10-2022

Relative meaningfulness and impacts of symptoms in people with early-stage Parkinson's disease

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et al.

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Word Counts

Title: 94 characters with spaces
Number of references: 27
Number of tables: 1
Number of figures: 4
Supplemental online materials: 5
Word count abstract: 246
Word count paper: 4047

Keywords: Parkinson's, digital health technology, qualitative, meaningfulness

Funding Source: This study was funded by the Critical Path for Parkinson's (CPP) Consortium. The CPP 3DT initiative is funded by the CPP Consortium members including: Biogen; GSK; Takeda; Lundbeck; UCB Pharma; Roche; AbbVie and Merck, Parkinson's UK, and the Michael J Fox Foundation. Critical Path Institute is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) and is 54.2% funded by the FDA/HHS, totaling $13,239,950, and 45.8% funded by non-government source(s), totaling $11,196,634. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.

Quality in qualitative research statement

This study used COREQ criteria to guide reporting of qualitative findings.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

			Page, line
Domain 1: Research team and reflexivity			
Personal Characteristics			Pg 5, para 2 (Methods; Data collection; Interview)
✓	1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Pg 5, para 2 (Methods; Data collection; Interview)
✓	3. Occupation	What was their occupation at the time of the study?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	4. Gender	Was the researcher male or female?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	5. Experience and training	What experience or training did the researcher have?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	Relationship with participants		Pg 5, para 2 (Methods; Data collection; Interview)
✓	6. Relationship established	Was a relationship established prior to study commencement?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Pg 5, para 2 (Methods; Data collection; Interview)
✓	8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Pg 5, para 2 (Methods; Data collection; Interview)
Domain 2: study design			
Theoretical framework			
✓	9. Methodological orientation and theory	What methodological orientation was stated to underpin the study? e.g. grounded theory,	Pg 4, para 2 (Methods; Data collection)
Participant selection			
✓	10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Pg 4, para 1 (Methods; Setting, Sample)
✓	11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Pg 4, para 1 (Methods; Setting, Sample)
✓	12. Sample size	How many participants were in the study?	Pg 4, para 1 (Methods; Setting, Sample)
✓	13. Non-participation	How many people refused to participate or dropped out? Reasons?	Pg 9, para 1 (Results; Sample and interview characteristics)
Setting			
✓	14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Pg 5, para 2 (Methods; Data collection; Interview)
✓	15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Pg 9, para 1 (Results; Sample and interview characteristics) and Table 1
Data collection			
✓	17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Pg 5, para 3 (Methods; Data collection; Rigor)
✓	18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	N/A
✓	19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	20. Field notes	Were field notes made during and/or after the interview or focus group?	Pg 5, para 3 (Methods; Data collection; Mapping)
✓	21. Duration	What was the duration of the interviews or focus group?	Pg 5, para 2 (Methods; Data collection; Interview)
✓	22. Data saturation	Was data saturation discussed?	Pg 6, para 1 (Methods; Data collection; Rigor) and Pg 9 para 1(Results, Sample and interview characteristics)
✓	23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Pg 5, para 3 (Methods; Data collection; Rigor)
Domain 3: analysis and findingsz			
Data analysis			
✓	24. Number of data coders	How many data coders coded the data?	Pg 7, para 2 (Methods; Data analysis)
✓	25. Description of the coding tree	Did authors provide a description of the coding tree?	Supplement A and Pg 7, para 1 (Methods; Data analysis)
✓	26. Derivation of themes	Were themes identified in advance or derived from the data?	Pg 7, para 2 (Methods; Data analysis)
✓	27. Software	What software, if applicable, was used to manage the data?	Pg 7, para 2 (Methods; Data analysis)
✓	28. Participant checking	Did participants provide feedback on the findings?	Pg 5, para 3 (Methods; Data collection; Rigor)
Reporting			
✓	29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	Results, Tables
✓	30. Data and findings consistent	Was there consistency between the data presented and the findings?	
✓	31. Clarity of major themes	Were major themes clearly presented in the findings?	
✓	32. Clarity of minor themes	Were minor themes clearly presented in the findings?	NA

Legends

Table legends

Table 1. Qualitative interview study demographics compared to parent study PD cohort

Figure legends

Figure 1. Sample participant map showing symptom map structure and appearance

Figure 2. Patient reported motor and non-motor symptoms in early PD

Figure 3. Impacts of disease in people with early PD by frequency and contributing symptom

Figure 4. Conceptual model of meaningful symptoms and stepwise categorical classification schema

Online only (supplemental materials)

Supplement A. Symptom mapping interview guide

Supplement B. Coding schema for symptom maps

Supplement C. Most bothersome symptoms of early PD curated by functional impact

Supplement D. Comparison of most important symptoms of early PD based on curation

Supplement E. Quotes supporting thematic findings

Abstract

Background: Patient perspectives on meaningful symptoms and impacts in early Parkinson's disease (PD) is lacking, and is urgently needed to clarify priority areas for monitoring, management, and new therapies.

Objective: To examine experiences of people with early-stage PD, systematically describe meaningful symptoms and impacts, and determine which are most bothersome or important.

Methods: Forty adults with early PD (≤ 2 years diagnosis) who participated in a study evaluating smartwatch and smartphone digital measures (WATCH-PD study) completed online interviews with symptom mapping to hierarchically delineate symptoms and impacts of disease from "Most bothersome" to "Not present," and to identify which of these were viewed as most important and why. Individual symptom maps were coded for types, frequencies, and bothersomeness of symptoms and their impacts, with thematic analysis of narratives to explore perceptions.

Results: The three most bothersome and important symptoms were tremor, fine motor difficulties, and slow movements. Symptoms most commonly impacted sleep, job functioning, exercise, communication, relationships, and self-concept—expressed as a sense of being limited by PD. Thematically, most bothersome symptoms were those that were personally limiting with broadest negative impact on well-being and activities. However, symptoms could

be important to patients even when *not* present, bothersome, or limiting (e.g., speech, cognition).

Conclusion: Meaningful symptoms of early PD can include symptoms that are present or anticipated future symptoms that are important to the individual. Systematic assessment of meaningful symptoms should aim to assess the extent to which symptoms are personally *important*, *present*, *bothersome,* and *limiting*.

Background

Parkinson's disease (PD) is a devastating neurodegenerative condition and current therapies are unable to prevent or delay progression.[1] One major challenge in development of new therapeutics has been a lack of sensitive, patient-centric endpoints that can be used to evaluate treatment efficacy.[2,3] Promising new digital measures that can capture objective data on key features of PD are under development and could address this critical gap.[3,4] However, there is limited understanding of the extent to which data captured via these technologies aligns with what is important to patients—which limits use as endpoints in clinical trials.[5,6] In light of recent FDA guidance highlighting the need for patient-focused drug development,[7,8] a better understanding of the *symptoms and impacts of disease* that are meaningful to people with early PD is urgently needed to clarify priority areas for monitoring and management.[9]

To date, research on symptoms and impacts of PD has focused mostly on populations with more advanced symptoms, and there is limited data as to whether symptoms and impacts are different in early-stage disease.[10] Recently published conceptual models of early PD have begun to clarify this, [11,12] however, further evidence is needed to understand prevalence and relative bothersomeness of symptoms and impacts, and to identify which are most important from the perspective of people living with PD. This knowledge can improve care, support the selection of appropriate outcomes measures for clinical trials, and guide development of future patient-centric measures.[9] Thus, the purpose of this study was to systematically identify and describe personally meaningful symptoms and impacts of disease, determine which are most bothersome and important, and explore these experiences of early PD.

Methods

Setting, Sample

This study was co-developed and conducted collaboratively by Critical Path Institute, US Food and Drug Administration, individuals with PD, and academic and industry partners. It was designed in follow up to the WATCH-PD study (NCT03681015), a 12-month multi-center observational study evaluating use of a smartwatch and custom-designed smartphone application to detect cognitive and motor progression over time in individuals with early, untreated PD (≤ 2 years diagnosis, Hoehn & Yahr stage ≤ 2).[4] A dual-purpose follow-up study was conducted for the purpose of (1) identifying meaningful symptoms and impacts of early PD and (2) exploring the extent to which the digital measures in the WATCH-PD study were perceived by participants as relevant to monitoring meaningful aspects of disease. This manuscript presents results from Aim 1. Individuals with PD who completed their final visit of the WATCH-PD study within the previous 6 months were eligible (N=54). Participants from the prior study were contacted via phone and screened for interested and eligibility. Forty of the 80 original participants (50%) were purposefully selected to represent parent study demographics with inclusion of all participants from underrepresented groups (N=4). Sample size was based on maximal ranges identifies in prior qualitative descriptive studies.[13] IRB approval was obtained (IRB# 00006429) and participants gave digital informed consent.

