]	1.00	0.59, 1.42		1.83	0.67, 2.99		0.187
15 to <20 Years[b]	1.54	0.99, 2.09		0.67	-1.86, 3.20		0.509
≥20 Years[b]	1.69	1.15, 2.24		-1.79	-5.21, 2.98		0.088
1st Year in Clinic[c]	-2.87	-4.17, -1.58		-1.12	-5.21, 2.98		0.422

Abbreviations: CI, Confidence Interval; SD, Standard Deviation

[a]Intercept

[b]Interval represents time since diagnosis with β representing annual rate of change

[c]One year rate of change

[d]Adjusted for mean standardized socioeconomic status and mean standardized cohort (birth year)

[e]Comparison of group differences

Figure 16. Plot of average rate of Parkinson disease UPDRS Motor progression by menopause type

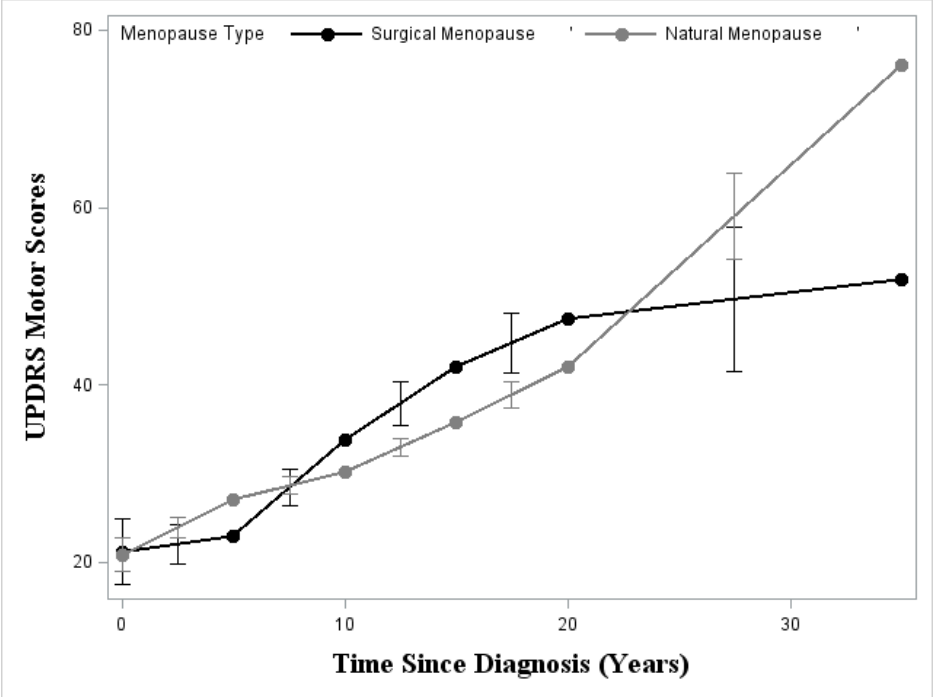


Figure 17. Plot of average rate of Parkinson disease UPDRS Motor progression by HRT use

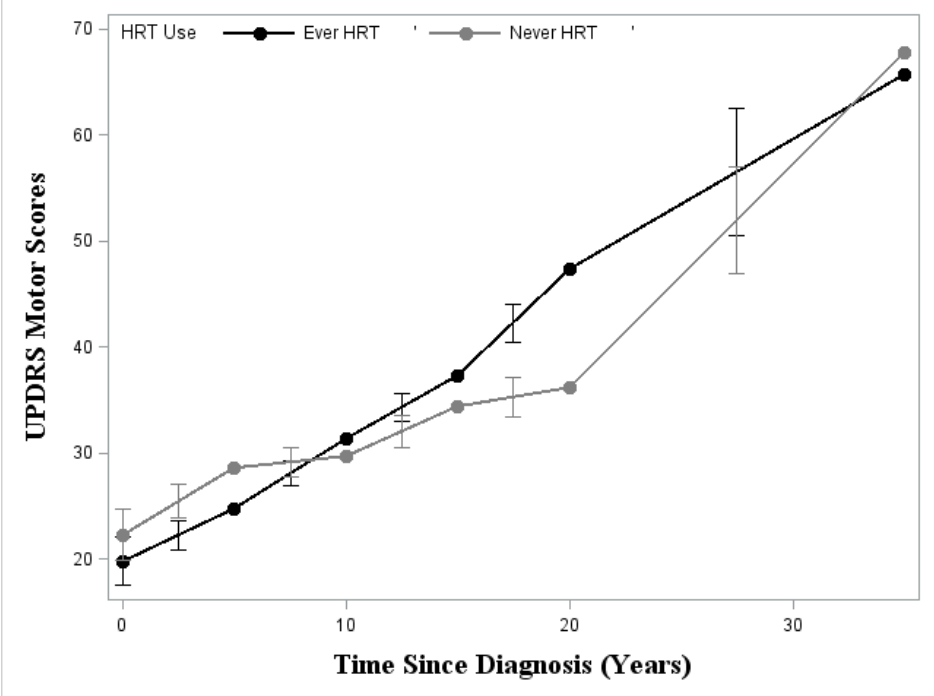
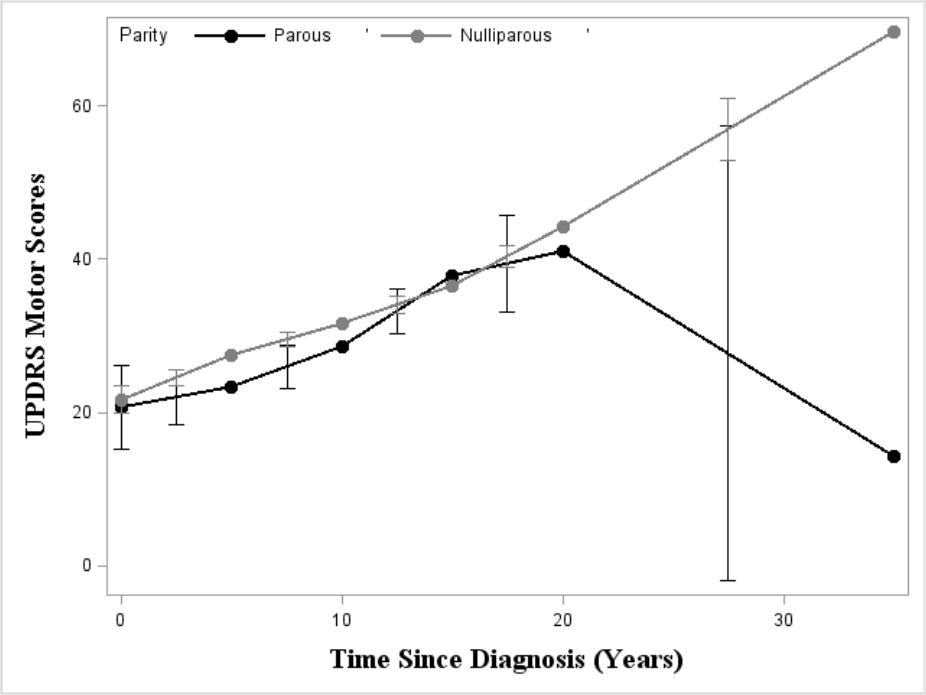


Figure 18. Plot of average rate of Parkinson disease UDPRS Motor progression by parity



With respect to disability (Table 31), the natural menopause group had worse disease progression late in the disease course between 15 and 20 years (β = 0.86, 95% CI: 0.64, 1.07 versus β = -0.15, 95% CI: -0.66, 0.36) and after 20 years (β = 1.14, 95% CI: 0.89, 1.39 versus β = 0.20, 95% CI: -0.29, 0.69) for OARS ADLs. For OARS IADLs and the Schwab & England scale, the natural menopause group had more severe progression after 20 years (β = 1.35, 95% CI: 1.05, 1.65 versus β = -0.05, 95% CI: -0.64, 0.54 on the OARS IADLs and β = -2.80, 95% CI: -4.00, -1.60 versus β = 1.02, 95% CI: -1.03, 3.07 on the S&E). In general, the surgical menopause group appeared to plateau and did not experience significant progression 15 years after diagnosis. For all disability outcomes, there were no significant differences between the groups at diagnosis or with respect to the first year in the clinic.

For HRT, there were many significant differences between the two groups. Although there were no differences at diagnosis between the groups for any outcome, for OARS ADLs, the ever HRT group experienced significantly worse progression between 5 and 10 years and 15 to 20 years with the never HRT group having significantly worse progression after 20 years. The never HRT group significantly improved in the first year in the clinic ($\beta = 0.82$, 95% CI: 0.17, 1.47) while the ever HRT group did not ($\beta = -0.53$, 95% CI: -1.14, 0.07). For OARS IADLs, the ever HRT group fared significantly worse from 5 to 10 years post-diagnosis and again, did not experience clinical benefit in the first year in the clinic ($\beta = -0.22$, 95% CI: -0.95, 0.50) while the never HRT group worsened in the first year in the clinic ($\beta = 1.62$, 95% CI: 0.84, 2.39). For S&E, the never HRT group fared worse than the ever HRT group between 0 to 5 years and after 20 years but fared better between 5 and 10 years.

There were limited significant differences by parity. No differences existed for OARS ADLs. The only significant differences were present for OARS IADLs between 15 to 20 years, with the parous group faring worse ($\beta = 0.97$, 95% CI: 0.71, 1.23 versus $\beta = -1.18$, 95% CI: -2.93, 0.57). For S&E, after 20 years, the nulliparous group significantly improved ($\beta = 10.89$, 95% CI: 1.15, 20.64) while the parous group significantly worsened ($\beta = -2.05$, 95% CI: -3.08, -1.01). There was no significant difference in any of the outcomes at diagnosis nor in the clinical benefit of the first year care in the clinic.

