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Frailty in Parkinson's disease: A systematic review and meta-analysis

Jacqueline M. McMillan [a,b,*], Quentin Michalchuk [c], Zahra Goodarzi [a,b,d]

[a] Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[b] O'Brien Institute of Public Health, University of Calgary, Calgary, Alberta, Canada
[c] University of British Columbia, Vancouver, British Columbia, Canada
[d] Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

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ABSTRACT

Introduction: Frailty and Parkinson's disease (PD) are common conditions that increase with age. Independently, frailty and PD lead to increased morbidity and mortality for patients. Few studies report on frailty in patients with PD. We performed a systematic review and *meta*-analysis of the prevalence, associations and outcomes of frailty in persons with PD.

Methods: We searched four electronic databases and grey literature from inception to May 19, 2020, for articles which reported the prevalence, associations and outcomes of frailty in persons with PD.

Results: One-thousand and sixty-three citations were identified, of which 127 articles were reviewed. Thirty studies were included. Twenty-eight studies were observational and the settings varied including 25 community and 5 inpatient studies.

The most common frailty screening measures were the frailty phenotype and clinical frailty scale. The prevalence of frailty in PD using the FP was 0.38 (0.24–0.55) with $I^2 = 92.6\%$ ($p < 0.01$). Frailty was associated with recurrent falls, cognitive impairment, dementia, orthostatic hypotension, fatigue, hallucinations, nursing home placement, dependency in activities of daily living and in-patient mortality. PD disease duration, motor impairment, non-tremor dominant PD (postural instability/gait difficulty dominant phenotype) and total daily levodopa dose were associated with frailty.

Conclusion: Frailty is common in PD. There is no agreed upon tool for identifying frailty, however, the importance of its identification is apparent given the high prevalence and the association between frailty and adverse outcomes in persons with PD. Future studies are required to guide clinicians in how best to identify and manage frail patients with PD.

Contents

* Corresponding Author at: Department of Medicine, 11th Floor, Rm 1104, South Tower, FMC, 1403, 29th Street NW, Calgary, AB T2N 2T9, USA.
E-mail addresses: Jacqueline.mcmillan@ahs.ca (J.M. McMillan), Zahra.Goodarzi@ahs.ca (Z. Goodarzi).

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1. Introduction

Frailty and Parkinson's disease (PD) are both more common with advancing age and independently contribute to increased morbidity and mortality for patients. In the Canadian Community Health Survey, 24% of Canadian community-dwelling seniors (≥65 years) were identified as frail [1]. This proportion increases with age, from 16% of 65–74-year-olds, to 52% of those ≥85 years of age [1]. PD is also more common with age with 1.2% of men and 0.6% of women 65–79-years are living with PD; increasing to 2.1% of men and 1% of women if >80 years [2]. Individuals with PD living in long term care are more likely to be frail than those without PD (odds ratio 1.45; 95% Confidence Interval 1.07 to 1.97) [3]. Despite the increasing prevalence with age the impact of frailty on persons with PD is poorly understood.

1.1. Methods to identify frailty

Different prevalence estimates of frailty are often obtained due to the various methods to identify frailty. Using Canadian data, the prevalence of frailty in adults ≥ 65 years of age was 20.2% according to a frailty index approach, and 7.8% according to the frailty phenotype approach [4].

The frailty phenotype (FP) was developed using data from the Cardiovascular Health Study [5]. The FP consists of measurement of grip strength, a timed 6-meter walk, unintentional weight loss, two questions about exhaustion, and a short, validated questionnaire assessing the presence of physical limitation. Frailty is defined by the presence of ≥3 of the 5 criteria [5].

The Canadian Study of Health and Aging clinical frailty scale (CFS) [6] is a judgement-based scale anchored by images and descriptions of where the individual fits on a continuum of fitness/frailty. Frailty is defined as a score of four or greater.

The frailty index (FI) is calculated using 30 to 40 potential health deficits (symptoms, signs, diseases, functional limitations or laboratory abnormalities) [7]. For each patient, the FI is the ratio of the number of health deficits present divided by the number considered. The FI is a continuous value between zero and one with higher numbers associated with increased frailty [8].

Frailty and PD independently contribute to increased morbidity and mortality for patients. Although it is known that frailty is common with advancing age there are few studies of the prevalence, associations and impact of frailty in persons with PD. The synergistic effects of frailty and PD on individuals and their experiences of health and disease is likely significant, however the research in this area is limited. The aim of the present study was to perform a systematic review and *meta*-analysis of the prevalence, associations and outcomes of frailty in persons with PD.

