Parkinsonism and Related Disorders 99 (2022) 51–57

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Frailty in Parkinson's disease and its association with early dementia: A longitudinal study

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ARTICLE INFO

Keywords:
Frailty
Dementia
Parkinson's disease
Older adults

ABSTRACT

Introduction: Frailty is recognized as a clinical condition associated with increased vulnerability for developing negative health outcomes but has been little studied in patients with Parkinson's disease (PD). Here, we investigated the risk of frailty in de novo PD patients and its association with subsequent development of dementia.

Methods: We conducted a three-year longitudinal population-based study of 192 drug-naive newly diagnosed PD patients and 172 controls (No-PD) matched for age, sex, and education. Frailty was measured using the frailty index (FI). Logistic regression models, adjusting for potential confounders, were conducted to assess the association between frailty at the time of PD diagnosis and the subsequent odds for developing PD dementia during follow-up.

Results: The mean baseline FI score was higher in the PD (0.21 ± 0.10) than in the No-PD group (0.11 ± 0.07, $p < 0.001$). One-third of PD patients had high-FI (>0,25), compared to 5% in the no-PD group. Participants with PD had an increased risk to present frailty with an odds ratio (OR) of 6.68 (SE 2.70 IC 95% [3.15; 15.62], p-value <0.001) compared to the No-PD group. PD Participants with greater FI measured at baseline had increased odds of having dementia within three years of follow-up, after adjustment for age and sex (OR 2.91 SE 1.00 IC 95% [1.54; 5.99] p-value = 0.002).

Conclusion: Frailty is common in people with newly diagnosed PD and associated with increased odds for subsequent development of dementia in a three-year follow-up. This study emphasizes the prognostic importance of frailty in PD from the earliest clinical stages.

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https://doi.org/10.1016/j.parkreldis.2022.05.004
Received 16 January 2022; Received in revised form 29 April 2022; Accepted 8 May 2022
Available online 13 May 2022

1. Introduction

Parkinson's disease (PD) is a progressive multisystem neurodegenerative disorder leading to a broad spectrum of potentially disabling motor and non-motor manifestations, including dementia [1]. In addition, age-related problems and other chronic diseases can interact to accelerate the functional decline in people with PD [2]. This process of deficit accumulation ultimately affects tissues, organs, and integrated organ action, especially under stress [3].

Frailty is characterized by a diminished ability of systems to self-stabilize in response to external forces across multiple physiologic systems with increased vulnerability to stress and a higher risk for adverse health outcomes such as disability, dependency, poor quality of life, and death [4].

Several tools are used to assess frailty; however, the two most common measurements are the Frailty Index (FI) and the Fried's phenotype [4]. Despite the used tool to categorize an individual as frail and their differences, frailty has shown to predict several adverse outcomes in older adults [4]. Moreover, frailty has been associated with functional, structural, and pathological brain changes and is reported to be an independent predictor of cognitive decline, Alzheimer's disease, neuropathologic burden, and dementia more broadly [5–8]. Besides, evidence suggests that interventions designed to prevent or treat frailty can delay or avoid negative health consequences [9]. Despite this, the concept of frailty in people with PD has received limited attention and consequently, such interventions have not been investigated in this patient group.

Against this background, we investigated the prevalence of frailty in early PD and its association with the subsequent odds of developing dementia, one of the most debilitating consequences of the disease. Identifying predictors of dementia is crucial for patients, families, and the health care system. Some demographic and clinical features have been associated with dementia, including age and severity of motor symptoms [10,11], but little is known regarding frailty in this population.

2. Materials and methods

2.1. Study design and setting

This is a longitudinal secondary analysis of the Norwegian ParkWest study, a prospective, population-based, longitudinal multicenter cohort study designed to investigate the incidence, neurobiology, and prognosis of people diagnosed with PD. The recruitment procedures and study design have been described previously in detail [12]. Search strategies for potential participants included referral letters, notification of regional hospitals and health careers, and screening of hospital databases. Briefly, we sought to recruit all new cases of PD between November 2004 and September 2006 within a defined geographical area in Western and Southern Norway.

The study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (#2010/1700) and performed according to the Declaration of Helsinki. All participants provided written informed consent before enrollment in the study.