Table 31. Linear mixed effects models for Parkinson disease disability progression by menopause type, HRT, and parity measured with two patient-reported measures (OARS ADLs and OARS IADLs) and one clinician-assessed measure (Schwab & England scale)

Effects	Fixed		Random	Fixed		Random	
	Surgical Menopause			Natural Menopause			
Parameters	β [d]	95% CI	SD	β [d]	95% CI	SD	p-value[e]
OARS ADLs							
At Diagnosis[a]	9.19	7.78, 10.60	4.66	8.19	7.47, 8.90	4.30	0.214
0 to <5 Years[b]	0.44	0.09, 0.80		0.37	0.20, 0.54		0.730
5 to <10 Years[b]	0.42	0.09, 0.75		0.56	0.42, 0.70		0.436
10 to <15 Years[b]	0.90	0.49, 1.32		0.54	0.39, 0.69		0.107
15 to <20 Years[b]	-0.15	-0.66, 0.36		0.86	0.64, 1.07		<0.001
≥20 Years[b]	0.20	-0.29, 0.69		1.14	0.89, 1.39		0.001
1st Year in Clinic[c]	-0.17	-1.15, 0.81		0.09	-0.41, 0.59		0.641
OARS IADLs							
At Diagnosis[a]	9.19	7.51, 10.88	5.55	8.23	7.38, 9.08	5.15	0.317
0 to <5 Years[b]	0.71	0.29, 1.13		0.42	0.22, 0.63		0.234
5 to <10 Years[b]	0.56	0.16, 0.97		0.70	0.53, 0.87		0.549
10 to <15 Years[b]	0.63	0.13, 1.14		0.67	0.49, 0.85		0.908
15 to <20 Years[b]	0.52	-0.10, 1.13		0.76	0.50, 1.02		0.474
≥20 Years[b]	-0.05	-0.64, 0.54		1.35	1.05, 1.65		<0.001
1st Year in Clinic[c]	0.20	-0.97, 1.37		0.66	0.07, 1.26		0.492
Schwab & England							
At Diagnosis[a]	86.90	81.28, 92.52	14.87	90.18	87.43, 92.92	12.00	0.304
0 to <5 Years[b]	-1.16	-2.75, 0.44		-2.01	-2.83, -1.18		0.356
5 to <10 Years[b]	-2.59	-4.03, -1.14		-1.63	-2.38, -0.88		0.250
10 to <15 Years[b]	-2.53	-4.40, -0.65		-1.63	-2.47, -0.79		0.391
15 to <20 Years[b]	-0.98	-3.65, 1.70		-3.16	-4.40, -1.93		0.146
≥20 Years[b]	1.02	-1.03, 3.07		-2.80	-4.00, -1.60		0.002
1st Year in Clinic[c]	-4.21	-8.31, -0.10		0.05	-2.19, 2.29		0.074

Table 31 Continued

	Ever HRT			Never HRT			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
OARS ADLs							
At Diagnosis[a]	8.27	7.41, 9.13	4.37	8.51	7.57, 9.45	4.33	0.717
0 to <5 Years[b]	0.31	0.10, 0.51		0.51	0.28, 0.74		0.191
5 to <10 Years[b]	0.73	0.56, 0.90		0.27	0.07, 0.48		0.001
10 to <15 Years[b]	0.62	0.44, 0.80		0.37	0.14, 0.60		0.095
15 to <20 Years[b]	1.06	0.80, 1.32		0.30	<-0.01, 0.59		<0.001
≥20 Years[b]	-0.02	-0.37, 0.33		1.41	1.13, 1.69		<0.001
1st Year in Clinic[c]	-0.53	-1.14, 0.07		0.82	0.17, 1.47		0.003
OARS IADLs							
At Diagnosis[a]	8.06	7.01, 9.10	5.45	8.78	7.65, 9.92	5.26	0.354
0 to <5 Years[b]	0.43	0.19, 0.67		0.59	0.32, 0.87		0.386
5 to <10 Years[b]	0.91	0.70, 1.11		0.34	0.09, 0.58		0.001
10 to <15 Years[b]	0.81	0.59, 1.03		0.32	0.05, 0.60		0.006
15 to <20 Years[b]	0.81	0.49, 1.12		0.61	0.24, 0.97		0.414
≥20 Years[b]	0.55	0.12, 0.97		1.28	0.95, 1.62		0.008
1st Year in Clinic[c]	-0.22	-0.95, 0.50		1.62	0.84, 2.39		0.001
Schwab & England							
At Diagnosis[a]	89.85	86.48, 93.23	12.92	88.81	85.20, 92.42	12.19	0.679
0 to <5 Years[b]	-1.11	-2.09, -0.12		-2.68	-3.78, -1.58		0.037
5 to <10 Years[b]	-2.68	-3.78, -1.58		-0.47	-1.53, 0.59		0.001
10 to <15 Years[b]	-1.93	-2.96, -0.90		-1.04	-2.23, 0.15		0.265
15 to <20 Years[b]	-3.41	-4.92, -1.90		-2.07	-3.73, -0.41		0.243
≥20 Years[b]	0.08	-1.34, 1.50		-3.74	-5.06, -2.42		<0.001
1st Year in Clinic[c]	-1.52	-4.25, 1.20		-0.62	-3.48, 2.24		0.653

Table 31 Continued

	Parous			Nulliparous			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
OARS ADLs							
At Diagnosis[a]	8.65	7.97, 9.34	4.51	8.03	5.62, 10.45	4.31	0.629
0 to <5 Years[b]	0.36	0.20, 0.52		0.29	-0.27, 0.85		0.801
5 to <10 Years[b]	0.58	0.44, 0.72		0.73	0.26, 1.20		0.553
10 to <15 Years[b]	0.56	0.40, 0.71		0.72	0.28, 1.15		0.490
15 to <20 Years[b]	0.91	0.69, 1.12		0.38	-1.01, 1.78		0.470
≥20 Years[b]	0.84	0.61, 1.08		1.03	-0.39, 2.45		0.798
1st Year in Clinic[c]	-0.07	-0.54, 0.41		1.07	-0.61, 2.75		0.200
OARS IADLs							
At Diagnosis[a]	8.86	8.04, 9.68	5.47	7.19	4.09, 10.29	5.83	0.308
0 to <5 Years[b]	0.39	0.20, 0.59		1.03	0.33, 1.72		0.084
5 to <10 Years[b]	0.77	0.60, 0.94		0.68	0.12, 1.25		0.766
10 to <15 Years[b]	0.58	0.39, 0.77		1.08	0.56, 1.60		0.077
15 to <20 Years[b]	0.97	0.71, 1.23		-1.18	-2.93, 0.57		0.017
≥20 Years[b]	0.98	0.70, 1.26		2.34	0.63, 4.04		0.124
1st Year in Clinic[c]	0.61	0.04, 1.17		0.19	-1.91, 2.28		0.703
Schwab & England							
At Diagnosis[a]	89.00	86.33, 91.66	12.92	87.71	78.14, 97.27	12.94	0.799
0 to <5 Years[b]	-1.78	-2.58, -0.99		-1.09	-3.83, 1.63		0.635
5 to <10 Years[b]	-1.91	-2.63, -1.19		-1.60	-3.99, 0.79		0.809
10 to <15 Years[b]	-1.29	-2.12, -0.47		-3.83	-6.97, -0.70		0.125
15 to <20 Years[b]	-3.12	-4.32, -1.92		-5.00	-11.52, 1.52		0.577
≥20 Years[b]	-2.05	-3.08, -1.01		10.89	1.15, 20.64		0.010
1st Year in Clinic[c]	-1.82	-3.97, 0.33		0.62	-7.17, 8.41		0.553

Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change
[d]Adjusted for mean standardized socioeconomic status and mean standardized cohort (birth year)
[e]Comparison of group differences

Table 32 demonstrates the significant differences in health-related quality of life (SF-12 PH and SF-12 MH) by the various reproductive health characteristics. No significant differences in presentation, progression, or initial benefit of clinical care at the Center were present for SF-12 MH scores by menopause type, HRT, or parity. The

results suggest limited significant SF-12 MH progression except for some significant progression mid to late in the disease course for some groups.

For SF-12 PH, there were no significant differences by menopause type. The surgical menopause group plateaued in terms of progression at 5 years while the natural menopause group experienced significant progression until 20 years. For HRT, the never HRT group's SF-12 PH scores worsened by 1.46 units (95% CI: -1.94, -0.97) while the ever HRT group worsened by only 0.71 units (95% CI: -1.13, -0.28) between 0 and 5 years. The pattern flipped between 5 and 10 years (ever β = -0.97, 95% CI: -1.34, -0.60; never β = -0.36, 95% CI: -0.79, 0.08). For parity, the nulliparous group had worse SF-12 PH progression, compared to the parous group, between 0 and 5 years (β = -2.22, 95% CI: -3.33, -1.12 versus β = -0.92, 95% CI: -1.27, -0.58) and after 20 years (β = -3.91, 95% CI: -6.45, -1.36 versus β = -0.09, 95% CI: -0.61, 0.42).

Table 32. Linear mixed effects models for Parkinson disease health-related quality of life progression by menopause type, HRT, and parity measured with two patient-reported measures (SF-12 Mental Health and SF-12 Physical Health)

	Surgical Menopause			Natural Menopause			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
SF-12 Mental Health							
At Diagnosis[a]	49.69	46.72, 52.66	8.05	50.20	48.67, 51.73	7.67	0.762
0 to <5 Years[b]	-0.59	-1.42, 0.24		-0.37	-0.79, 0.04		0.651
5 to <10 Years[b]	-0.05	-0.85, 0.74		-0.18	-0.53, 0.18		0.783
10 to <15 Years[b]	-1.27	-2.25, -0.28		-0.36	-0.74, 0.03		0.092
15 to <20 Years[b]	0.74	-0.61, 2.09		-0.52	-0.61, 0.03		0.088
≥20 Years[b]	0.52	-0.60, 1.65		-0.24	-0.89, 0.41		0.249
1st Year in Clinic[c]	0.92	-1.45, 3.29		0.94	-0.28, 2.15		0.990
SF-12 Physical Health							
At Diagnosis[a]	40.93	37.88, 43.99	10.23	44.64	43.19, 46.10	8.59	0.032
0 to <5 Years[b]	-0.91	-1.65, -0.17		-1.07	-1.42, -0.71		0.704
5 to <10 Years[b]	-0.49	-1.19, 0.21		-0.76	-1.06, -0.45		0.490
10 to <15 Years[b]	-0.21	-1.06, 0.65		-0.77	-1.09, -0.44		0.231
15 to <20 Years[b]	-0.06	-1.24, 1.12		-0.59	-1.06, -0.12		0.412
≥20 Years[b]	-0.14	-1.23, 0.94		-0.41	-0.97, 0.15		0.670
1st Year in Clinic[c]	2.43	0.35, 4.51		1.76	0.71, 2.80		0.572
	Ever HRT			**Never HRT**			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
SF-12 Mental Health							
At Diagnosis[a]	49.42	47.57, 51.26	8.03	50.53	48.50, 52.55	7.63	0.427
0 to <5 Years[b]	-0.38	-0.87, 0.11		-0.48	-1.04, 0.07		0.778
5 to <10 Years[b]	<0.01	-0.43, 0.43		-0.19	-0.70, 0.31		0.564
10 to <15 Years[b]	-0.53	-0.99, -0.06		-0.27	-0.84, 0.30		0.496
15 to <20 Years[b]	-0.03	-0.70, 0.64		-0.87	-1.65, -0.10		0.107
≥20 Years[b]	0.28	-0.54, 1.11		-0.18	-0.90, 0.55		0.413
1st Year in Clinic[c]	0.91	-0.56, 2.37		0.84	-0.73, 2.42		0.955
SF-12 Physical Health							
At Diagnosis[a]	43.18	41.37, 44.99	9.35	45.08	43.16, 47.01	8.54	0.158
0 to <5 Years[b]	-0.71	-1.13, -0.28		-1.46	-1.94, -0.97		0.023
5 to <10 Years[b]	-0.97	-1.34, -0.60		-0.36	-0.79, 0.08		0.035
10 to <15 Years[b]	-0.62	-1.02, -0.23		-0.72	-1.20, -0.23		0.771
15 to <20 Years[b]	-0.79	-1.36, -0.22		-0.19	-0.86, 0.49		0.181
≥20 Years[b]	0.25	-0.52, 1.02		-0.61	-1.23, 0.02		0.090
1st Year in Clinic[c]	1.83	0.57, 3.09		1.59	0.24, 2.95		0.802