Data collection

A mixed-methods approach was used,[13] consisting of a preliminary survey followed by 1:1 online interviews using symptom mapping and a semi-structured interview protocol developed in collaboration with people with Parkinson's disease (**Supplement A**).

Survey

Participants first completed a brief online survey using Redcap, which is a secure, web-based software platform designed to support survey data capture for research studies.[14,15] The purpose of the survey was to gather demographic data and preliminary qualitative information on personally important symptoms, which was used as a starting point for in-depth exploration and symptom mapping during the 1:1 interviews, as described below. For the survey, participants were asked to describe all symptoms of PD that they experienced in detail and explain which were most bothersome and why using open response items.

Online Interview

One-week later, 1:1 online interviews (average 100 minutes) were conducted via Zoom video-conferencing with participants at home. Symptom mapping[16] was used to systematically delineate all personal symptoms and impacts of early PD as shown in **Figure 1**. Interviews were conducted by an qualitative researcher with experience in the methods (JM; white, female, PhD-prepared advanced practice nurse, unacquainted with participants). Interviews were audio-visually recorded with permission.

Symptom mapping.[16] During the interview, a detailed concept map of the individual's PD symptom experience was developed by the interviewer, while observed and directed by the participant using Zoom screen sharing.[17] Individual symptom maps were created using Xmind™ software, with map levels organized hierarchically top to bottom from "Most bothersome" to

"No current issues," with an additional category "Not [personally] relevant to early PD". This is described below.

Step 1. Prior to the interview, the researcher reviewed the Redcap qualitative survey data and entered all reported symptoms into the preliminary map, with each symptom represented as a single yellow node.

Step 2. At the beginning of the interview, the participant was oriented to the mapping process and shown the preliminary map via screensharing. They were then asked to further co-develop their map by listing and describing all symptoms of PD they experienced and how these impacted their life (past or present). The researcher entered this information as directed into the mutually viewable map.

Step 3. Next, the researcher probed for common symptoms of PD (difficulties with tremor, walking, balance, fine motor, speech, thinking, mood, daytime sleepiness, fatigue, depth perception) if not spontaneously reported by the participant. Symptoms not currently experienced were categorized under "No current issues", or "Not [personally] relevant to early PD" based on the participants' perspective.

Step 4 - Bothersomeness. Once symptoms and impacts were fully described, supporting details were collapsed (i.e., hidden) leaving only primary yellow "symptom" tiles visible. The participant was then asked to rank symptoms according to bothersomeness (i.e. how bothersome the symptom was from most to least).

Step 5 - Importance. Lastly, participants identified which symptoms were most important to them and explained what the difference was between important versus

bothersome. A final opportunity was provided to review and edit the map. Copies of maps were given to participants at the end of the interview, if desired.

Data analysis

Content coding was performed on symptom maps [18] with thematic analysis of verbatim transcripts.[19] Maps were coded for type, frequency, and bothersomeness of symptoms and impacts. As shown in **Supplement B**, each heirarchical level in the map was associated with a Patient Reported Symptom Score (**PRSS**; range 0-4), where scores 1-4 indicated the symptom was *present* and degree of bothersomeness, 0 indicated the symptom was *not present* but still viewed as important to the participant, and "." indicated that the symptom was not present or personally relevant.

Coding was performed in cycles by two coders (JM, PY) and differences resolved by consensus. In Cycle 1, open coding (i.e., no *a priori* coding schema) was performed on maps to develop a comprehensive list of symptom types using spreadsheets. Cycle 2, maps were coded again quantify frequencies and bothersomeness of each symptom by participant. In Cycle 3, maps were coded to derive a comprehensive list of all impacts with details on symptoms that contributed to the impact. Cycle 4, maps were re-coded to quantify frequencies of impacts by contributing symptoms for each participant. In Cycle 5, the frequencies of symptoms and impacts were compared to the Staunton conceptual model of early PD,[11] with attention to divergence or alignment with conceptual domains and domain items.[18] Lastly, in Cycle 6, inductive thematic analysis was conducted on narratives using Nvivo12, with pattern coding to identify themes regarding how participants experienced and perceived early PD symptoms

within and across interviews.[20,21] Independent T-tests were conducted in SPSS 28 to assess for differences in symptoms frequencies between those taking versus not taking PD medication. Descriptive statistics were computed for demographic survey items.

Rigor. Procedures to ensure rigor included: co-development and pretesting of study procedures (i.e., surveys interview guide, mapping procedures) with people with Parkinson's (JC, JH), observing of interviews for consistency (RS), triangulated data collection (preliminary survey, mapping, cognitive interviewing), member-checking during interviews, peer-debriefing on codes and thematic findings at weekly scheduled meetings, use of multiple coders, participant identifiers to show representativeness of quotes, and a formal audit trail.[22] Symptom maps were also returned to participants who reviewed and confirmed validity of their personal data. Data saturation was assessed to determine adequacy of sample size.[23] Saturation was considered complete at the point after which no new or additional symptoms/impacts was identified in succeeding interviews.

Data availability statement

Data are available to Critical Path for Parkinson's (CPP) Consortium 3DT Initiative Stage 2 members. Non-members may submit proposals for de-identified datasets to CPP 3DT via the corresponding author.

Results

Sample and interview characteristics

Of 54 eligible WATCH-PD participants, one declined to participate, 5 could not be reached (12.5%), and 8 were not solicited for interviews due to having achieved targeted sample size of 40. **Table 1** presents demographic data comparative to parent study demographics**.** Participants were mostly white, male, and not taking PD medication at the time of interview. Data saturation for symptoms, impacts and themes was achieved by the 17th of 40 interviews, after which no new findings were identified.

Symptoms and Impacts

Symptoms frequencies in early PD (All bothersome symptoms; PRSS 1-4)

Motor and non-motor symptoms of early PD are displayed by frequency of bothersomeness in **Figure 1.** There were no significant differences in symptom between those taking PD medications (N=16/40; 40%) and those not taking PD medications ($p>0.05$; range 0.083—0.986). For all, tremor was the most commonly reported motor symptom (95%), followed by fine motor (87%), and slow movements (80%). Over half of people also reported gait changes, stiffness/rigidity, and quiet voice. For example:

> ***P14****: I move in slow motion like I'm a sloth. It's just so frustrating…I can't [ever] hurry. [It's] like I'm turning into a stone.*

The most common non-motor symptoms were nocturia (65%), feeling tired or fatigued (62.5%), difficulty concentrating (62.5%), and insomnia (60%), with more than half of participants reporting slow thinking, difficulty remembering, and anxiety.

"Most bothersome" symptoms (PRSS 4)

Participants identified an average of 10 "most bothersome" symptoms (range 0-28). Difficulties with tremor (63%), fine motor (48%), and slow movements (40%) were most commonly reported. However, when evaluating symptoms categorically by the area of impact (e.g. mobility & balance, speech, mood, cognitive changes) rather than individually, symptoms affecting mobility and balance (gait, posture, balance, slowness, stiffness/rigidity) were most bothersome to 57% (**Supplement C)**. Other most bothersome symptom categories included changes to speech (40%), disturbed sleep (30%), altered thinking (27%), and altered mood (22%).

"Most important" symptoms of early PD

Participants identified an average of 2 symptoms that they felt were "most important" (range 1-7), which typically were listed at the top of the most bothersome category. These were tremor (27%), fine motor (25%), slow movements (12.5%), and word finding difficulties (10%). As shown in **Supplement D,** when evaluated categorically rather than as individual symptoms, 32.5% identified a "most important symptom" relating to mobility and balance, and 12.5% identified mood changes and cognitive difficulties.

Impacts of early PD symptoms

Figure 3 displays the frequencies of different impacts of early PD, along with contributing symptoms with reference to Staunton conceptual model domains, which included activities of daily living (ADL), physical, social, and emotional & psychological functioning, and

fine motor.[11] In our analysis, "fine motor skills" (i.e. computer/smartphone use, handwriting) was subsumed under ADL based on descriptive patterns that indicated these impacts typically occurred within the context of other ADLs, such as work as described below.

ADL. The most commonly discussed ADL impacts were altered sleep patterns and increased difficulty performing one's job (70%). Writing (70%) and using a computer mouse/keyboard (68%) contributed largely to job-related difficulties, with close to half (42.5%) referencing cognitive changes, including slower thinking, increased difficulty following sequences, and multitasking as contributing issues.

> ***P8****: I am scared to death of failing and [doing] the wrong thing - If you give me five things to do, I will do three successfully and mess up two.*

Difficulty using a computer appeared to have greatest impact on job function (sending emails, working in spread sheets), whereas handwriting affected both job and social interactions (ability to write notes/letters, holiday cards, or sign documents). Difficulties with the computer were most commonly due to slow fine motor movements (missing keys, double striking, holding down keys too long, difficulty manipulating the mouse, click/drag function).