2.2. Participants and Follow-up

In this study, we included 192 drug-naive newly diagnosed PD patients who fulfilled the Gelb and UK Parkinson's Disease Society Brain Bank clinical criteria for PD [13], and none of them had a history of dementia within 1 year of motor onset. A group of 171 healthy people (No-PD group) matched for age, sex, and education were recruited in the same geographical area and free from parkinsonism, dementia, and major depression at inclusion. All participants were Caucasian.

Standardized examinations were conducted by trained health professionals every 6 months, with an extended examination program performed at baseline and after 1 year and 3 years of follow-up in both patients and controls. At baseline, we collected information on demographics, medical history, and comorbidities in the presence of a caregiver whenever possible, and performed semi-structured interviews and a general medical and neurological examination.

2.3. Clinical and neuropsychological assessment

Data regarding current diagnoses at baseline and during the study period was used for further analyses (see Frailty section) to obtain a detailed overview of the demographic and clinical status of the included subjects.

The de-novo diagnosis of PD was made by two neurology specialists in movement disorders, following the standardized criteria and assessments (see Participants and Follow-up section). Similarly, the diagnosis of dementia associated with PD (PDD) was conducted according to the published consensus criteria and re-evaluated during the follow-up [11,12,14].

We assessed the motor severity using the Unified PD Rating Scale (UPDRS) motor examination subscale (part III). Neuropsychiatric symptoms were evaluated using the Norwegian version of the Neuropsychiatric Inventory (NPI) 12 items, and its NPI total score. Global cognition was assessed using the 30-item Mini-Mental State Examination (MMSE). As a measurement of global health-related quality of life, the Short Form Health Survey (SF36) was used. A detailed description of PD and PDD diagnosis in the ParkWest cohort, as well as various motor and non-motor symptoms structured examinations outlined before can be found elsewhere [11].

In addition, patients underwent a neuropsychological battery of tests that are considered minimally affected by motor performance to assess cognitive domains known to be affected in PD, as detailed elsewhere [11]. The neuropsychological battery included verbal memory, attention, executive functioning, and visuospatial abilities. For verbal memory, the total immediate recall, short delay, and long delay free recall (after 20 min) were evaluated using the California Verbal learning test II [11]. Visuospatial abilities were examined using the Silhouettes and Cube subtests of the Visual Object and Space Perception Battery. Attention and executive functions were assessed through different tests (i.e. verbal fluency in 1 min, serial 7 test from the MMSE, and the sum of color and word conditions in the Stroop test). A detailed description of the neuropsychological assessment can be found elsewhere [15].

2.3.1. Frailty

Following the criteria for inclusion of health-related variables/deficits as outlined by Searle et al. we determined frailty at baseline using the FI approach. The FI is a widely used instrument which has been validated in different populations, clinical and research scenarios [16]. The criteria for the determination of the FI includes: 1) exclusion of candidate deficits not related to age, 2) exclusion of deficits with too low or too high prevalence to not be informative, 3) exclusion of potential deficit variables missing more than 5% data, and 4) exclusion of participants missing more than 20% of variable data in the FI.

A health deficit can be any health variable in which the deficit/riskier state increases with age, and is associated with death or other adverse outcomes of interest, such as hospitalization or nursing home admission [16]. Our FI included 31 deficits: 1. Hypertension, 2. Hypotension, 3. Arrhythmia or flutter, 4. Hypercholesterolemia, 5. Depression, 6. Anxiety, 7. Cardiac failure, 8. Myocardial infarction, 9. Stroke, 10. COPD, 11. Diabetes mellitus, 12. Ulcer disease, 13. Cancer, 14. Renal disease, 15. Rheumatic disease, 16. Unable to drive, 17. Urinary dysfunction, 18. Constipation, 19. Daytime sleepiness (Epworth scale), 20. Self-rated health, 21. Pain in any part of your body during the last 4 weeks, 22. Fatigue, 23. Problems with dressing alone, 24. Problems doing own hygiene tasks, 25. Cutting food, 26. Falls, and Unable to perform: 27. Moderate efforts, such as moving a table, vacuuming, bowling, or walking for more than 1 h, 28. Take or carry the shopping

bag, 29. Climb several floors up the stairs, 30. Crouching or kneeling, 31. Walkabout 100 m. See appendix 1 for a better comprehension of FI.