Table 32 Continued

	Parous			Nulliparous			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
SF-12 Mental Health							
At Diagnosis[a]	49.21	47.78, 50.63	7.66	50.59	45.01, 56.17	9.25	0.638
0 to <5 Years[b]	-0.23	-0.63, 0.16		-1.10	-2.45, 0.24		0.225
5 to <10 Years[b]	-0.29	-0.63, 0.05		-0.33	-1.49, 0.82		0.940
10 to <15 Years[b]	-0.40	-0.79, -0.01		-0.87	-1.98, 0.24		0.440
15 to <20 Years[b]	-0.58	-1.12, -0.05		0.77	-2.48, 4.03		0.419
≥20 Years[b]	0.08	-0.51, 0.65		-3.01	-6.09, 0.07		0.054
1st Year in Clinic[c]	0.99	-0.16, 2.15		3.64	-0.30, 7.58		0.206
SF-12 Physical Health							
At Diagnosis[a]	43.86	42.47, 45.26	9.03	47.94	43.40, 52.48	7.37	0.092
0 to <5 Years[b]	-0.92	-1.27, -0.58		-2.22	-3.33, -1.12		0.027
5 to <10 Years[b]	-0.72	-1.01, -0.42		-1.11	-2.06, -0.16		0.438
10 to <15 Years[b]	-0.66	-1.00, -0.33		-0.47	-1.39, 0.45		0.698
15 to <20 Years[b]	-0.59	-1.04, -0.13		0.67	-1.99, 3.33		0.363
≥20 Years[b]	-0.09	-0.61, 0.42		-3.91	-6.45, -1.36		0.004
1st Year in Clinic[c]	1.13	0.13, 2.13		4.26	1.02, 7.51		0.070

Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change
[d]Adjusted for mean standardized socioeconomic status and mean standardized cohort (birth year)
[e]Comparison of group differences

Sensitivity Analyses

The first sensitivity analysis comparing characteristics between those with imputed versus non-imputed menopause status found minimal significant differences. Those with imputed menopause status were more likely to have an onset at 70+ years (Fisher's exact test p-value = 0.045), lower UPDRDS motor scores (t-test p-value = 0.016), and better self-efficacy for managing chronic conditions (t-test p-value = 0.045) at diagnosis. At initial PD visits to the Center, females with an imputed menopause status were more educated (Chi-square p-value = 0.012), were older (t-test p-value <0.001), had an older age at diagnosis (t-test p-value = 0.003), had fewer complications

of therapy (Wilcoxon p-value = 0.015), and had better cognition (Wilcoxon p-value <0.001).

The second sensitivity analysis explored the interaction between menopause type and HRT. Examining sociodemographics, clinical characteristics, treatment, and outcomes by menopause status-HRT characteristics, there were only two significant differences at diagnosis—the proportion with musculoskeletal/skin disease (Fisher's exact test p-value = 0.007) and endocrine/metabolic/breast disease (Fisher's exact test p-value = 0.012). Those with surgical menopause and ever HRT usage were most likely to have muculoskeletal/skin disease (n = 9, 81.8%) while those with natural menopause and no HRT usage were the least likely (n = 8, 28.6%). Endocrine/metabolic/breast disease was most common among those with natural menopause and ever HRT usage (n = 12, 37.5%). At initial PD visits, there were no significant differences across groups in sociodemographics or treatments. With respect to clinical characteristics, there were significant differences in BSI anxiety T-scores (t-test p-value = 0.029) and the proportion with vascular disease (Fisher's exact test p-value = 0.046). The surgical menopause group with never HRT reported the greatest anxiety symptoms (mean = 57.3, SD = 10.88) and were the most likely to have vascular disease (n = 4, 15.4%). Table 33 displays outcomes at first visit by menopause type-HRT groupings. There were significant differences in mortality (Chi-square p-value = 0.015), OARS ADLs score (ANOVA p-value = 0.003), and OARS IADLs scores (ANOVA p-value = 0.008). Mortality was worst in the surgical, never HRT group (n=6, 20.7%); OARS ADLs disability was worst in the surgical menopause, ever HRT group (mean = 13.2, SD =

16.22); and OARS IADLs disability was worst in the surgical menopause, ever HRT group (mean = 14.2, SD = 6.78).

Table 33. Outcomes at initial PD visit to the clinic by menopause type-hormone replacement therapy (HRT) categories

Outcomes	Natural, HRT+ (n=149)	Natural, HRT- (n=159)	Surgical, HRT+ (n=64)	Surgical, HRT- (n=29)	p-value
Died	15 (10.1)	8 (5.0)	10 (15.6)	6 (20.7)	0.015[a]
UPDRS Motor, mean (SD)	25.1 (12.46)	27.6 (14.47)	30.6 (16.22)	25.4 (11.01)	0.083[b]
OARS ADLs, mean (SD)	10.2 (3.90)	11.3 (5.29)	13.2 (5.87)	10.3 (3.63)	0.003[b]
OARS IADLs, mean (SD)	10.7 (4.75)	11.7 (6.60)	14.2 (6.78)	11.1 (4.21)	0.008[b]
S&E, mean (SD)	82.1 (15.59)	78.6 (19.11)	74.9 (19.71)	79.8 (14.78)	0.083[b]
SF-12 MH, mean (SD)	48.4 (11.45)	48.8 (10.36)	45.8 (11.01)	48.9 (12.12)	0.407[b]
SF-12 PH, mean (SD)	39.8 (11.87)	40.5 (12.18)	35.2 (12.24)	37.9 (13.75)	0.066[b]

Abbreviations: SD, Standard Deviation
[a]Chi-Square Test
[b]ANOVA F-test

Table 34 shows the results of stratifying the relationship between HRT and UPDRS motor presentation and progression by menopause type. Among those with natural menopause, the same significant differences were seen whereby those with ever HRT usage have significantly worse progression between 5 and 10 as well as 15 and 20 years. Among those with surgical menopause, the postmenopausal females with ever HRT usage had significantly worse progression between 10 and 15 years; however, the never HRT group has worse progression between 15 and 20 years.

Table 34. Linear mixed effects model for Parkinson disease impairment progression by HRT and stratified by menopause type

SURGICAL MENOPAUSE							
	Ever HRT			Never HRT			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
At Diagnosis[a]	21.89	17.25, 26.53	11.40	22.08	16.06, 28.10	10.05	0.961
0 to <5 Years[b]	0.45	-0.68, 1.57		0.35	-1.41, 2.12		0.929
5 to <10 Years[b]	2.21	1.26, 3.16		1.36	-0.90, 3.62		0.496
10 to <15 Years[b]	2.21	1.02, 3.39		-1.43	-4.01, 1.15		0.012
15 to <20 Years[b]	-0.23	-2.23, 1.78		2.94	0.84, 5.04		0.033
≥20 Years[b]	0.39	-1.11, 1.90		0.39	-1.26, 2.10		0.982
1st Year in Clinic[c]	-1.78	-4.89, 1.33		1.67	-3.69, 7.02		0.274
NATURAL MENOPAUSE							
	Ever HRT			Never HRT			
Effects	**Fixed**		**Random**	**Fixed**		**Random**	
Parameters	**β [d]**	**95% CI**	**SD**	**β [d]**	**95% CI**	**SD**	**p-value[e]**
At Diagnosis[a]	19.10	16.52, 21.67	10.18	22.32	19.71, 24.93	9.91	0.085
0 to <5 Years[b]	1.18	0.54, 1.83		1.38	0.70, 2.05		0.685
5 to <10 Years[b]	0.98	0.45, 1.50		0.16	-0.42, 0.75		0.042
10 to <15 Years[b]	0.97	0.42, 1.53		1.18	0.59, 1.78		0.613
15 to <20 Years[b]	2.49	1.71, 3.26		<-0.01	-0.81, 0.80		<0.001
≥20 Years[b]	2.00	0.99, 3.01		2.63	1.82, 3.44		0.341
1st Year in Clinic[c]	-3.31	-5.31, -1.31		-3.37	-5.22, -1.52		0.965

Abbreviations: CI, Confidence Interval; SD, Standard Deviation
[a]Intercept
[b]Interval represents time since diagnosis with β representing annual rate of change
[c]One year rate of change
[d]Adjusted for mean standardized socioeconomic status and mean standardized cohort (birth year)
[e]Comparison of group differences

Lastly, mortality was explored. The time to event analysis demonstrated no significant differences in time to death by menopause type (Log-rank p-value = 0.840) and HRT (Log-rank p-value = 0.628). Nulliparous, post-menopausal females had a faster time to death than parous females (Log-rank p-value = 0.006). However, date of death data was very sparse for post-menopausal females (n = 9 surgical menopause, n = 10 natural menopause, ever HRT = 8, never HRT = 11, parous = 3, nulliparous = 14).

CHAPTER 5. DISCUSSION

A. Aim 1

Progression Patterns

This study found that UPDRS motor scores significantly increased annually between 0.68 to 1.18 points per year. No adjacent years had significantly different increases in UPDRS motor scores, suggesting that PD impairment progression is relatively linear over time. The clinically meaningful difference on the UPDRS motor scale is 2.5 units (168). During the worst years of progression, in this study, this difference would be seen over a period of just over two years.