Other common ADLs impacts affecting more than half of participants included eating and drinking (choking, trouble using utensils due to tremor/fine motor) and increased difficulty driving (depth perception, anxiety, reaction times).

Physical Functioning. Changes in walking, which affected exercise, were most common (75%; 63%, respectively). Less than one-third of participants experienced difficulties in other physical functioning areas, such as falling, getting up from sitting, standing, or climbing stairs.

Most were physically active, exercised regularly, and had few physical limitations that were apparent to others.

Social. Many indicated PD affected their ability to communicate as usual (78%), including energy to maintain social interactions (fatigue), ability to express ideas rapidly within a group context (cognitive), speak clearly (articulation) and be easily heard (quiet voice), or formulate written communications. PD also impacted personal relationships with others. This was most commonly reported with respect to immediate family, but also affected friends and co-workers. Impacts on relationships were due to increased dependence on others, tremor, cognitive issues affecting interactions, and mood changes.

> ***P25***: *I'm a very social person, and I feel like I'm being muted. I used to be this flamboyant, happy, outgoing, vivacious person. I feel like I'm not that person anymore.*

Emotional/Psychological. Nearly three-quarters of participants (73%) reported altered self-concept—i.e. viewing oneself as less capable, less competent, and less healthy, translating to decreased sense of well-being. Many also described preoccupation with PD (60%) and hypervigilance towards monitoring for symptoms and impacts or fear of the future and inevitable disease progression (53%).

> ***P16***: *I'm clumsy. I've never been clumsy before…when I see myself walking, I see myself as a sick person.*

> ***P13***: *Am I going to be in a wheelchair someday? That's [something] I worry about now.*

Approximately half (55%) reported embarrassment, most commonly with respect to tremor (47.5%) or other socially apparent symptoms (e.g. gait disturbances, flat affect) which sometimes led to feeling stigmatized (38%).

***P11**: [Tremor] is embarrassing– you appear weak or infirm.*

***P8**: [My lack of expression is] interpreted as if I'm angry. I'm not angry. It's just the way I look. It has a real negative impact on [relationships]*

Global. In all, over 90% of participants reported a sense that PD limited what they could do, with many indicating doing things in general required substantially more effort than prior to having PD.

***P5**: [I] have to slow down if I don't want to make mistakes—it's probably added 50 % to the time it takes to answer emails or to write something.*

A large number (40%) also reported increased personal discomfort ranging from pain to being unable to get comfortable and relax due to stiffness, cramping, or tremor.

Themes

Three key themes were identified with regards to what made symptoms meaningful from the perspective of people with early PD. Meaningful symptoms were those that were (1) personally important—whether actively present or not, with symptoms becoming more meaningful as (2) bothersomeness of an actively experienced symptom increased and (3) the symptom became more limiting. These themes are described below and supporting data are presented in **Supplement E**.

Theme 1. Symptoms can be important even when not present, or present but not important.

Personally important symptoms fell into two categories: (1) symptoms currently experienced that actively impacted physical and psychosocial functioning, and (2) symptoms *not* currently experienced that had potential to impact future physical and psychosocial functioning. For example, many people felt speaking and cognitive symptoms were very important (i.e. "staying me"[P28]) and they actively monitored for onset of cognitive and speech difficulties or engaged in activities to strengthen speech and cognition, even though currently without symptoms in that area. As one woman explained:

> ***P6**: I don't experience [trouble speaking] but I want to be able to speak clearly. Speaking is important to me.*

Theme 2. Symptoms can be bothersome even when not limiting, or limiting but not bothersome.

Similar to theme 2, symptoms did not have to be limiting in order to be perceived as bothersome. For example, tremor was often perceived as bothersome, even though it did not actually limit ability to do things. For example:

> ***P14**: [Tremor] has less to do with my quality of life than slow movement. It's annoying, but it doesn't stop me from doing anything.*

The more limiting a symptom was, the more bothersome it was generally perceived to be, as seen here:

> ***P26**: Anxiety is screwing up my life – it affects what you can do, where you can go, and who you can see.*

However, in some instances, symptoms caused limitations that were *not* viewed as bothersome. One individual who experienced substantially slower walking speed explained it this way:

> ***P3**: It slows me down, but I've got too many other things that are more important, so I'd say it's almost not bothersome. I can't worry about every little thing.*

Theme 3. Most bothersome symptoms are those which are limiting and have the greatest current negative impact on an individual's sense of well-being and usual activities.

> ***P2**: [Tremor is] less of a concern. It makes me self-conscious, but I don't let that get in the way of activities in my life. …For the moment, I would say fatigue is more bothersome…. although I'm anticipating that they will probably switch [in time].*

When discussing personally meaningful symptoms, individuals prioritized aspects of bothersomeness based upon a hierarchy of needs similar to that described by Maslow:[24] (1) physiologic needs (e.g. eating, breathing, sleep, pain/injury prevention, and ability to perform ADLs that meet these basic needs), (2) safety & security needs (symptoms affecting security, including employment or fear of the future, anxiety), (3) love and belonging needs (symptoms adversely impacting ability to communicate with others or interpersonal relationships), and (4) self-esteem needs (symptoms causing social embarrassment or affecting sense of oneself as a healthy competent person). When higher risk symptoms were not present, lower risk symptoms were prioritized instead.

For example, choking (Maslow level 1) was a very bothersome symptom, as were other symptoms that threatened personal safety, as shown in this comment:

> ***P9**: Hyposmia is a safety issue for me… I can't trust my sense of smell… I'm concerned I won't know if something's gone bad …[or] if there's a toxic odor. …once, there was plastic melting in the ceiling…and I wasn't aware of it. (**PRSS 4**)*

Similarly, tremor was less bothersome when lacking direct impact, and more bothersome when it caused pain or discomfort (Maslow level 1), interfered with work (Maslow level 2), or was apparent in social situations, resulting in a sense of stigma and embarrassment (Maslow levels 3-4). When individuals were able to mitigate the impact of the symptom or find work-arounds (i.e. protecting hierarchy of needs), the symptom was viewed as less bothersome. For instance, loss of fine motor skills and slower movements were more bothersome when they affected the individual's job and less bothersome *after* retirement when extensive computer work was not required. Similarly, when symptoms improved with medication use and became less limiting, they were viewed as less bothersome but still important.

Discussion

To our knowledge, this is the first study to systematicaly delineate prevalence, personal importance and relative bothersomeness of symptoms and impacts in people with early PD. We found the three most common motor symptoms were tremor, fine motor difficulties, and slow movements, whereas most common non-motor symptoms were nocturia, fatigue, insomnia and cognitive changes. Notably, when clustering symptoms by related impacts, those affecting mobility (e.g. slowness, stiffness/rigidity, and gait changes) and balance were cumulatively most important to a larger percentage of people than tremor alone (32.5% vs. 27.5% respectively), which is consistent with other literature.[12,25] Thus, our data support inclusion of mobility and balance among highest priority symptoms for people with early PD.

Our results corresponded well with prior studies that have investigated bothersomeness of PD symptoms.[5,11,12,25-27] Similar to others, tremor and mobility issues were the most common symptoms in our sample.[11,12] However, our data point to a much higher rate of fine motor difficulties (87.5%) than has been previously reported. Furthermore, nearly 90% of participants expressed broad-spectrum (not domain-specific) impacts not reflected in previous models – namely, feeling limited as a result of PD with the effect that things which were once intuitive take more time, effort, and intent. Recognizing the global impact of PD on the person, which supersedes domain specific effects on ADLs or physical/social/emotional functioning, is essential, as feeling limited appears to be one of the most common experiences for people at this stage.

Also distinct from previous works, we observed that fine motor tasks of handwriting, computer and smartphone use were inseparably intertwined with ADLs, and consequently

merged these categories. Based on this, we would propose amending impact domains to: ADL (inclusive of fine motor skills and use of phones, tablets, and computers), physical functioning, social, emotional/psychological, and *global*, so as to reflect the broader impacts of PD across domains. Reevaluation of existing clinical tools and outcome measures might be warranted in light of these findings.

Most importantly, this study adds to what is known about meaningful symptoms and impacts of early PD by revealing that the extent to which a symptom is viewed as bothersome is in fact *contingent on impact*, with symptoms hierarchically prioritized by individuals based on the effect on physical safety, security, relationships and self-esteem. While superficially logical, this relationship between bothersomeness and personal impacts has implications that bear consideration from a measurement perspective. Specifically, we found that "meaningfulness" appeared to be a function of the extent to which a symptom was personally *important* (present or not) *and* the degree to which it was actively *bothersome*, which related to physical and psychosocial impacts. "Important" symptoms often aligned with, but were not entirely equivalent to, "bothersome" symptoms—which is an essential distinction. Bothersome symptoms were always viewed as personally important, and more bothersome symptoms were generally more important; however, symptoms that were *not present* (e.g., cognitive or speech difficulties) or bothersome were also viewed as important and "something to keep an eye on." This led to hypervigilance towards onset of important symptoms, and self-monitoring for decline in speech or cognition in people who had not experienced these symptoms. Thus, monitoring for onset of future symptoms that are important to people with early PD (i.e., early meaningful symptoms) may be warranted, even when not actively present.