Binary variables were transformed into a zero (no deficit) or one (deficit) value. Variables with more than two responses were coded as a fraction of the complete deficit. For example, self-rated health-related quality of life had five response options, resulting in the following coding: excellent = 0, very good = 0.25, good = 0.5, fair = 0.75 and poor = 1 (Appendix 1). Finally, to calculate the FI score for each individual, deficits were summed and divided by the total number of deficits measured. Individual FI scores range theoretically from zero to one with zero indicating the lowest level of frailty [17]. For the analysis here, an FI score of 0.25 or above was considered high frailty [18]. For detailed information about the FI construction and scoring method, see appendix 1.

2.4. Statistical analysis

We performed a descriptive analysis by calculating percentages for categorical variables and means and standard deviations for quantitative variables after normality was confirmed. We compared differences between the PD and no-PD control group using t-tests for continuous variables and Pearson's chi-square tests for categorical variables.

For baseline cross-sectional analysis of PD concerning frailty, we fitted a logistic regression model to assess the association between diagnostic group (PD vs. no-PD controls) and a high FI score. This model takes the baseline FI score equal or greater than 0.25 as the dependent variable, diagnostic group as the independent variable, and was adjusted for age, sex, neuropsychiatric symptoms, and cognition.

A logistic regression model was also adjusted to analyze the association between baseline frailty with subsequent probability of developing dementia within the next 3 years among people with PD. A first model was fixed including the standardized continuous FI score as the exposure variable (model 1), then, we fixed a second model adjusting by age and sex (model 2). Besides, we performed some extra models adjusting for baseline cognition (model 3) and neuropsychiatric symptoms (NPI total score), and motor severity (UPDRS part III score) (model 4). The performance of the classification in the prediction for each model was evaluated as well through Receiver Operating Characteristic (ROC) curves. Significance probability was set at 0.05. All analyses were performed in R statistical software.

3. Results

Considering our matched design, PD and No-PD control groups were comparable in age and sex, while PD patients had higher scores on clinical scales as expected. The mean UPDRS motor examination score was 23.56 ± 11.34 in the PD group (Table 1).

The mean FI score at baseline was significantly higher in people with PD than No-PD controls (0.21 ± 0.10 vs. 0.11 ± 0.07, $p < 0.001$; Table 1). About a third of PD patients (n = 65, 33.9%) had a high FI (FI > 0.25) compared to only 5% (n = 9) among the no-PD controls p-value < 0.001; Fig. 1A. The frailty index tended to increase across the studied age ranges, particularly in the PD group; Fig. 1B.

Model estimation showed an adjusted odds ratio (OR) of 6.682 (SE 2.703, p-value: <0.001) for having a high-FI at baseline (FI ≥ 0.25) in the PD group when compared to No-PD, as shown in Appendix 2.

During the three-year study period, 14 out of 192 patients with PD developed PDD (7.9%). Our model estimations in the PD group showed consistently a direct association between FI and odds of developing PDD, as summarized in Table 2 and Fig. 2. The unadjusted model (model 1) showed a significantly increased OR for developing dementia in those PD patients with greater FI (OR 3.25 SE 0.99 IC 95% [1.85; 6.18] p-value < 0.01). Similarly, in the age- and sex-adjusted model (model 2), PD patients with greater FI had a statistically significant increased odds of developing dementia within the first 3 years after PD diagnosis (OR 2.91 SE 1.00 IC 95% [1.54; 5.99] p-value = 0.002). In line with the above models, significance was maintained even after adjusting by global cognitive performance, global neuropsychiatric symptoms, and PD severity (models 3 and 4).

Table 1
Sample characteristics at baseline.