The rate of progression in this study was somewhat slower than what has been documented in the literature. A study among patients (n = 237) evaluated by movement disorders specialists found an annual rate of change of 1.5 units (61). The patients in that study had an older average age at onset (66.1 years) than in our study (60.6) years), which could influence progression rates (10, 77, 79). A study by Reinoso et al. (2015) (n = 526) found that progression rates, over 9 years, among those evaluated by movement disorders specialists, ranged from 0.67 to 3.96 units per year with the most mild progression occurring during the middle of the follow-up period (2 to 7 years) (68). Our study found the most mild UPDRS motor progression between 10 and 20 years post-diagnosis. The more mild progression in this study could be related to differences in patient case-mix, as reflected by differences in age at diagnosis; more prolonged follow-up; improvements in specialty care over time; and accounting for time-varying progression in models.

For all disability outcomes, progression was less uniform. Although progression significantly increased over all years, progression alternated between slower and faster progression over the study time frame. OARS ADLs scores worsened (increased) between 0.36 and 1.10 units per year, OARS IADLs scores worsened (increased) between 0.43 and 1.10 units per year, and S&E scores worsened (decreased), on average, between 0.86 and 2.38 percentage points per year. A change of 4 points on either OARS sub-scale would be reflective of an individual transitioning from no difficulty in performing an activity to completely unable to perform that activity. For the S&E, a 10 percentage point change (10%) is clinically meaningful (168) with a minimum detectable difference of 12.33% (174).

For health-related quality of life, there were no significant differences between adjacent years of progression and, unlike what was seen for impairment and disability outcomes, progression was not significant over all years. Progression ranged between -0.90 to +1.07 units for SF-12 Mental Health and -1.67 to 0.79 for SF-12 Physical Health. SF-12 Mental Health scores plateaued between 10 and 20 years with subsequent extremely fast progression after 20 years (largest declines). For SF-12 Physical Health, progression plateaued at 15 years and progression was fastest (largest declines) in the first 5 years. The clinically important difference on both the SF-12 MH and SF-12 PH is 3 to 5 units (175)

It was hypothesized that the rate of progression would be fastest later in the disease course. This hypothesis was based on the UPDRS motor score improvement phase, stable phase, and decline phase findings of Reinoso et al. (2015) (68). In actuality, for our study, there were no consistent findings with respect to progression patterns

across outcomes. UPDRS Motor Scores followed a linear pattern, all disability outcomes followed an inverse Gompertz function (a Gompertz function would follow a slow, fast, slow progression pattern but disability followed a fast, slow, fast pattern), and SF-12 outcomes followed a fast early and slow late progression pattern (although SF-12 PH increased drastically after 20 years from diagnosis). Although based primary on UPDRS total and motor score progression, researchers have found PD progression to follow a linear pattern (70); an improve, stable, decline pattern (68); a fast early, slow late pattern (1, 54, 63), and a Gompertz (slow, fast, slow) pattern (slow, fast, slow) (66, 67). The different patterns across outcome measures suggests that different underlying processes may drive the different disease outcome measure presentations and progression (64). Additionally, different patient characteristics, such as psychological distress and social support, may differentially impact these outcome measures. Further studies are needed to determine if such long-term progression patterns in these domains are replicated in other patient samples.

Inter-Individual Heterogeneity

There was a large amount of inter-individual heterogeneity found in this study. It was hypothesized that the majority of heterogeneity would be present early in the disease course. This hypothesis was based on heterogeneity in the choice and the commencement of drug therapy in early PD (176). This study found that heterogeneity in outcomes, in general, was greatest mid to late in the disease course. In one study based on HOME data, one-third of patients improved, one-third of patients declined, and one-third of patients remained stable in their UPDRS total scores one year from a given baseline measurement (177). The baseline measurement for these patients was an

average of 7.9 years from their diagnosis, which supports the general finding in our study.

This heterogeneity, particularly after an individual has been managed for PD for quite some time, would make prognostic counseling difficult. Understanding underlying reasons for heterogeneity in PD progression has been identified as a priority research area (178). This Aim did not explore underlying drivers of disease progression heterogeneity and future studies should tackle this question. However, given the complicated heterogeneity seen in our study, the results suggest the need for machine learning analyses or more advanced prediction analyses to develop better, individualized predictive models of PD progression. These models could then be used for the improved, individualized, prognostic counseling. One such example of this application in PD is found in the study by Latourelle et al. (2017), which developed predictive models via machine learning analyses utilizing clinical and genetic data (82). Within the HOME study, a joint project is underway with the University of Maryland, College Park Department of Computer Science to develop better predictive models and data visualization platforms to improve patient-clinician communication and prognostic counseling.

Benefit of Specialty Care

The models developed in this study demonstrated a clear, significant initial benefit of care at the University of Maryland Parkinson Disease and Movement Disorders Center. Patients experienced a significant, 2.31 unit improvement (decline in scores) in UPDRS motor scores (95% CI: -2.94, -1.68) in the first year of clinical care at the Center. This improvement is clinically meaningful and consistent with reversing the effects of 2

to 4 years of disease progression, depending on the time since diagnosis. Patients experienced significant improvements in the first year of clinical care for OARS ADLs scores (β = -0.31, 95% CI: -0.51, -0.12) and Schwab & England scores (β = 1.34, 95% CI: 0.48, 2.21) but not OARS IADLs scores (β = -0.15, 95% CI: -0.39, 0.09). This improvement was also found for SF-12 Mental Health scores (β = 1.31, 95% CI: 0.74, 1.87) and SF-12 Physical Health scores (β = 1.12, 95% CI: 0.61, 1.62). For all of these other outcome measures, the first year of clinical care at the Center counteracted a minimum of one year of disease progression.

It has been demonstrated that patients seen by neurologists have improved outcomes compared to those seen by primary care providers (28, 179, 180). One reason for this difference in outcomes may be due to better treatment administration and management (28). Additionally, health-related quality of life is impacted by clinic of care (144). Although we do not know if this was the first time patients were seeing a movement disorders specialist or how patients would have progressed had they not sought out care at the Center, this study still lends support to the need for specialty care. In a 2011 study, Willis et al. (2011) found that over a 48 month period, less than half (42%) of Medicare beneficiaries with PD saw a neurologist (179). Underlying drivers of this lower utilization are multi-factorial (180). Telemedicine efforts are underway to try and improve patient access and utilization of specialists (181).

Limitations

There are several limitations to this Aim of this current study, many of which are also applicable to Aim 2 and Aim 3.

Model Specification

One concern for Aim 1 was that models may have been misspecified. Other functional forms may have been more appropriate to model PD progression. However, extensive exploratory analysis was undertaken to select the final, piece-wise linear mixed-effects models with five-year knot placements. This model allowed progression complexity to be assessed without prohibiting interpretability.

Missing Data

Individuals with missing diagnosis dates had their dates imputed based on a calculated algorithm that differed by age. There was a concern that those with imputed diagnosis dates would be systematically different from those without imputed dates. Diagnosis dates were only imputed for 146 patients (out of 1,463). However, those with imputed diagnosis dates were more likely to have been diagnosed in late life and were older at their initial PD visit. Although there were no significant differences by cognitive status, they did have more comorbidities. Consequently, these individuals could have had a more difficult time remembering diagnosis information. Those with imputed diagnosis dates had more variability in progression estimates; however, this may have been a function of instability due to a smaller sample size. Additionally, those with imputed diagnosis dates derived more benefit from the first year of clinical care at the Center than those with non-imputed diagnosis dates.

As form completion was integrated with clinical care, questionnaires and items were often missed or the questionnaires administered change over time. Patients were excluded if they had insufficient outcome data (n = 413). Multiple imputation was considered as a means to impute data. However, this would only have addressed data

that is missing at random, which was unlikely. Instead, maximum likelihood based approaches were used to examine PD progression.

Information Bias

Information bias may have been a concern in this study. Self-reported health outcomes are particularly vulnerable to misclassification. For example, PD patients report lower levels of disability than what is objectively assessed in-clinic (182). However, because disability and health-related quality of life are patient reported outcomes, this limitation was actually a strength of the study. It is important to capture the patient's self-perception, regardless of objective outcomes. Additionally, these self-reported outcomes may be more meaningful and important to patients with respect to care goals (30).

Additionally, some patients completed questionnaires with the assistance of a caregiver or a caregiver completed the questionnaire on behalf of the patient. In PD, proxies have been found to rate health systematically worse than patients (141). A sensitivity analysis was undertaken to address this limitation (183). However, proxies were the sole completer of questionnaires for only 70 patient visits out of 13,820 total visits. Given the trivial number of proxy reports, the likelihood that proxy reporting would substantially impact estimates was slim; however, co-reporting could also have influenced estimates

Outcome assessments could have biased based on whether assessments were taken when fluctuators were on or off. One prior study made the assumption that patient on/off status was likely random and not systematically different (61). Information on whether fluctuators were on or off was only available for a proportion of visits; among

these visits, a greater proportion of visits were recorded on. It is unclear if on/off status impacted estimates of progression patterns. Disease outcome assessments would be biased toward more mild disease if fluctuators were on but more severe disease if fluctuators were off. However, if an individual fluctuator were consistently assessed on or off, estimates of progression rates should not be biased.

Selection Bias

Selection bias was potentially present in this analysis if those that consented to participate in the HOME study were not representative of the larger clinic population. With respect to this concern, for PD patients, there was over a 72% consent rate making the suspicion of selection bias somewhat low.

There was also the potential for selection bias due to loss to follow-up. The HOME study database does not have information on why individuals no longer present to the Center for care. These individuals could have switched providers, been admitted to a nursing home, declined so much that they were unable to come to the Center, or died. Consequently, the progression data from late in disease course likely reflects a biased sample. Because individuals who are diagnosed at a younger age will live longer with their disease (184), data on the later stages of disease may have been more reflective of the experience of individuals who were diagnosed at a younger age, who were inherently different from patients with middle or late age onset (136). This limitation may not be detrimental given that the goal of this study was to examine progression in patients under clinical care.

Mortality was assessed with a time-to-event analysis. However, only 88 patients had a death date available. Consequently, this study was limited in its ability to examine

selective survival and the role of loss to follow-up due to mortality. Additional, future efforts should attempt to obtain outcome data (e.g., mortality, nursing home placement) on patients lost to follow-up to study mortality outcomes as well as reasons for attrition.

Generalizability

Generalizability may also be worrisome for this study given that patients seeking care at a tertiary, specialty center may not represent the general PD population in the community or primary care clinics (26). However, again, the goal of this study was to describe progression under clinical care—subjects in this study may just have been receiving ideal clinical care.