2. Methods

2.1. Literature search

Four electronic databases were searched (OVID Medline, Embase, PsycINFO and the Cochrane Database of Systematic Reviews) from inception to May 19, 2020. Subject headings and key words included Parkinson's disease and frailty (Supplementary Table 1). A grey literature search was performed using the CADTH Grey Literature Matters Tool [9].

2.2. Study selection

Titles and abstracts were reviewed in duplicate. Included studies enrolled patients with Parkinson's disease and investigated frailty in the PD patient population. Randomized controlled trials, cohort, case-control and cross-sectional studies were included. Due to the small number of included citations, abstracts and conference proceedings were also included. Case reports, study protocols, commentaries, reviews, *meta*-analyses and book chapters were excluded. The reference lists of included articles were manually searched for additional relevant articles. Retrieved full text articles were reviewed in duplicate for inclusion or exclusion.

2.3. Data extraction

A data extraction template was employed to collect the following data from each included study: 1) study author; 2) year of publication; 3) study aim/purpose; 4) source country; 5) study population; 6) sample size; 7) study design/methodology; 8) intervention/comparator (if applicable); 9) study duration; 10) outcome measurements; 11) key findings.

One author extracted data independently and this was verified by a second author.

2.4. Data synthesis

To determine the prevalence of frailty we planned a *meta*-analysis of the reported point prevalence in each study. Given the divergence in how frailty is defined we planned to do pooled *meta*-analyses by frailty measure (e.g. frailty phenotype, frailty index, clinical frailty scale, etc.). Point prevalence was extracted from each study as above, and standard error was calculated in excel. The double arcsine transformation was applied to stabilize variance [10]. Proportion data, which are inherently binomial, were combined with the *metaprop* command in STATA; using random effects models and exact calculation of confidence intervals [11,12]. Heterogeneity was examined visually with forest plots and statistically with the I^2 and the associated p-value (alpha 0.05 as significant) from the Cochran Q Statistic. If