Cumulatively, our findings suggest that measuring "meaningfulness" of symptoms might require evaluating four discrete components: personal *importance*, *presence*, *bothersomeness*, and the extent to which a symptom *impacts or limits* quality of life and usual activities. **Figure 4** presents a proposed model and categorical classification schema of meaningfulness that could enable better understanding of what matters to people with PD. Use of a systematic evaluation approach, such as proposed here, could improve understanding of the extent to which measures (e.g., digital or non-digital tools and patient reported outcomes) target personally important *and* bothersome symptoms via a stepwise approach to meaningfulness.

Limitations and future directions

This study was conducted in predominantly higher socio-economic status, higher health/technologically literate, white individuals at a single time-point. Findings may not reflect experiences of individuals from underrepresented groups or those with lower technological and health literacy. Also, no significant differences in symptoms/impacts were found between those taking and not taking PD medications, which could due to small sample size. Lastly, longitudinal data would be needed to support understanding of how meaningful symptoms change over time. Our data tentatively indicated that as life contexts change—e.g. transitions from working to retirement or change in living situations—symptoms that are "most" bothersome may also change. Thus, reevaluation of meaningful symptoms over time, with the goal of developing population-based models to predict normative trends in PD symptom progression, are warranted to guide long-term therapeutic objectives.

Conclusion

The findings and approaches described here are important and can support rigorous, systematic identification and grading of meaningful symptoms and impacts of early PD, which is critical to selection of valid patient-centered endpoints for therapeutic trials. We believe the conceptual model and categorical classification of meaningfulness proposed here can be broadly relevant. Future work is needed to determine the extent to which this classification system can support interpretable evaluation of different types of outcomes assessments relevant to patients.

Acknowledgements

The researchers thank the many individuals who contributed to this work. The content is based solely on the perspectives of the authors and do not necessarily represent the official views of the Critical Path Institute, the US FDA or other sponsors. BrainBaseline application screenshots reprinted with permission from Clinical ink.

Author contributions

Authorship contributions were as follows: planning and development of study (all), data collection (JM, JA, PY, MK), data analysis (JA, JM, PY, GS, RS), drafting and revising of manuscript (all).

Disclosures

GTS is an employee of Rush University and has consulting and advisory board membership with honoraria for: Acadia Pharmaceuticals; Adamas Pharmaceuticals, Inc.; Biogen, Inc.; Ceregene, Inc.; CHDI Management, Inc.; the Cleveland Clinic Foundation; Ingenix Pharmaceutical Services (i3 Research); MedGenesis Therapeutix, Inc.; Neurocrine Biosciences, Inc.; Pfizer, Inc.; Tools-4-Patients; Ultragenyx, Inc.; and the Sunshine Care Foundation. He has received grants from and done research for: the National Institutes of Health, the Department of Defense, the Michael J. Fox Foundation for Parkinson's Research, the Dystonia Coalition, CHDI, the Cleveland Clinic Foundation, the International Parkinson and Movement Disorder Society, and CBD Solutions, and has received honoraria from: the International Parkinson and Movement Disorder Society, the American Academy of Neurology, the Michael J. Fox Foundation for Parkinson's Research, the FDA, the National Institutes of Health, and the

Alzheimer's Association. **JC** is Director of Digital Health Strategy at AbbVie and Industry Co-Director of CPP. **TD** Is Executive Medical Director at Biogen. **JH** Is Senior Scientist, Patient Insights at H. Lundbeck A/S, Valby, Denmark. **TS** has served as a consultant for Acadia, Blue Rock Therapeutics, Caraway Therapeutics, Critical Path for Parkinson's Consortium (CPP), Denali, General Electric (GE), Neuroderm, Sanofi, Sinopia, Sunovion, Roche, Takeda, MJFF, Vanqua Bio and Voyager. She served on the ad board for Acadia, Denali, General Electric (GE), Sunovion, Roche. She has served as a member of the scientific advisory board of Caraway Therapeutics, Neuroderm, Sanofi and UCB. She has received research funding from Biogen, Roche, Neuroderm, Sanofi, Sun Pharma, Amneal, Prevail, UCB, NINDS, MJFF, Parkinson's Foundation. **ERD** Has stock ownership in Grand Rounds, an online second opinion service, has received consultancy fees from 23andMe, Abbott, Abbvie, Amwell, Biogen, Clintrex, CuraSen, DeciBio, Denali Therapeutics, GlaxoSmithKline, Grand Rounds, Huntington Study Group, Informa Pharma Consulting, medical-legal services, Mednick Associates, Medopad, Olson Research Group, Origent Data Sciences, Inc., Pear Therapeutics, Prilenia, Roche, Sanofi, Shire, Spark Therapeutics, Sunovion Pharmaceuticals, Voyager Therapeutics, ZS Consulting, honoraria from Alzeimer's Drug Discovery Foundation, American Academy of Neurology, American Neurological Association, California Pacific Medical Center, Excellus BlueCross BlueShield, Food and Drug Administration, MCM Education, The Michael J Fox Foundation, Stanford University, UC Irvine, University of Michigan, and research funding from Abbvie, Acadia Pharmaceuticals, AMC Health, BioSensics, Burroughs Wellcome Fund, Greater Rochester Health Foundation, Huntington Study Group, Michael J. Fox Foundation, National Institutes of Health, Nuredis, Inc., Patient-Centered Outcomes Research Institute, Pfizer, Photopharmics, Roche, Safra

Foundation. **JLA** Has received honoraria from Huntington Study Group, research support from National Institutes of Health, The Michael J Fox Foundation, Biogen, Safra Foundation, Empire Clinical Research Investigator Program, and consultancy fees from VisualDx.

The following authors (JRM, RMS, MLTMM, PY, MC, JEC, SJR, MK, KWB, DS) have no conflict of interest to disclose.

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Table 1. Qualitative interview study demographics compared to parent study Parkinson's cohort

	Sample n = 40	Parent study (n = 82)
Age, years	63.9 (SD 8.8)	63.3 (SD 9.4)
Female, n (%)	19 (47.5%)	36 (43.9%)
Race/ethnicity, n (%)		
White	37 (92.5%)	78 (95.1%)
Asian	3 (7.5%)	3 (3.7%)
Not specified	-	1 (1.2%)
Hispanic or Latino, n (%)	1 (2.5%)	3 (3.7%)
Education > 12 years, n (%)	40 (100.0%)	78 (95.1%)
PD duration, years	2.1 (SD 0.9)	0.8 (SD 0.6)
Taking medications for PD, n (%)	16 (40.0%)	-

Note. Difference in Parkinson's duration and medication use reflects qualitative study data collection up to 1.5 years after the start of the parent study.

Figure 1. Symptom Mapping

Example of a participant map showing map structure and appearance

(Zoom in online for details)