A community-based study or study at a primary care clinic would have been unfeasible. PD is too rare, and it is too expensive and time consuming to find new cases in the community (27). For example, one Italian study screened 2,863 community-dwelling older adults and found only 42 cases of idiopathic PD in the community (27). Additionally, the collection of such detailed, longitudinal data on PD patients is truly only realistic in a specialty center. However, this study merits replication in a non-specialty care setting. The burgeoning amount of data collected on patients via electronic medical records may make such a study feasible in the future.

One additional limitation of this study is that it stems from a non-inception cohort of patients. However, a proportion of patients were initially diagnosed in-clinic. When progression patterns for those initially diagnosed in-clinic (incident cases) were compared to those who sought care at the clinic after diagnosis (prevalent cases) at overlapping follow-up times, estimates were relatively similar. However, differences were substantial between 10 and 15 years post-diagnosis. This difference is likely due to limited incident

subjects with data during this interval. Incident cases also experienced more improvement in the first year of clinical care at the Center. One must bear in mind that PD remains underdiagnosed and the diagnosis date is somewhat amorphous given that symptom onset is often many years prior to diagnosis making the concept of an "incident" case somewhat arbitrary (7, 25).

Strengths

Despite these limitations, there were many strengths to this study. There has been a call for clinicians to implement routine, longitudinal collection of various scales to assess progression (30). This was one of the key strengths of our study. It utilized a unique database that has collected longitudinal data on many PD patients for almost 15 years. The use of longitudinal data allowed progression to be captured without the assumption of a constant, linear pattern of progression or the assumption that individuals were diagnosed at a disease severity of zero (58).

Several additional modeling choices greatly benefitted this study. Given the irregular pattern of clinic visits, the use of mixed models to examine progression allowed for valid parameter estimates despite the unavailability of data at all time points. Furthermore, the addition of random slope and intercept terms accounted for inter-individual heterogeneity in progression, a factor often overlooked.

The HOME study has extensive data on self-reported measures. This unique feature allowed progression of patient reported outcome measures (disability and health-related quality of life) to be assessed in conjunction with clinician assessed disease severity (impairment and disability). There is only one other study that has examined disease progression including impairment, disability, and health-related quality of life

outcomes; however it was limited to 5 years of follow-up and examined progression linearly (71).

Lastly, specialists are much better than general neurologists at correctly diagnosing PD (185). Consequently, using a sample of patients with diagnoses of PD confirmed by specialists ensured the specificity of diagnoses. Other studies of PD patients often use administrative claims or survey data. Such sources of data are likely to have poor specificity and overestimate the number of individuals with PD (26).

B. Aim 2

Sex Differences in Presentation

This Aim demonstrated that females, were, in general, worse off than their male counterparts both at diagnosis and at initial PD visits to the Center. This outcome was in agreement with the hypothesis that females would have more severe disease at care milestones.

Consistent with the literature (34), at diagnosis, female patients were less likely to be married and more likely to reside alone (no spousal caregiver) and had more comorbidities. Additionally, at diagnosis, females were more likely to have anxiety symptoms but not depressive symptoms, although greater depressive symptoms among females has been documented in the literature (34). Differences at initial PD visits worth noting include that females were less educated, were less likely to be married, were less likely to live at home, and had a lower income. This disadvantage would drastically impact their resources available for chronic disease management. Female patients, at their initial PD visits, were older, had more falls, had more treatment complications, had

more somatization symptoms, had more depressive symptoms, had more comorbidities, and had more advanced Hoehn & Yahr staging.

There were no differences at diagnosis or initial PD visit between males and females in any clinician-assessed outcome measure (UPDRS motor scores or S&E score). However, females reported worse OARS IADLs disability at diagnosis and worse OARS ADLs disability, OARS IADLs disability, SF-12 Mental Health, and SF-12 Physical Health at initial PD visits. This finding is consistent with other studies (34, 38, 94, 99). This indicates that females, on average, perceive their disease to be worse than their male counterparts, despite similar UPDRS motor scores and Schwab & England Scale scores (38, 54, 55).

One additional interesting finding was that at diagnosis and initial PD visits, female patients were significantly more likely to see female physicians. This finding could suggest that female patients prefer female clinicians. In one study, over 90% of individuals, when asked, had no preference for male or female neurologists (186). Among those with a preference, females were more likely to prefer female neurologists, and males were more likely to prefer male neurologists (186). However, the same-sex preference was only statistically significant for males (186). Feeling more comfortable in conversations and comfortable for sensitive examinations were the most commonly cited reasons by patients for same-sex preferences in physicians across specialties (186). For neurologists, females also indicated that they thought female physicians were more personally interested in them (186). In a virtual simulation, female patients were most satisfied after physician encounters when they were presented with a female physician who adopted a high caring, low dominance communication style (187). Further research

is needed to understand female patient preferences with respect to selection of a movement disorders physician.

Delays in Care or Treatment

Some of the differences seen at initial PD visits, such as more falls, more treatment complications, and more advanced Hoehn & Yahr staging, suggest that female patients may have experienced delays in specialist referral, which has been found in the literature (96). However, in this study, contrary to what was hypothesized, there were no significant differences by sex in timing between any two care milestones. In a prior study in a tertiary care clinic, there was a significant delay in symptom onset to specialty visit (96). In our study, the time from symptom onset to visit to the University of Maryland Parkinson Disease and Movement Disorders Center was, on average, 6 months longer for females, compared to males. There were no differences in median times. There were still no significant differences when those with imputed diagnoses dates, whose inclusion would have biased estimates towards the null, were excluded. In the HOME study, the patient's referring physician was not recorded. As a result, it was unclear if a patient's first visit to a specialist occurred at the Center or at a prior date elsewhere, which would impact timing estimates. Given that females and minorities are less likely to see specialists (179), further studies are needed on careseeking patterns for females, including understanding referral patterns for those who never make it to see specialists.

There was a substantial sex difference of almost 1.5 years in the time from diagnosis to DBS therapy, with females experiencing a longer delay; however, this finding only trended toward statistical significance. DBS dates were missing for several patients; consequently, sex difference in timing were potentially biased toward or away

from the null. DBS is less common in female patients (34), and responses to DBS differ by sex (92). Additional research is needed to understand why females are less likely to receive this treatment and why they receive it later than male PD patients.

Sex Differences in Progression

Despite hypothesizing the contrary, based on linear mixed effects models with five year spline intervals, males and females had relatively similar rates of progression across all outcomes. However, there were two significant differences in slopes. First, females had significantly faster UPDRS motor progression after 20 years. This difference could have been the result of selection bias due to survival whereby sicker males had died. More males died in the study; however, females had a slightly faster time to death, albeit non-significant. Consequently, it is unclear what is driving this difference. Additional mortality data would be helpful to pinpoint whether selective survival did play a role. Second, males had significantly faster SF-12 Mental Health progression between 5 and 10 years since diagnosis. It is unclear what may explain this difference. The minimal differences between sexes suggests that, for the most part, sex is not a prognostic factor for PD progression as measured by any outcome domain. Additionally, there were no sex differences in the amount of inter-individual heterogeneity in slopes.

In the mixed effects models, significantly worse scores at diagnosis were present for females with respect to OARS IADLs scores and SF-12 Physical Health scores. Borderline significant differences were seen for OARS ADLs and SF-12 Mental Health scores—again with females reporting worse scores. Given that there was only one significant sex difference in slope (SF-12 Mental Health). The models suggest that these

baseline differences persisted over time (level effect) with no sex by time interaction in progression.

Despite females have inferior characteristics in sociodemographics, clinical characteristics, and patient-reported outcomes at diagnosis, the lack of differences in prognosis is surprising, but not inconsistent with other studies. Although faced with methodological limitations, several other studies have found that sex is not a prognostic factor in PD progression (45, 61, 80, 83-85).

Lastly, it is worth noting the females derived more benefit from their first year in clinical care at the Center for UPDRS for scores while males derived more benefit for OARS ADLs and OARS IADLs scores. Neither sex fared better in the first year in the clinic for Schwab & England scores or either SF-12 measure.

Mediation Analysis

As hypothesized, in the assessment of controlled direct effects, it was found that multiple interventions attenuated sex differences in patient reported outcome measures (OARS ADLs, OARS IADLs, SF-12 MH, and SF-12 PH) at initial PD visits. Intervening on psychological distress (anxiety, depressive, and somatization symptoms) had the most pronounced impact in attenuating the effect of sex to the null. The one exception was intervening on depressive symptoms in the context of SF-12 Mental Health scores. Although the effect of changing BSI-18 T-scores to one standard deviation below population norms was assessed, setting a more modest goal of managing patient's psychological distress to population norms (T-score = 50) was sufficient. Managing psychological distress in PD is difficult and may be both part of the disease etiology as well as a response to worsening disease (188). Interventions exist to manage

anxiety and depression in PD, including medications and psychosocial interventions like cognitive behavioral therapy (14, 189, 190). Given that anxiety and depressive symptoms are often missed by neurologists (191), our study suggests that it is important to screen or assess for these symptoms and appropriately manage them, particularly for female patients, once they are under specialist care. Such management may improve disability and health-related quality of life experiences and perceptions for female PD patients.

Limitations

Aim 2 was subject to the same limitations with respect to model specification, missing data, information bias, selection bias, and generalizability that were discussed with respect to Aim 1. Two additional limitations are worth discussion. The same linear, mixed-effects models with five year spline intervals were used for both males and females. This decision allowed for easier testing of progression differences. However, males and females may have needed different models of progression specified. Estimates of sex differences in progression may have been biased by the imputation of diagnosis date. However, the proportion of patients who needed diagnosis date imputation did not significantly differ by sex.

With respect to missing data, last observation carried forward was used to impute missing time-varying covariate data. There are extensive limitations to using this approach (192). These covariates were intended for use in the mediation analysis. However, due to the lack of differences in progression, the mediation analysis was only conducted with initial PD visit data. Consequently, covariates that underwent last

observation carried forward imputation were not used in this Aim nor any of our other study Aims.

Strengths

The major additional strength of this Aim was the use of causal inference approaches. These approaches allowed for the isolation of the causal effect of sex on disease progression as well as the exploration of important mediators of sex differences in initial presentation to a specialty care center. Based on a thorough literature search, the application of causal mediation in this PD context is novel.

C. Aim 3

Differences in Presentation by Reproductive Characteristics

It was hypothesized that individuals with reproductive health characteristics indicative of lower estrogen exposure (surgical menopause, never HRT, and nulliparous) would have worse disease presentation. There were minimal differences at diagnosis by reproductive health characteristics. The majority of differences were present in comorbidities. The surgical menopause group was more likely to have musculoskeletal/skin disease and the ever HRT group was more likely to have endocrine/metabolic/breast disease. Although not significantly different, females who had undergone surgical menopause or who were ever HRT users had an average older age, which could account for the greater comorbidity burden. Additionally, oopherectomy can also lead to increased risks for other comorbidities, such as osteoporosis (173). Similar to Cereda et al. (2013), no differences in disease symptoms were found at diagnosis in our study (46). There were several significant differences between parous and nulliparous females at diagnosis. Given that only six nulliparous

females were diagnosed in clinic (compared to 96 parous), the significant differences may be spurious due to small sample sizes and are not useful for discussion.