Variable	PD	No-PD	P-value
	n (%) or Mean ± Standard Deviation		
Sample size	192 (52.75)	172 (47.25)	0.2945
Frailty Index	0.21 ± 0.10	0.11 ± 0.07	<0.001
Low frailty (FI 0-0.25)	127 (66.15)	163 (94.77)	<0.001
High frailty (FI 0.26-1)	65 (33.85)	9 (5.23)	
Age at baseline	68.13 ± 9.32	67.50 ± 9.09	0.5169
40–70 years	108 (56.25)	98 (57.31)	0.6120
70–80 years	65 (33.85)	61 (35.67)	
80–90 years	19 (9.90)	12 (7.02)	
Sex			
Men	117 (60.94)	101 (58.72)	0.6670
Women	75 (39.06)	71 (41.28)	
NPI Total score	4.71 ± 7.90	0.70 ± 2.63	<0.001
UPDRS motor	23.56 ± 11.34	–	–
MMSE Total score	27.66 ± 2.53	28.56 ± 1.49	<0.001

PD: Parkinson's disease, No-PD: Control subjects without Parkinson's disease, MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, UPDRS: Unified Parkinson's Disease Rating Scale. P-value indicates differences between PD and No-PD groups.

4. Discussion

To our knowledge, this is the first study of frailty in newly diagnosed PD patients and the first to study the association between frailty and dementia in PD. We found an increased adjusted odds of presenting a high FI in patients with a de-novo diagnosis of PD when compared to controls and increased odds of developing PDD in those who had a greater FI at baseline.

Frailty is an aging-related condition of physiological decline, characterized by increased vulnerability and higher risk for developing adverse health-related outcomes. This risk arises in relation to the number of health deficits that people have and is diminished by protective factors. The clinical relevance of frailty has been shown in many other diseases, such as COPD, Diabetes, cancer, Alzheimer disease, between others [3].

People living with PD, even in the early stages, have motor and non-motor symptoms, a high burden of comorbidities, and associated functional limitations [19]. According to a recent systematic review, five studies provided data regarding the presence of frailty in PD patients, with reported a prevalence ranging between 29 and 67% [20]. As a complement to the above studies conducted in patients with a longer duration of PD, our study showed that 33.9% of de-novo PD patients had a high frailty index (i.e. FI ≥ 0.25).

Although current reports show that frailty is common in people living with PD, there might be biased estimations when it comes to defining frailty. Despite the potential overestimation of index-based methods [17], frailty has consistently been shown (regardless of the tool or definition used for its estimation) to be a significant predictor of negative outcomes, both general and disease-specific, across several different diseases, settings, and regions [4,21]. In addition, one study conducted in the US from Medicare beneficiaries reported that severe frailty was associated with higher 1-year mortality, hospitalization, emergency department visits, and fall-related injury in patients with PD [22]. A negative effect of frailty on important patient-reported outcomes such as quality of life scores in Community-Dwelling Persons with PD has also been reported [23].

Dementia is a devastating event for people living with PD, their families, and their caregivers. And a key factor in a decline of function leading to dependency. Cognitive decline has been associated with increased mortality, poor quality of life, poor well-being, increased