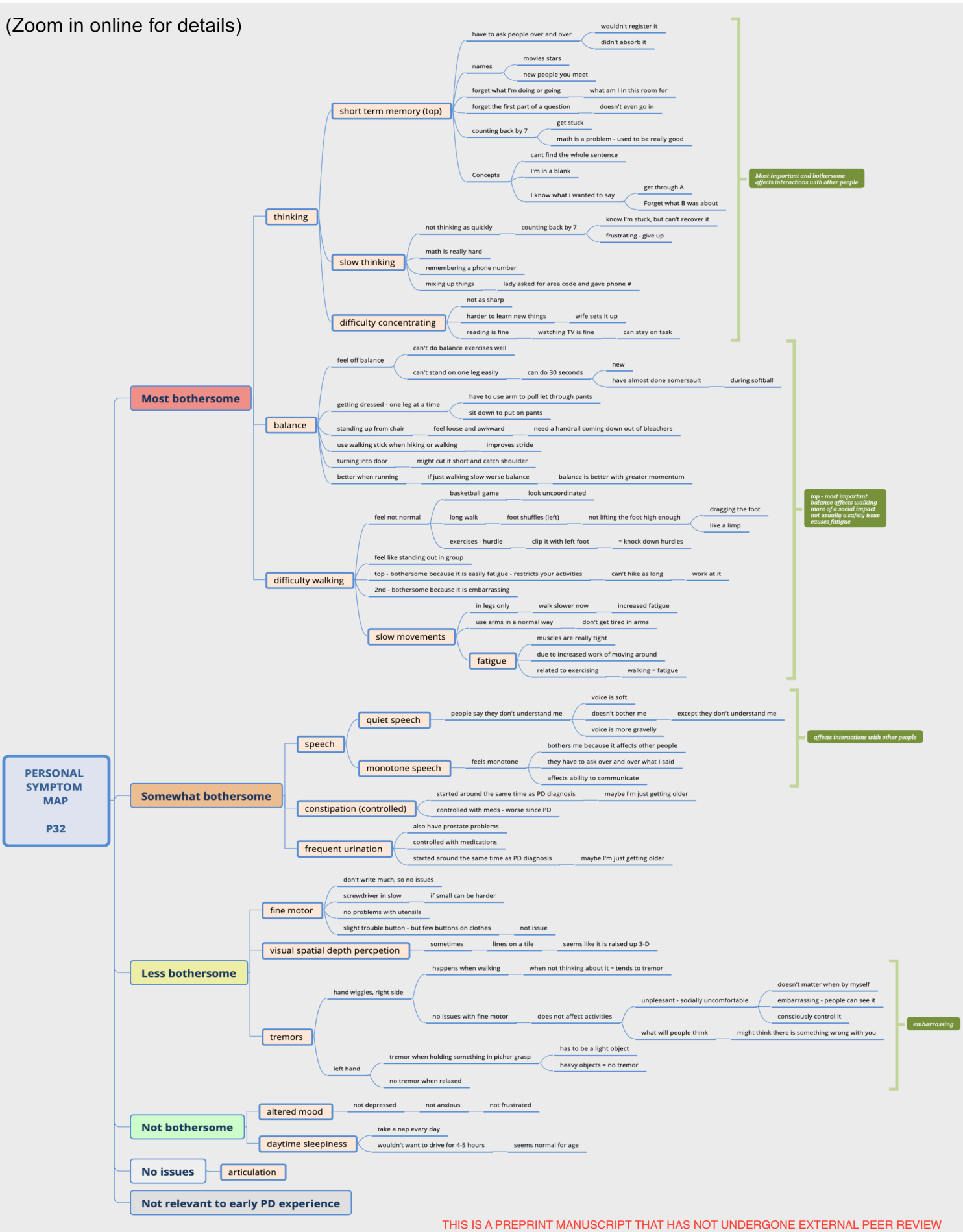
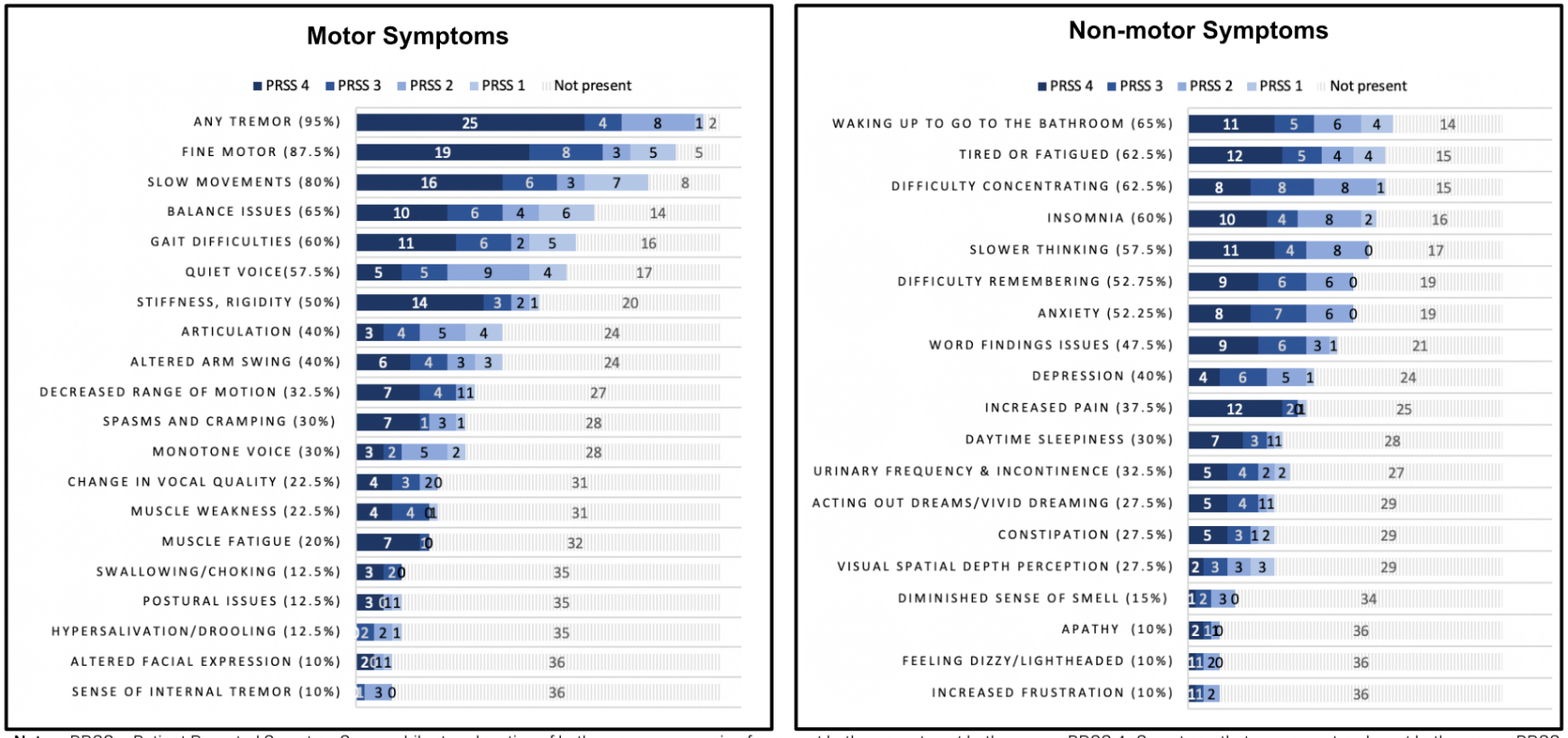
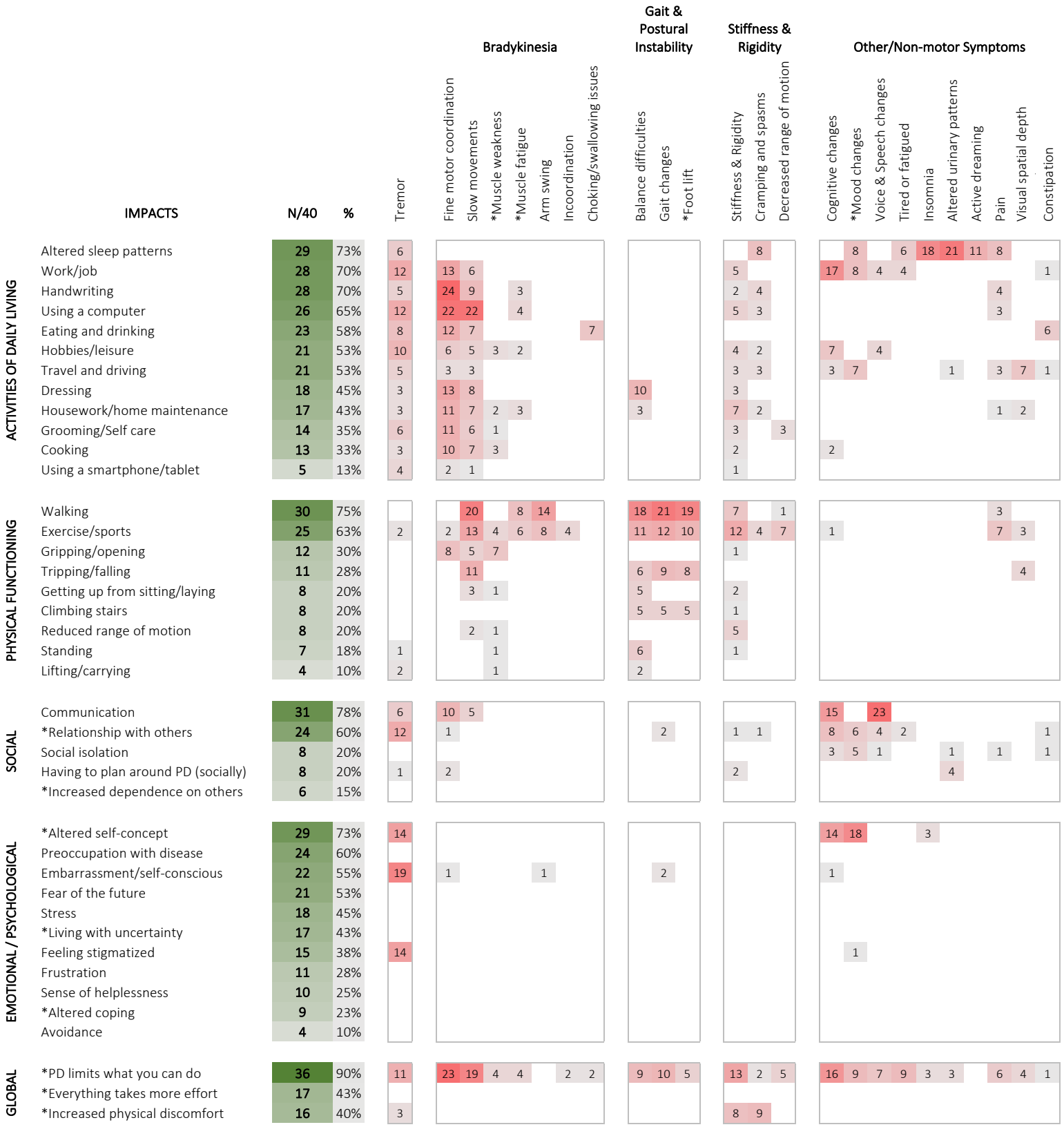