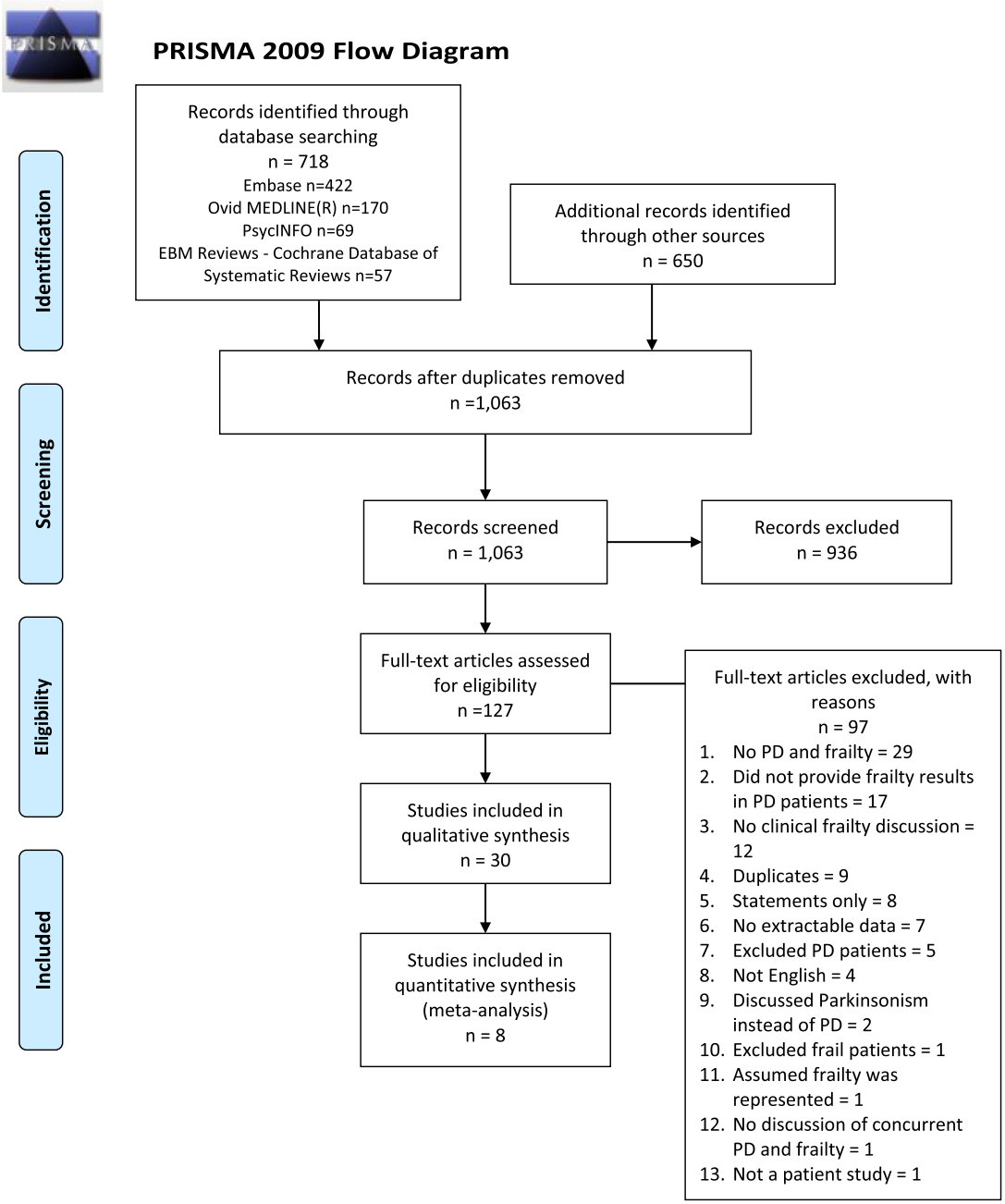

Fig. 1. PRISMA Flow Diagram.

heterogeneity was present, we planned to do subgroup analyses, however we did not have enough studies to do so.

2.5. Data availability statement

Any data not published here will be shared by request from any qualified investigator.

3. Results

3.1. Search results

A total of 718 records were identified in the electronic databases (Fig. 1). An additional 650 records were identified through a Grey Literature Search utilizing the CADTH Grey Literature Matters tool [9] as well as Parkinson's disease websites. After removal of duplicates, 1,063 titles and abstracts were screened for inclusion/exclusion. Nine-hundred and thirty-six records were excluded after review of title and abstract. This resulted in 127 full text articles which were reviewed for inclusion/exclusion and 97 articles that were excluded after full text review (29 did not investigate on PD and frailty; 17 did not provide frailty results in PD patients; 12 did not discuss frailty; 9 were duplicates; 8 provided commentary/statements only; 7 provided no extractable data; 5 excluded PD patients; 4 were non-English; 2 described parkinsonism, rather than PD). Thirty articles remained and were included in the systematic review, 8 of which were included in *meta*-analysis.

Table 1
Study and Patient Characteristics.

Author	Year	Country	Study design	Study setting	Sample Size with PD (n)	% Female	Mean Age (SD)	Diagnosis of PD
Adenwalla*	2019	Wales	Retrospective	Day hospital	132	39%	77 (50–97)	Clinical Chart Notes
Ahmed	2008	United States	Cross-sectional	Outpatient	49	33%	70.8 (9.2)	Clinical Diagnosis by Specialist
Aithal*	2016	UK	Retrospective	Outpatient	115	51%	71	NR
Borda*	2019	Norway	Prospective longitudinal study	NR	147	NR	NR	NR
Buchman	2013	USA	Cohort	Outpatient	159 with Lewy Body Pathology 106 with nigral neuronal loss	NR	NR	Clinical Diagnosis by Clinician (Parkinsonism)
Chen	2018	Taiwan	Cross-sectional	Outpatient	61	61%	62.6 (8.6)	Idiopathic PD according to the UK Brain Bank criteria
Firat-Ozer*	2018	Turkey	Cross-sectional	Out-patient	66	NR	NR	Clinical Diagnosis
Hippisley-Cox	2017	UK	Prospective cohort	Outpatient	5,308	NR	NR	NR
Holland*	2019	UK	Cohort	NR	119	33.6%	66.9 (10.5)	NR
Kotani	2020	Japan	Intervention	Outpatient	8	50%	68.6 (8.3)	Clinical Diagnosis by Specialist
Khwaja*	2019	UK	Cross-sectional	Inpatient	38	13%	80.5	NR
Lawson	2020	UK	Cross-sectional	Inpatient	44	NR	72.7 (+/- 12.6)	UK Brain Bank criteria
Lee*	2018	Australia	Cohort	Inpatient	NR	NR	NR	NR
Lin	2019	Taiwan	Case-control	Outpatient	76	54%	62.6 (9.2)	United Kingdom Brain Bank criteria
McManus*	2019	Ireland	Intervention	Outpatient	18	39%	64.5 (8.3)	NR
Mohamed*	2016	Wales	Cohort	Outpatient	41	32%	78	NR
Peball	2018	Austria	Cross-sectional	Outpatient	104 (PD Cohort in Tertiary Care Centre) 18 (Community PD Cohort)	39% 50%	73.8 (5.2) 78.7 (8,1)	UK Brain Bank criteria
Roberts *	2010	UK	NR	Outpatient	57	NR	71.8 (7.8)	NR
Roland	2012	Canada	Cross-sectional	Outpatient	15	100%	65 (9)	NR
Roland	2012	Canada	Cross-sectional	Outpatient	17	100%	66 (8.5)	NR
Roland	2012	Canada	Cross-sectional	Outpatient	29	41%	66.4 (8.5)	NR
Roland	2014	Canada	Cross-sectional	Outpatient	13	100%	67 (8)	NR
Smith*	2019	UK	Cohort	Outpatient	120	34%	70.2 (8)	NR
Tan	2018	Malaysia	Case-control	Outpatient	93	45.2%	66 (8.5)	Queen Square Brain Bank clinical diagnostic criteria
Tom	2013	International	Longitudinal Cohort	Outpatient	256	100%	NR	NR
Torsney	2018	UK	Retrospective	Inpatient	393	42%	82.8 (5.0)	Clinical Diagnosis
Wang	2019	Taiwan	Case-control	Outpatient	25	80%	63.6 (5.5)	Parkinson's Disease Society's criteria
Wei*	2019	Malaysia	Case-control	NR	33	48.5%	68.9 (9.4)	NR
Wells*	2019	Wales	Retrospective	Outpatient	275	40%	81.3 (8.0)	Movement Disorders Patients
Williams*	2016	Wales	Cross-sectional	Long-term care	63	62%	80	NR