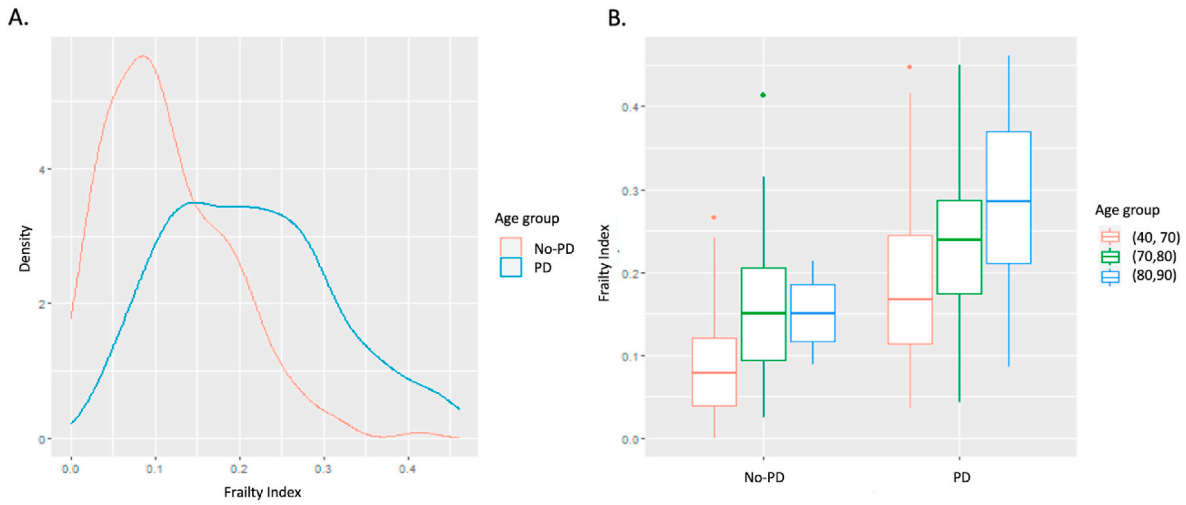

Fig. 1. Frailty Index distributions
Figure caption: A) Frailty index distributions among people with Parkinson's disease (PD; blue) and healthy controls (No-PD; red). B) Frailty index distributions among people with Parkinson's disease and healthy controls by age. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Fixed models for developing PDD during the study period among people with PD.

Variable	Model 1 (unadjusted)				Model 2			
	OR	S.E.	95% CI	P-value	OR	S.E.	95% CI	P-value
Frailty Index[a]	3.25	0.99	[1.85;6.18]	**< 0.01**	2.91	1.00	[1.54;5.99]	**0.002**
Age								
70–80 years					6.47	5.30	[1.52;44.59]	**0.023**
80–90 years					3.49	3.61	[0.45;31.50]	0.228
Sex (Woman)					0.82	0.50	[0.24;2.66]	0.741
	Model 3				**Model 4**			
Frailty Index[a]	2.49	0.87	[1.30;5.19]	**0.009**	2.63	1.03	[1.26;6.00]	**0.014**
Age								
70–80 years	5.32	4.46	[1.19:37.59]	**0.046**	5.73	4.91	[1.23;41.67]	**0.042**
80–90 years	2.68	2.89	[0.30;25.55]	0.361	2.80	3.04	[0.32;27.13]	0.343
Sex (Woman)	0.88	0.55	[0.25;3.00]	0.839	0.82	0.53	[0.22;2.86]	0.756
MMSE	0.84	0.08	[0.69;1.01]	0.067	0.98	0.04	[0.89;1.04]	0.532
NPI					1.00	0.03	[0.95;1.06]	0.902
UPDRS motor					0.85	0.08	[0.70–1.02]	0.089

Logistic regression. **MMSE: Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, UPDRS: Unified Parkinson's Disease Rating Scale.**
Est = Estimation; S.E. = Standard Error; CI = Confidence Interval.
[a] Standardized.

caregiver burden as well as increased healthcare and institutionalization costs [24]. Therefore, the identification of risk factors for cognitive decline and dementia in people with PD is crucial. Early biomarkers and manifestations of PDD, including frailty, are of most importance since the early intervention of modifiable targets could prevent adverse health outcomes.

We are aware of only one cross-sectional study of the association between dementia and frailty in PD, reporting a 9–11 fold increased odds ratio for having dementia in frail PD patients with a long duration of PD [25]. In the current study, we reported an increased odds of developing PDD in those with greater FI at drug-naïve PD diagnosis, pointing out that FI might be an early marker of future development of PDD. Our findings complement previous reports made in Alzheimer's disease, where dementia has been predicted by frailty, even when adjusting for specific Alzheimer pathology burden [5] and other types of dementia-related neuropathological markers [26].

Previous findings in non-PD cohorts have shown that the risk of dementia that is attributed to frailty (using index-based measurements) can be equivalent to the attributed burden of neuropathology markers [8,27]. In neurodegenerative diseases, particularly PD, FI might complement the conventional focus on motor and non-motor symptom, and providing an estimate of the health-related burden and capacity to respond to stressors [3].

Frailty is a potentially modifiable target that might contribute to improving the prognosis of people diagnosed with PD. Evidence has shown that frailty is sensitive to change with interventions such as physical activity, protein-calorie supplementation, and de-prescription of unnecessary medications [9,28,29]. Such interventions have the potential to be implemented in PD care to improve prognosis [30]. Even so, it remains unknown if treating frailty might prevent dementia in at-risk patients, and this seems a promising objective for future research.