Figure 2. All patient reported symptoms of early Parkinson's by frequency of occurrence and bothersomeness as shown in symptom maps (N=40)



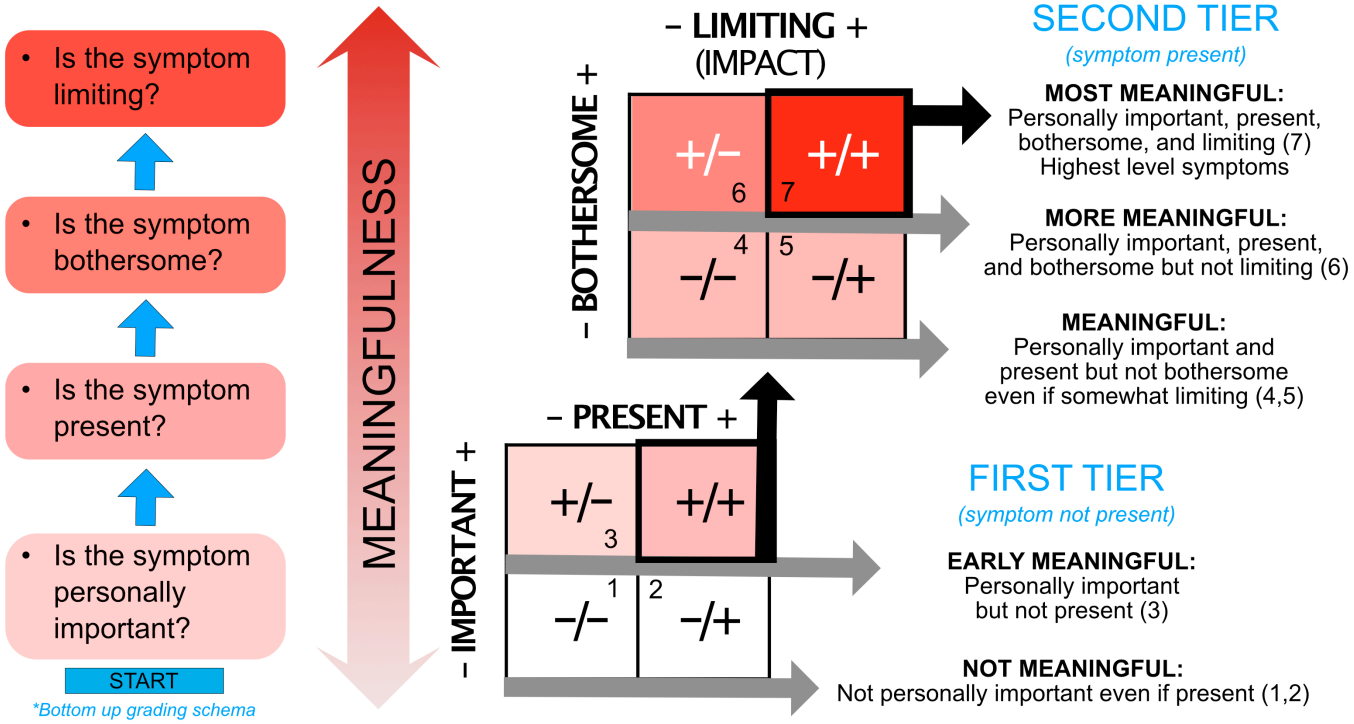
Notes. PRSS = Patient Reported Symptom Score – Likert scale rating of bothersomeness ranging from most bothersome to not bothersome. PRSS 4=Symptoms that are present and most bothersome; PRSS 3= Symptoms that are present and somewhat bothersome symptoms; PRSS 2= Symptoms that are present and less bothersome; PRSS 1= Symptoms that are present but not bothersome; Not present = Symptom not experienced. PRSS Scores are absolute. Figure includes both primary and contributing symptoms for each PRSS level.
Percentage (%) represents the total percent of participants who experience the symptoms (encompassing 1-4).
Tremor subcategories included: Hand tremor (85%) Leg/foot tremor (42.5%; Face/neck/Jaw tremor 12.5%). The following symptoms were reported by <10% sample and are not represented in the graphs: dyskinesia (0%); dry mouth (5%), diminished sensation, temperature dysregulation, sexual dysfunction, tearing of eyes, loss of appetite, double vision, right/left confusion, hemi-spatial neglect

Figure 3. Impacts of disease in people with early PD by frequency and contributing symptoms



Notes. Table comparative to the Patient-Centered Conceptual Model of symptoms and impacts in early PD from Staunton et. al (2022). Items with * were modified from or not present in the original model. Impacts affecting <10% of total sample (N=4/40) are not reported. Green shaded boxes visually represent number of participants reporting a particular impact as present. Red shaded boxes visually represent number of participants reporting a specific symptom as contributing to or causing the listed impact. Relative bothersomeness of impacts was not quantified and occurred across multiple symptom levels. Impacts were counted only once per participant.

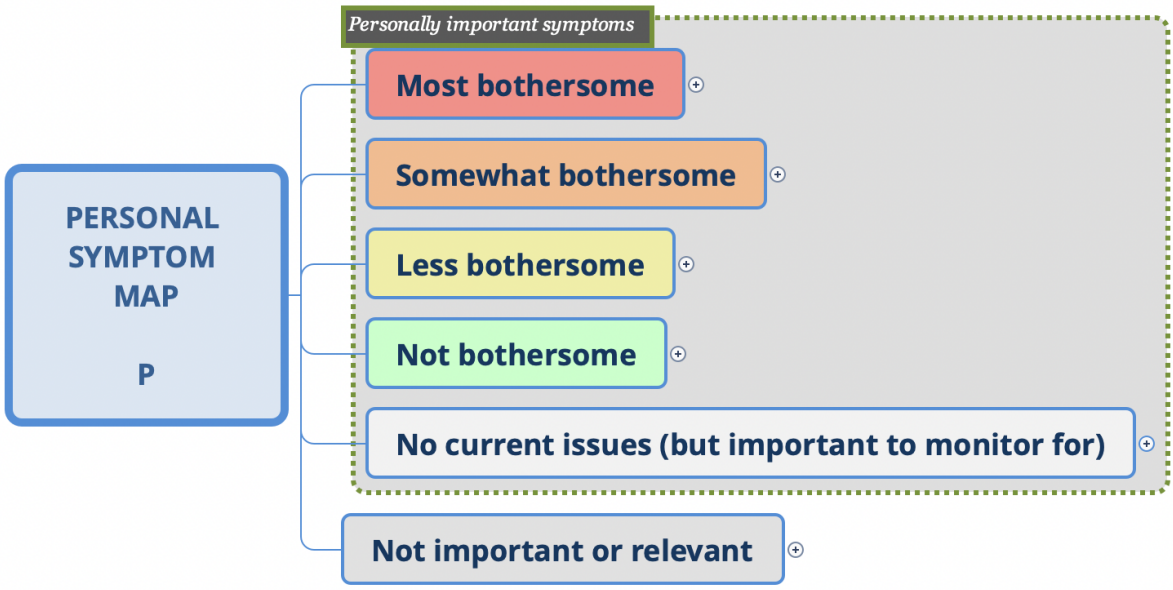
Figure 4. Conceptual model of meaningful symptoms and proposed stepwise grading schema



Supplement A. Symptom Mapping Interview Guide

1. First, would you tell me what Parkinson's disease-related symptoms you experience? From your responses on the survey, I see that you listed….

   [Step 1 of the symptom mapping activity begins here. As the participant directs, the interviewer will map the participants symptoms by order of personal importance.]



   - Probe: Are there other symptoms that you experience that you have not told me about and that I don't have in your map?
   - Probe [*yes/no*] on any they do not spontaneously state (tremor, slow movements, gait disturbances, fine motor coordination, speech articulation, cognitive impairment, daytime sleepiness, mood symptoms).