At initial PD visits, of note, females who had undergone surgical menopause were worse off. They experienced more falls, greater psychological distress, and more vascular disease. Outcome measures were also worse for the surgical menopause group with females reporting worse IADL disability, reporting worse physical health-related quality of life, and experiencing more mortality. The increased mortality among the surgical menopause group is not surprising. Oopherectomy in pre-menopausal women is protective against ovarian and breast cancer; however, it increases the risk for earlier mortality, cardiovascular disease, cognitive impairment, osteoporosis, poorer psychological well-being, and impaired sexual function (173). The ever HRT group had poorer health with more comorbidities and more pain. Again, this could be a reflection of non-significant but substantial age differences.

The finding of worse health outcomes at initial PD visit among those with lower endogenous estrogen exposure (surgical menopause group) and no difference by HRT is somewhat perplexing. However, those who have undergone oopherectomy are often given HRT (47, 173). A sensitivity analysis compared outcomes by menopause type-HRT cross-classifications. Surprisingly, OARS ADLs and OARS IADLs scores were the worst among the surgical menopause, ever HRT group. Mortality was worst in the surgical, never HRT group. This finding is consistent with HRT attenuating some of the oopherectomy-mortality association (173).

The nulliparous group, at initial PD visit, was more educated, less likely to be married, and more likely to live alone, compared to the parous group. These factors are likely more reflective of social factors associated with childlessness (193).

Differences in Progression by Reproductive Characteristics

The lack of difference in progression by sex seen in Aim 2 suggests that underlying biological differences between males and females, although they may play a role in disease risk and presentation, may not impact disease progression. Exploring progression by reproductive characteristics in Aim 2.3 allowed for additional examination of how underlying biological factors may impact PD progression. It was hypothesized that those with greater endogeneous/exogeneous estrogen exposure would have more mild disease progression. Findings were highly inconsistent across domains and by reproductive health characteristic suggesting these risk factors for PD may, like sex, not be prognostic factors (30). The overall heterogeneity of findings precludes any conclusions from being made about the impact of reproductive factors on PD progression.

For menopause type, one key finding was that the natural menopause group fared worse after 20 years of disease for impairment and disability progression. There were no significant differences in health-related quality of life progression. For HRT, the ever HRT group had worse progression early to mid in the disease course while the never HRT group fared worse extremely late in the disease course for impairment and disability outcomes. There were no differences in SF-12 MH progression; for SF-12 PH, the never HRT group had more pronounced progression between 0 to 5 years followed by a subsequent five years of the ever HRT group having more pronounced progression.

Ignoring parity, in general, a contradiction was found whereby those with greater endogeneous estrogen exposure (natural menopause) and lower exogeneous estrogen exposure (never HRT) fare worse late in the disease course. For menopause type, this may be a survivorship effect, although no significant differences were found in the time to event sensitivity analysis.

Currently, it is suggested that estrogen administration may improve symptoms and cognition in PD patients; however, findings are mixed (194). In the POETRY pilot study, post-menopausal, female patients were randomized to estrogen replacement therapy or placebo and followed for two months (195). There was a non-significant benefit among those randomized to HRT, compared to placebo; however, there was a trend toward benefit in UPDRS scores (including motor scores) and Schwab & England scores but not in neuropsychological battery testing (195). The findings of this Aim with respect to HRT provide little additional information to the discourse on the utility of HRT in PD.

For parity, there were no significant differences in UDPRS motor scores. The nulliparous group surprisingly showed drastic improvements in OARS IADLs and Schwab & England scores but drastic declines in SF-12 Mental and Physical Health late in the disease course. The findings by parity are likely the result of small sample sizes.

Limitations

Exposure Operationalization and Misclassification

Although this Aim was intended to be exploratory in nature, the findings are quite inconsistent. One of the main problems with this Aim, in addition to the limitations

discussed for Aim 1, was that very crude proxies were used for endogeneous and exogeneous estrogen exposure.

For this study it would be ideal to have HRT data on all patients at all time points as well as other reproductive characteristics (e.g., age at menses) to allow for the impact of estrogen on PD progression to be examined. Studies suggest that cumulative estrogen exposure (47), duration of certain exposures (49), or critical periods of estrogen exposure (31, 35) may be more important in PD. The proxy exposures in this study were simply too crude to explore such relationships. Classifying HRT users, due to small numbers, as ever or never users epitomizes this limitation. To better explore the relationship between estrogen and PD progression, future studies will need to utilize cohort studies with extensive reproductive health data. It will be particularly challenging to obtain data on a sufficient number of PD patients from these studies, so pooling of data will be necessary.

Data was also limited on HRT therapy type. The type of HRT (estrogen versus estrogen plus progesterone) may differ by whether an individual has had a hysterectomy/oophorectomy (196). Stratifying by both menopause type and HRT in the sensitivity analysis may have helped tease out this difference. However, HRT type data would truly be needed to explore such differential impacts on PD progression.

Additionally, this study makes the assumption that those reporting an oophorectomy had a bilateral (not unilateral) oophorectomy, which would be required for complete surgical menopause. However, studies suggest that unilateral oophorectomies may have an impact estrogen levels as well (43). Unilateral oophorectomies are also associated with earlier menopause (197).

Information on parity was also sparse in the dataset. Ideally, there would have been a large enough sample to examine the parous versus nulliparous group as well as examine the impact of the number of children within the parous group. There was also no way to separate the number of biological children, which are reflective of endogeneous estrogen exposure, from stepchildren or adoptive children. Consequently, some nulliparous females could have been misclassified; however, this misclassification would be rare.

Unfortunately, in the reproductive health portion of the intake questionnaire, no information was collected on the year of oophorectomy or menopause. The lack of date of menopause information makes it impossible to confirm that PD diagnosis occurred after menopause. This problem may be somewhat small given that in one study only 14.2% of females had PD onset prior to menopause (46). It is also impossible to determine if a female who underwent natural menopause had her ovaries removed post-menopause. Thus, females could have incorrectly been classified by menopause type.

Residual Confounding

Although this analysis adjusted for SES and cohort effects, residual confounding could still remain. SES, as captured by median zip code income, and cohort effects, as captured by year of birth, were treated as continuous covariates. It may have been more appropriate to categorize these two confounders (e.g., collapse birth year into decades). For the HRT group, confounding by indication, which may have accounted for some differences, was not addressed in the models. Additionally, given that this group had more comorbidities, there was insufficient data available to examine the impact of other medications on disease progression.

Missing Data

Lastly, menopause status was imputed for a small number of females based on age or prior oopherectomy. A sensitivity analysis demonstrated few differences between the imputed and non-imputed groups. The imputed group, at diagnosis, was more likely to have lower UPDRS motor scores and higher self-efficacy for managing chronic conditions. They were also more likely to have a later age at onset.

Strengths

Despite the many limitations of this exploratory Aim, it does have one major strength. This is the first study to examine the impact of reproductive characteristics on PD progression as measured by multiple domains. Only one other longitudinal study has explored the relationship between estrogen and UPDRS motor score prognosis (45).

CHAPTER 6. CONCLUSIONS

Using longitudinal data from 1,463 patients over 13,820 visits, this study was able to successfully model PD progression and its heterogeneity from diagnosis to 35 years post-diagnosis. Overall, the pattern of PD progression differed by the outcome domain selected. Physician assessed impairment progression followed a linear progression pattern while disability and health-related quality of life, which were predominantly patient-reported outcomes, followed a non-linear pattern. This finding emphasizes the need to consider both physician assessed and patient reported outcome measures, which are not always commensurate, with respect to patient goals. Additionally, inter-individual heterogeneity in progression was high. This highlights the difficulty of prognostic counseling in PD, a disease where patients have unique experiences and follow unique trajectories.

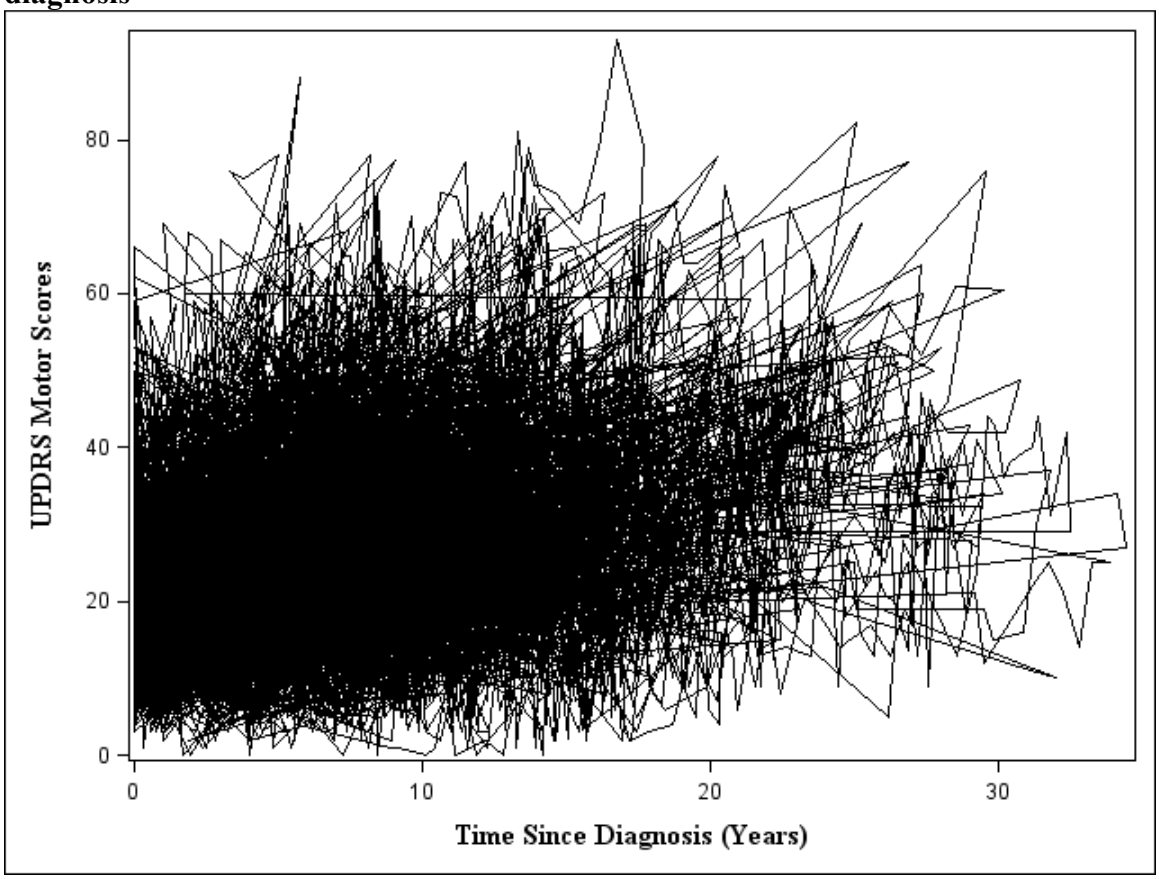
This study was able to address whether sex was a prognostic factor for PD progression. From this study, one can surmise that females present differently, but do not progress differently while in specialty care, compared to their male counterparts. At presentation to specialty care, females perceive their disease to be worse (e.g., OARS ADLs, OARS IADLs, SF-12 Mental Health, SF-12 Physical Health), although this was not found in physician assessments (UPDRS Motor Scores, S&E). Again, this stresses the importance of the patient experience. Based on this study's leverage of causal inference and mediation analysis, it was found that addressing psychological distress stands to attenuate this sex difference. Emphasis is needed on screening and management of psychological distress in PD, particularly among female patients.