FI can be reproduced in various settings and has an operationalized creation method facilitating its validation. However, calculating the FI is time-consuming, future automatization of index-based estimations generated from medical records could facilitate its implementation in dementia-prevention initiatives, geriatrics, and mental health centres. For the purposes of our study and the context of PD, the FI is particularly useful compared to other instruments. For example, some other tools include physical performance tests that are difficult to interpret in a patient with PD. Moreover, the granularity of the FI allows a broader

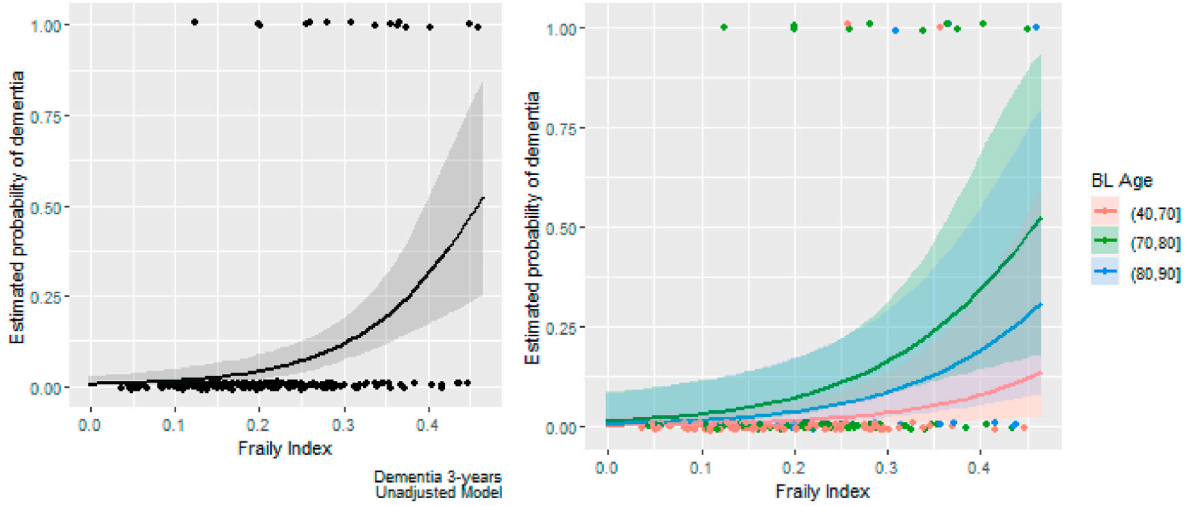

Fig. 2. Estimated probability of dementia at three years according to baseline frailty index.
The unadjusted model 1 (left) and the adjusted by age and sex model 2 (right).

assessment of these individuals and a better understanding of the complexity of an older adult with PD.

Some methodologic limitations must be considered.

We acknowledge that some variables included into the FI are common features of PD, (e.g., problems in cutting food), possibly resulting in an overestimation of the FI scores or circular associations. In addition, the FI implemented in this study was only possible to be calculated at baseline and included a limited number of deficits, as the ParkWest study was not targeted initially to assess frailty. The three-year study period may be too short for presenting the outcome since PDD risk increases with the duration of PD. Strengths of the study include the longitudinal design and inclusion of drug-naïve patients, and thus all variables used for the FI were measured in the absence of potentially confounding effects of medication for PD. Finally, the inclusion of a No PD control group, the standardized approach for clinical diagnosis of PD and PDD, and the low attrition rate during follow-up support our conclusions.

Statement of ethics

This study was approved by the regional ethics committee (approval code: REK 131/04) for the collection of medical data. All data was handled and kept following national health and data privacy protocols. All participants signed an informed consent form before inclusion in the study.

Declaration of conflicts of interest

The authors have no potential conflicts of interest to declare regarding research, authorship, and/or publication of this article.

Funding sources

This paper represents independent research supported by the Norwegian government, through hospital owner Helse Vest (Western Norway Regional Health Authority). Also, funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. LW is supported by a Canadian Institutes of Health Research Banting Postdoctoral Fellowship award.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgments

We want to thank all the participants, researchers, and technical staff that have made the ParkWest study possible.