2. Of those symptoms you mentioned, explain to me which are the most bothersome to you. What specifically makes those symptoms bothersome, and in what situations?

   [The interviewer will add concise details to the symptom map delineating what makes specific symptoms important/bothersome. Example: if gait, is it foot lift or gait speed? Does it occur at home during regular daily activities or mostly when out exercising?]

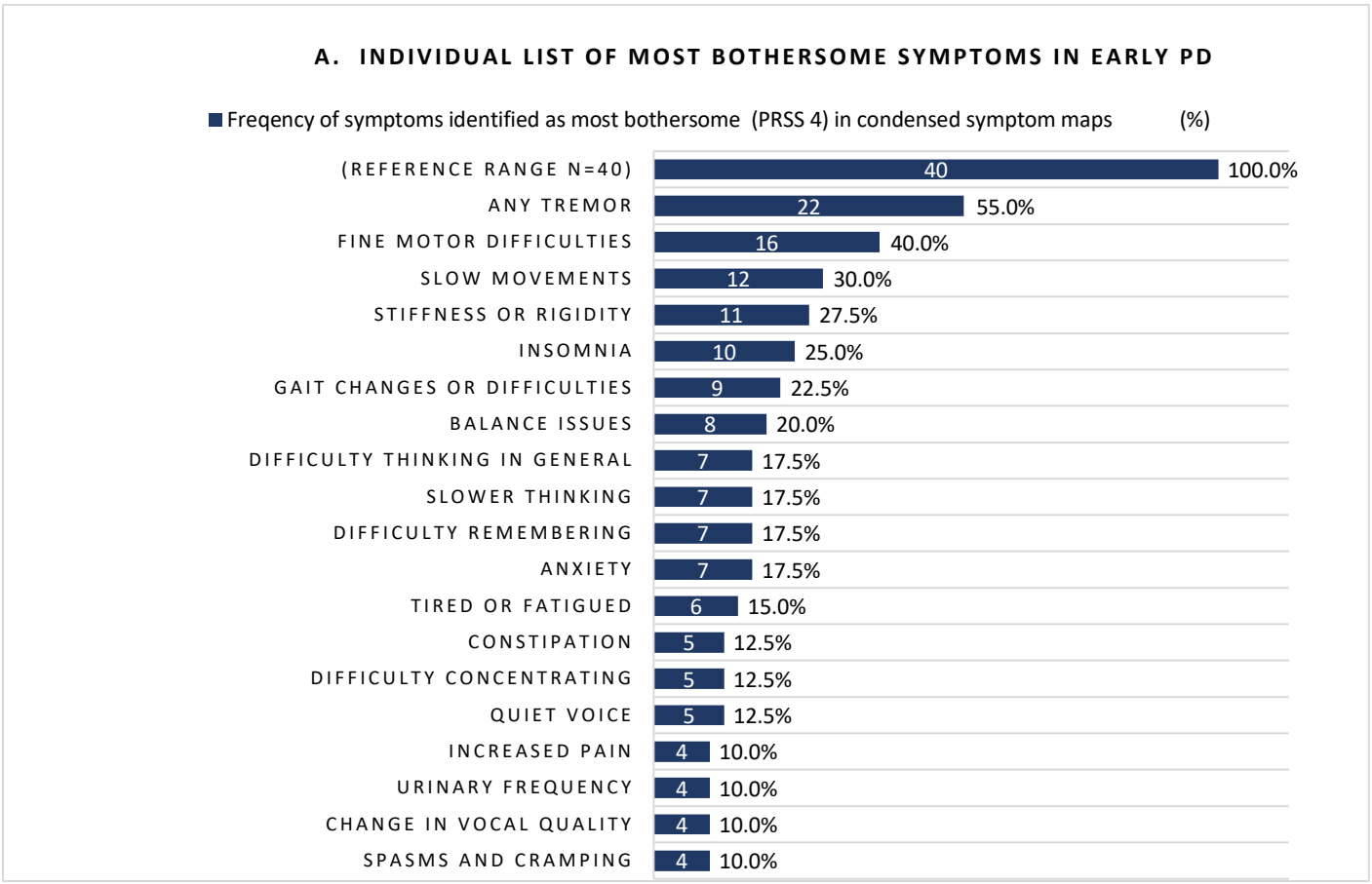
3. Are the symptoms that are <u>most bothersome</u> also the <u>most important</u> to you, or is that different in some way?

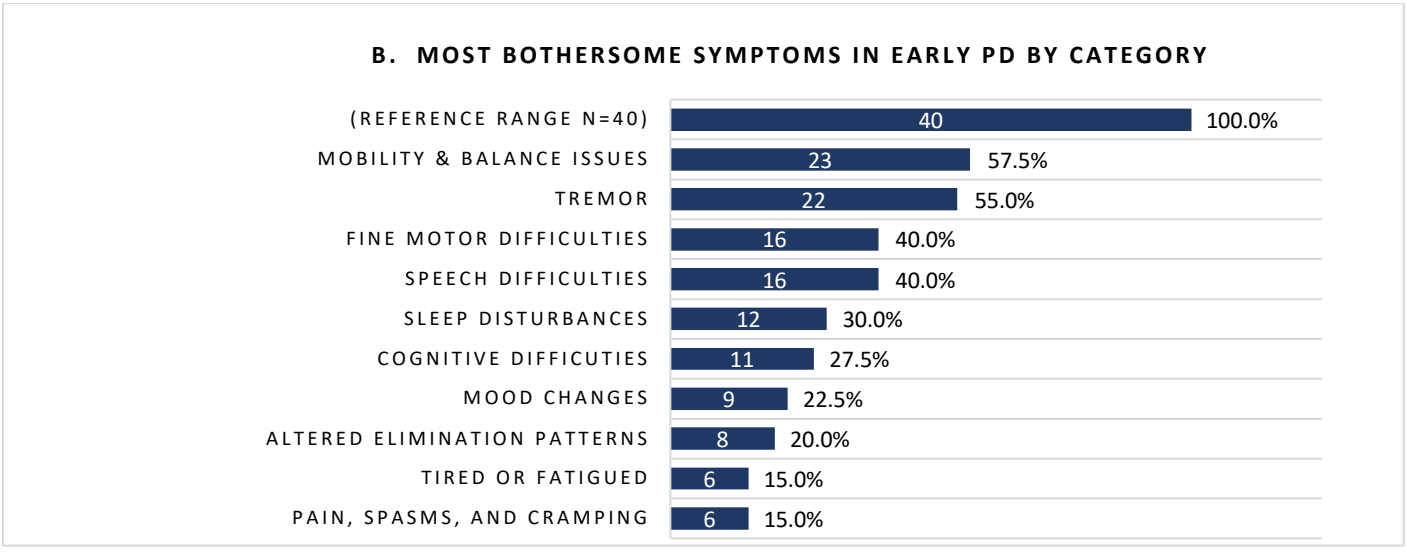
   - Probe: Have we captured all the symptoms that you experience correctly? Is there anything we missed?

Supplement B. Coding schema for hierarchical levels in symptom map

Map level (Node)	PRSS	Description
Most bothersome	4	Symptoms and impacts are present and most bothersome
Somewhat bothersome	3	Symptoms and impacts are present and somewhat bothersome
Less bothersome	2	Symptoms and impacts are present and less bothersome
Not bothersome	1	Symptoms and impacts are present but NOT bothersome
Not present	0	Symptoms and impacts are NOT present but are still personally important
Not relevant	.	Symptoms and impacts are NOT present and NOT relevant to early PD

Supplement C. Comparison of most bothersome symptoms of early PD in symptom maps based on curation