This study was only the second to address the impact of reproductive characteristics, specifically proxies of estrogen exposure, on PD severity. However, it was the first to examine in the relationship with outcomes besides UPDRS motor scores. Findings were inconsistent across outcome domains and by reproductive health characteristics. Based on limitations in reproductive characteristic assessment, further studies are needed to explore whether estrogen exposures are prognostic in PD.

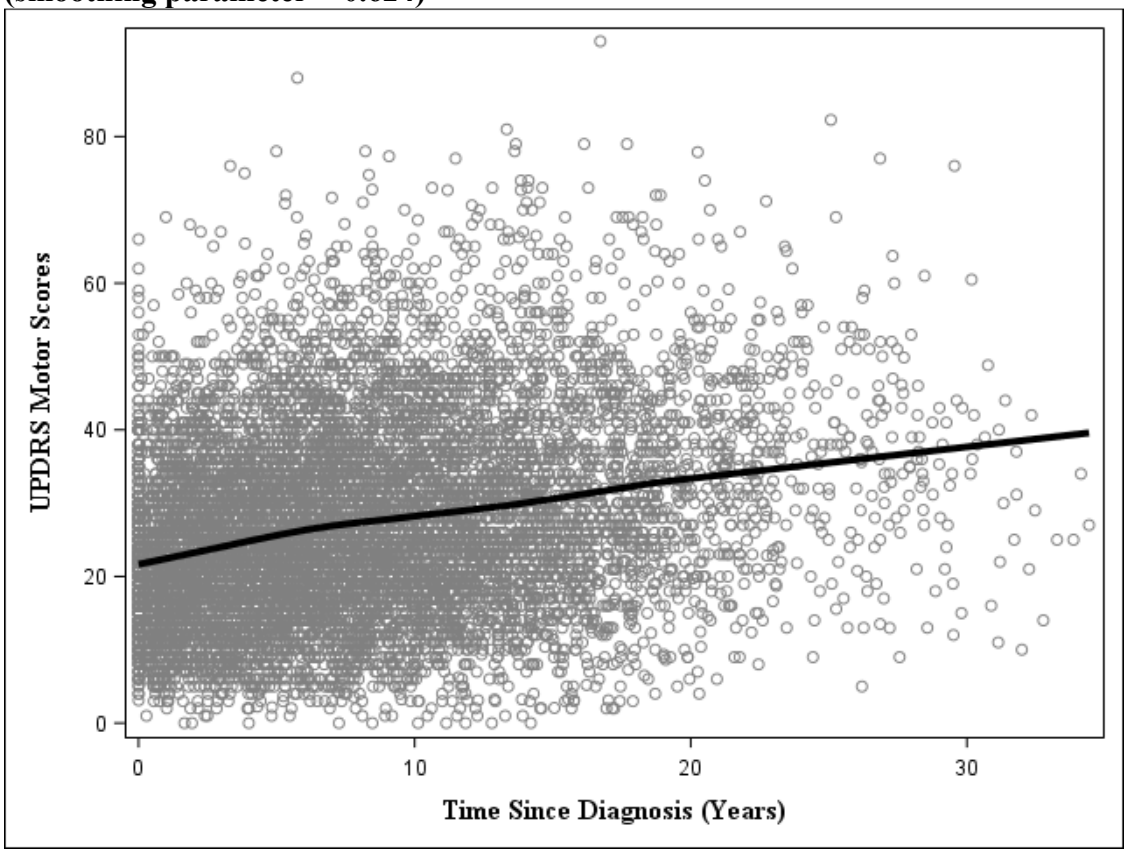
Lastly, this study demonstrated the beneficial impact of care by movement disorders specialists on patient outcomes. With one year of specialty care, patients recovered, depending on outcome, one to four years of disease progression. This improvement underscores the need to refer patients to specialists for care. Additional efforts are needed to improve the access to and proportion of patients receiving specialist care for PD.

CHAPTER 7. APPENDICES

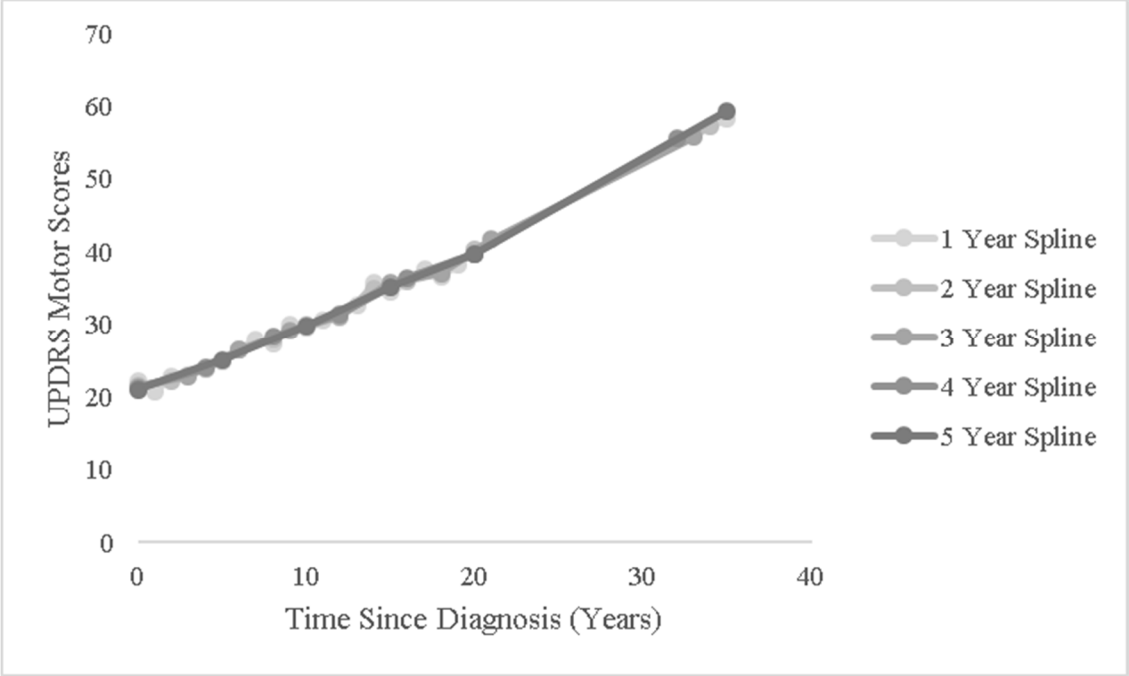
Appendix A. Example spaghetti plot of UPDRS Motor Scores by time since diagnosis



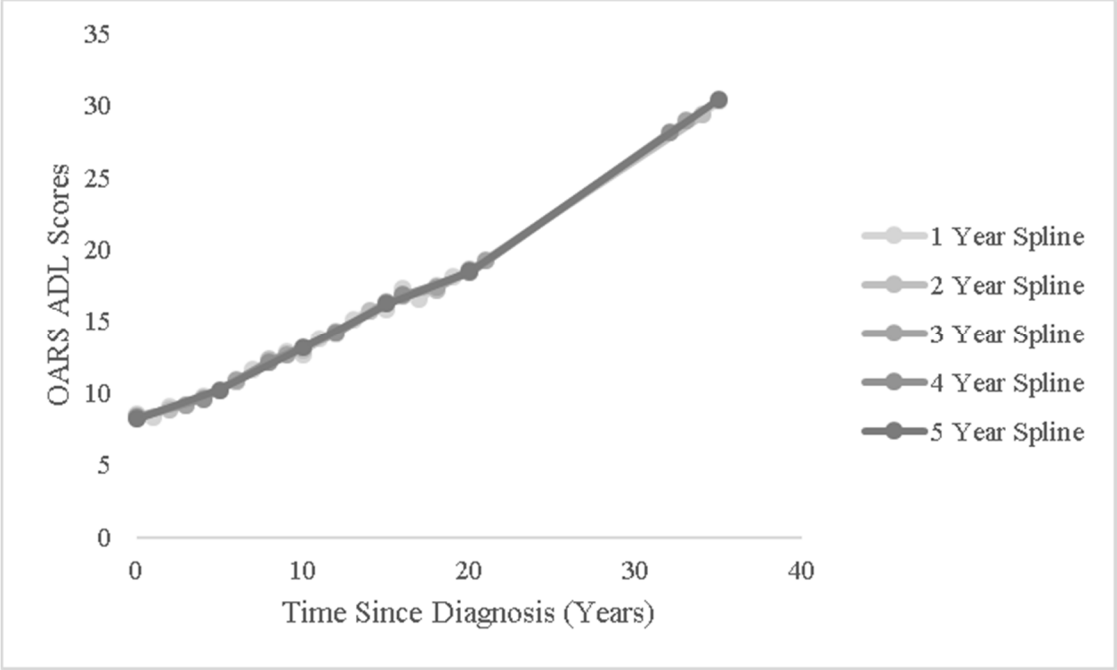
Appendix B. Example LOESS plot of UPDRS Motor Scores by time since diagnosis (smoothing parameter = 0.624)