Appendix 1. Deficit selection for frailty index creation

Deficit	Age related	Prevalence %	Frequency	Total answers
1. Hypertension	**yes**	**41.97**	**175**	**417**
2. Hypotension	**yes**	**0.48**	**2**	**417**
3. Arrythmia o flutter	**yes**	**6**	**25**	**417**
4. Hypercholesterolemia	**yes**	**8.87**	**37**	**417**
5. Depression	**yes**	**9.11**	**38**	**417**
6. Anxiety	**yes**	**2.16**	**9**	**417**
7. Cardiac failure	**yes**	**2.4**	**22**	**417**
8. Miocardial infarction	**yes**	**5.28**	**22**	**417**
9. Stroke	**yes**	**5.04**	**21**	**417**
10. COPD	**yes**	**6.24**	**26**	**417**
11. Diabetes	**yes**	**6.47**	**27**	**417**
12. Ulcer disease	**yes**	**2.4**	**10**	**417**
13. Cancer	**yes**	**10.07**	**42**	**417**
14. Renal Disease	**yes**	**0.24**	**1**	**417**

(*continued on next page*)

(*continued*)

Deficit	Age related	Prevalence %	Frequency	Total answers
15. Rheumatic diseases	**yes**	**5.04**	**21**	**417**
16. Not able to drive	**yes**	**23.29**	**97**	**417**
17. Urinary dysfunction	*			**417**
	0	**63.55**	**263**	
	0.33	**27.58**	**115**	
	0.66	**7.91**	**33**	
	1	**1.44**	**6**	
18. Constipation	**yes**			**417**
	0	**72.66**	**303**	
	0.33	**20.86**	**87**	
	0.66	**5.76**	**24**	
	1	**0.72**	**3**	
19. Epworth sleepiness scale	*			**417**
	0	**63.55**	**265**	
	0.5	**19.42**	**81**	
	1	**17.03**	**72**	
20. Self rated health	*			**417**
	0	**8.39**	**35**	
	0.25	**20.14**	**84**	
	0.5	**38.61**	**161**	
	0.75	**22.78**	**95**	
	1	**10.07**	**42**	
21. Moderate efforts, such as moving a table, vacuuming, bowling, or walking more than 1 h	*			**417**
	0	**12.95**	**54**	
	0.5	**42.45**	**177**	
	1	**44.6**	**186**	
22. Take or carry the shopping bag	*			**417**
	0	**69.3**	**289**	
	0.5	**21.58**	**90**	
	1	**9.11**	**38**	
23. Climb several floors up the stairs	*			**417**
	0	**56.83**	**237**	
	0.5	**31.65**	**132**	
	1	**11.51**	**48**	
24. Crouching or kneeling	*			**417**
	0	**47.72**	**199**	
	0.5	**34.77**	**145**	
	1	**17.51**	**73**	
25. Walk about 100 m	*			**417**
	0	**83.93**	**350**	
	0.5	**12.23**	**51**	
	1	**3.843**	**16**	
26. Did you have pain in any part of your body during the last 4 weeks?	**yes**	**45.08**	**188**	**417**
27. Fatigue	**yes**	**41.25**	**172**	**417**
28. Dressing	*			**417**
	0	**62.59**	**261**	
	0.33	**30.22**	**126**	
	0.66	**6.71**	**28**	
	1	**0.48**	**2**	
29. Hygiene	*			**417**
	0	**73.38**	**306**	
	0.33	**22.78**	**95**	
	0.66	**3.12**	**13**	
	1	**0.72**	**3**	
30. Cutting food	*			**417**
	0	**66.91**	**279**	
	0.33	**27.58**	**115**	
	0.66	**4.8**	**20**	
	1	**0.72**	**3**	
31. Falls	*			**417**
	0	**90.41**	**337**	
	0.33	**8.63**	**36**	
	0.66	**0.72**	**3**	
	1	**0.24**	**1**	

*From best to worst score.

Appendix 2. Adjusted risk of having frailty if PD is present

	OR	SE	P value
PD	**6.682**	**2.703**	**<.001**
Age (40, 70]			
(70, 80]	2.781	0.954	0.003
(80, 90]	2.853	1.492	0.045

(*continued on next page*)

(*continued*)

	OR	SE	P value
Sex (Woman)	1.720	0.549	0.089
NPS	1.074	0.024	0.001
MMSE	0.813	0.056	0.003

NPS: Neuropsychiatric symptoms.

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