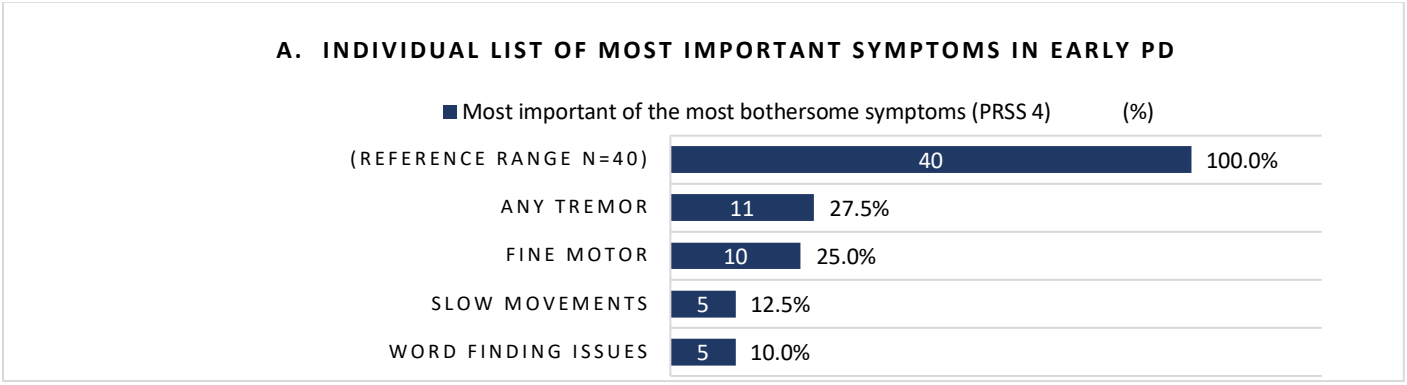


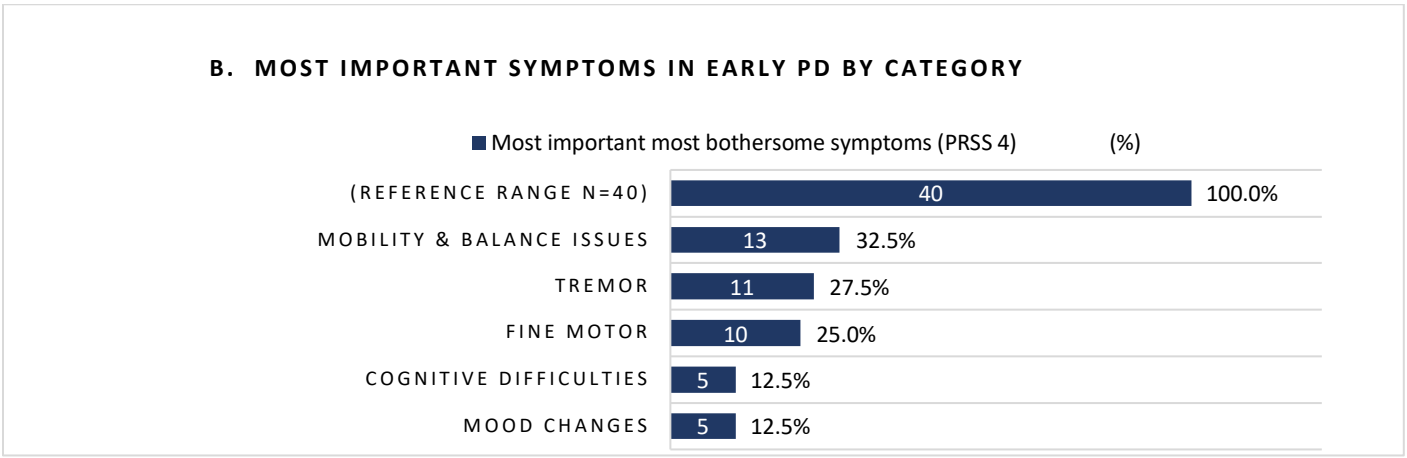


Notes. Conceptual categories in graph B curated as follows:

a. Mobility & balance: slow movements, stiffness/rigidity, gait changes, balance issues, muscle fatigue, muscle weakness, decreased range of motion, altered arm swing, postural issues
b. Tremor: Hand/arm, Leg/foot, and Jaw/face/neck tremors
c. Fine motor: fine motor difficulties
d. Speech changes: quite voice, monotone voice, difficulty forming sounds (articulation)
e. Sleep disturbances: insomnia, disturbed/active dreaming, excessive daytime sleepiness, waking up to go to the bathroom
f. Cognitive difficulties: slow thinking, difficulty remembering, difficulty concentrating, word finding issues
g. Mood changes: anxiety, depression, frustration, apathy
h. Altered elimination: urinary frequency, constipation
i. Tired or fatigued: feeling tired or fatigued
j. Pain, spasms, cramping: pain, muscle spasms, muscle cramping

Supplement D. Comparison of most important symptoms of early PD in symptom maps based on curation





Notes. Participants identified an average of 1.78 "most important" most bothersome symptom; total number of "most important" symptoms is thus greater than the sample size of 40. Symptoms reported by <10% are not shown. Tremor combines: Hand/arm tremor (22.5%); face/jaw tremor (7.4% total; 75% of people experiencing symptom), and leg/foot tremor (5%)

Conceptual categories in the lower graph were curated as follows:

a. Mobility & balance: slow movements, stiffness/rigidity, gait changes, balance issues, muscle fatigue, muscle weakness, decreased range of motion, altered arm swing, postural issues
b. Tremor: Hand/arm, Leg/foot, and Jaw/face/neck tremors
c. Fine motor: fine motor difficulties
d. Cognitive difficulties: slow thinking, difficulty remembering, difficulty concentrating, word finding issues
e. Mood changes: anxiety, depression, frustration, apathy
f. Speech changes: quite voice, monotone voice, difficulty forming sounds (articulation)
g. Altered elimination: urinary frequency, constipation
h. Sleep disturbances: insomnia, disturbed/active dreaming, excessive daytime sleepiness, waking up to go to the bathroom
i. Pain, spasms, cramping: pain, muscle spasms, muscle cramping

Supplement E. Illustrative quotes supporting thematic findings

Theme 1. Most bothersome symptoms are those which have the biggest current negative impact on an individual's sense of well-being and usual activities and can change over time.

P8: Depressed mood is the thing that impacts me, my family, and people I know the most. How I impact others negatively bothers me, and potential that this can only get worse.

P5: As far as the symptom that really I feel like is affecting my life. This is [fine motor] is the one that's most annoying. The tremor is there, and it might bother my sleep, in terms of getting back to sleep once in a while, but it's not affecting my ability to function. [Fine motor] is annoying 'cause my job involves a lot of emails, and writing when I'm working.

P2: [Tremor is] less of a concern for me. Obviously it does make me self-conscious, but I don't let that get in the way of activities in my life. …For the moment, I would say fatigue is more bothersome…. although I'm anticipating that they will probably switch.

P9: I'm a physician, so I know all of the potential things I could have in Parkinson's. I think about becoming slow, [and] I guess I would put it as no issues [for now]. I remember saying to my son, "You know, one day, we'll be hiking, and I'm gonna be going slower," and he said, "That's okay."

P11: I guess it's a combination of somewhat embarrassing and at other levels it's just kind of a nuisance. But the nuisance becomes more bothersome over time

P17: Trouble speaking is socially more acceptable than me having a peeing accident on somebody's carpet.

P39: I feel funny that I'm taking such a long time to find a word. I tell whoever I'm talking to, that I have this problem 'cause they're waiting, and I'm the problem.

P34: I've just learned to live [these symptoms] with for so long that it doesn't seem to bother me as much anymore.

P18: Slow movement and the fine motor hands [are most bothersome] - My plans for my 80s was to write an autobiography, and do some other writing, and I'm not sure I can do any of that, so that's a big change for me…. Spasms and cramping…They occupy my mind. They inhibit me. They are there all the time.

Theme 2. Symptoms can be important even when the symptom is not present or present but not particularly important.

P3: [It's] scary because I don't want to ignore something that really should be a symptom or a set of clues that, "Hey, you need to be more careful or you need to watch this more carefully."…[it's] something I'm keeping a very close watch on.

P1: I hear that some people's voices get much softer. The first thing I ever did was the speech therapy. Because of my profession, it was real important that it wasn't diminishing.

P14: I would want to know if my voice is getting [weak or] trails off. I don't know that I'm there yet, but it could come. It's like it's one of those down-the-road symptoms good to keep an eye on.

P12: I'm not experiencing [trouble speaking], but I would imagine that at some point within the disease, progression it will happen - but nothing now. [It could affect] communication, working with my employees, working with customers.

P11: I didn't generally have a problem with [cognitive decline], but I might in the future.

P39: [I have to urinate] very often…and I have some trouble with fine motor…[but] it doesn't bother me.

Theme 3. Symptoms can be bothersome even when the symptom is not actually limiting or limiting but not particularly bothersome

P5: The tremor in itself it doesn't really affect things… It's [just] annoying I guess, is the best way to describe it,

P3: It slows me down, but I've got too many other things that are more important, so I'd say it's almost not bothersome. I can't worry about every little thing that slows me down. I have to ignore some things that I know I'm not as good at or not as competent with and focus on the things that I can still do well, and what will help speed me up if I can find those things and processes that will give me not an edge, but give me the skills or the attitude that I can keep going.

P4: I'm left-handed, so it's unfortunate the tremor is on the left side, but it doesn't really stop me from doing anything. It just impacts how easily it is to do things.

P18: I'm concerned about having increasing problems with balance, because that will diminish my mobility. I don't think I'm there yet, but I can see that I'm having more problems than I used to.

P1: Professionally, I'm a preacher. To be in front of an all church gathering preaching and my hand is shaking… I just try to hide that. It doesn't restrict any of my activities. It's just something I wish wasn't happening.