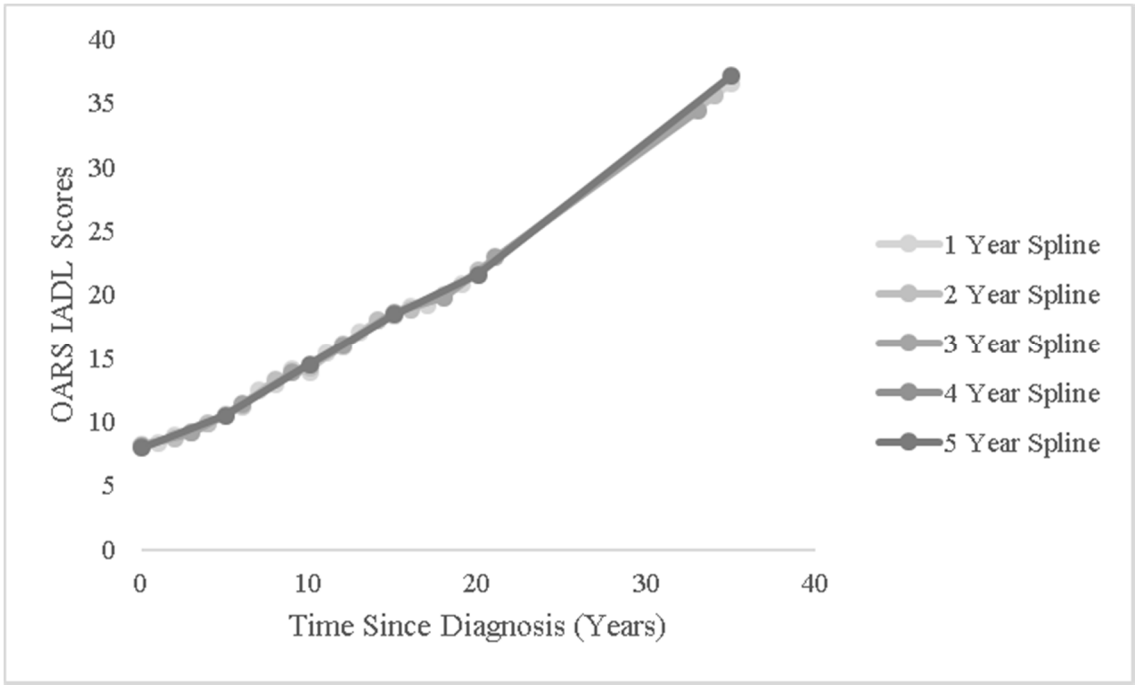
Appendix C. Plot of progression random intercept models with various spline knot intervals for UPDRS Motor Scores



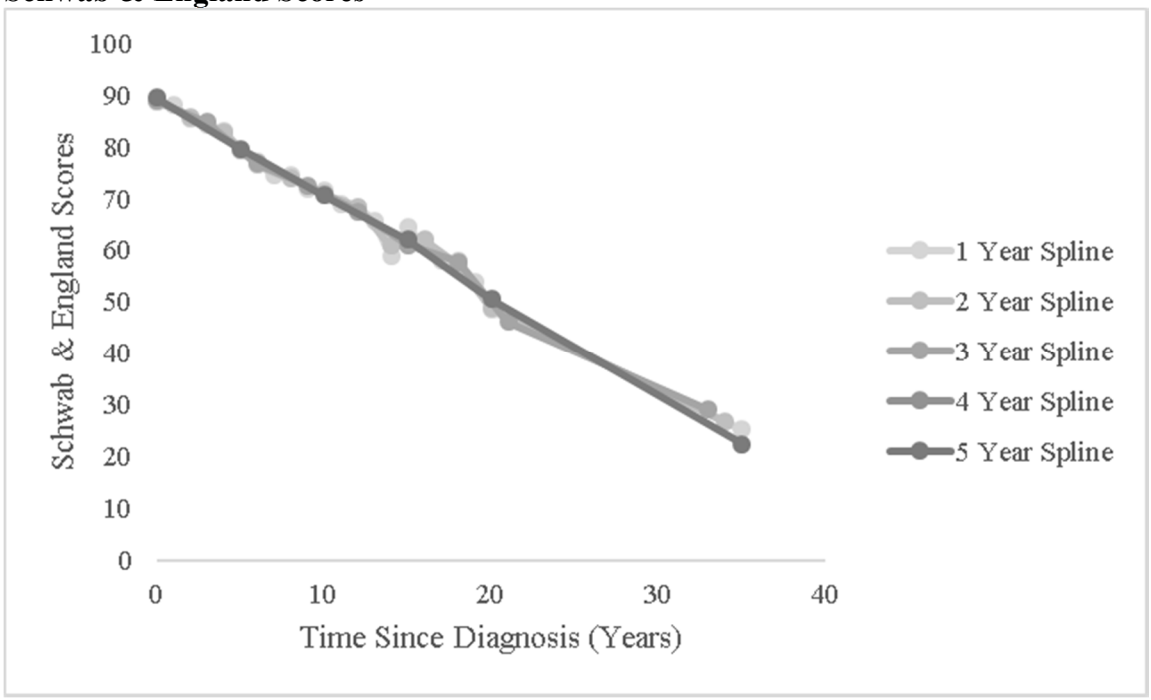
Appendix D. Plot of progression random intercept models with various spline knot intervals for OARS ADLs Scores



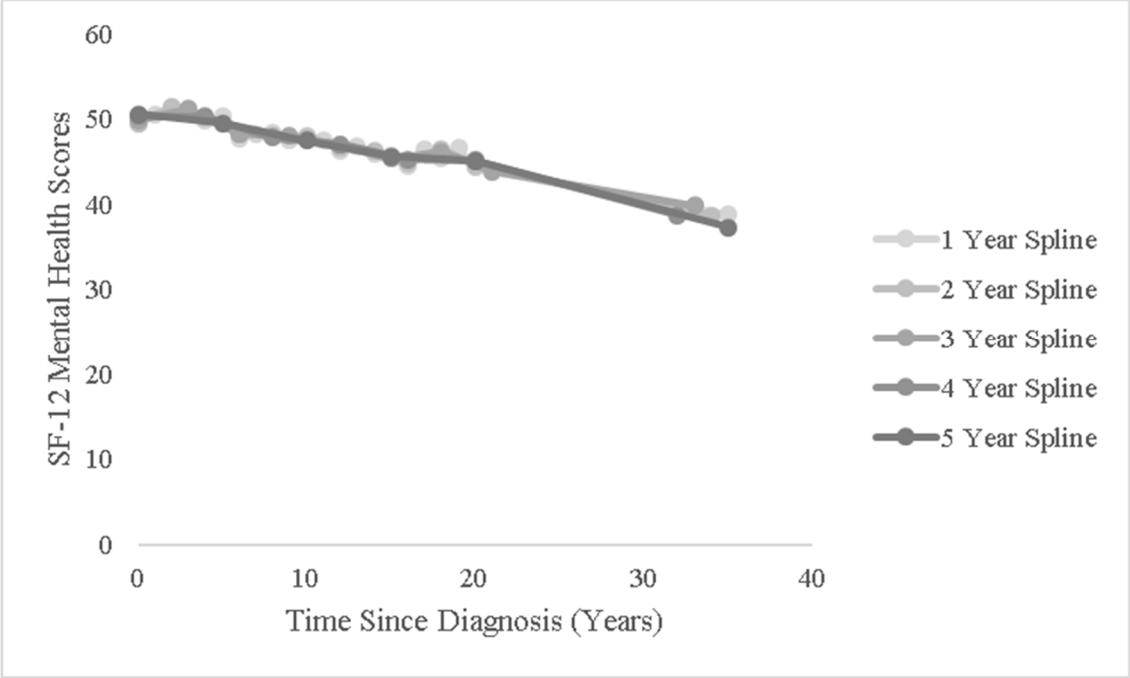
Appendix E. Plot of progression random intercept models with various spline knot intervals for OARS IADLs scores



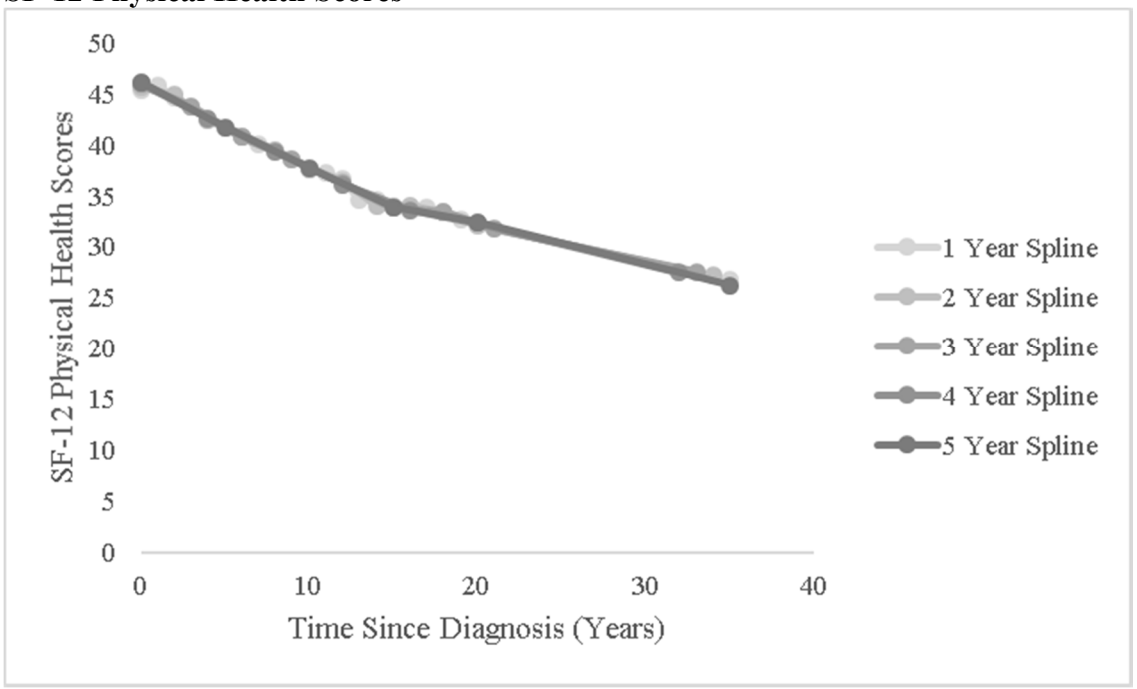
Appendix F. Plot of random intercept models with various spline knot intervals for Schwab & England Scores



Appendix G. Plot of random intercept models with various spline knot intervals for SF-12 Mental Health Scores



Appendix H. Plot of random intercept models with various spline knot intervals for SF-12 Physical Health Scores



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