* Abstract only. PD Parkinson's disease; SD standard deviation; CFS Clinical Frailty Scale; NR not reported; FP Frailty phenotype; FI frailty index; UPDRS Unified Parkinson's disease Rating Scale; US United States; UK United Kingdom; OR odds ratio; CI Confidence Interval; IADL instrumental activities of daily living; GCS Glasgow Coma Scale; H & Y Hoehn and Yahr scale; TUG Timed up and go; LTC long-term care; AF atrial fibrillation.

3.2. Study characteristics

Thirty studies were included in the systematic review. Table 1 presents the study and participant characteristics and Table 2 presents study objectives and outcomes. Fourteen (47%) of the included citations were published as abstract only marked by an asterisk in Table 1. Twelve studies (40%) were published in 2019 or 2020. The proportion of female participants ranged from 13 to 100% and the mean age of participants ranged from 63 to 83 years. Twenty-eight were observational and two were interventional studies. The majority (25/30) enrolled community-dwelling participants and 5 enrolled inpatients. [13–16] Study sizes ranged from 8 to 5,308 participants with PD. Sixteen studies were set in Europe, 6 in North America, 6 in Asia, 1 in Australia and 1 was a multisite international study.

3.3. Tools employed to screen for frailty

Fifteen studies employed the frailty phenotype method [17–30] and 9 studies employed the clinical frailty scale [13–15,31–36]. Four studies employed the frailty index, or cumulative deficit model [19,27,37,38]. In one study frailty index values range from 0 to 1 and a cut-off of >0.2 was employed to identify frailty [19].

Five studies used an alternative frailty screening measure, and four studies employed more than one measure. One study used the Edmonton Frail Scale [15]. Another used routinely collected data to derive a mortality prediction equation, as well as unplanned hospitalization prediction equation, which when combined, were utilized to categorize patients into frailty groups. One study combined a timed-up-and-go with a frailty index to calculate a QTUG Frailty Index [39]. One study did not report which measure was used [16].

3.4. Risk of bias

Ten cohort studies were included and most enrolled a selected, or somewhat representative group of PD patients (Supplementary Table 2). Ascertainment of PD was most often through secure record. None of the studies demonstrated that frailty was not present at the start of the study. Fewer than half controlled for other factors associ-

Table 2
Study Objectives and Outcomes.

Author	Year	Primary Study Objective	Frailty Measure	Proportion with Frailty	Mean or Median Frailty Score	Reported Frailty Related Outcomes
Adenwalla*	2019	Examining the day hospital model of interdisciplinary care in persons with PD	Clinical Frailty Scale (CFS)	NR	4 (Range 3–7)	NR
Ahmed	2008	Determine the prevalence of frailty in PD	Frailty Phenotype	32.6%	NR	• All patients included were "optimally managed" and still had 30% frailty • UPDRS scored were significantly higher in frail vs non-frail • Number of components of frailty correlated directly with UPDRS score • Measures of "weekly caloric expenditure" measured by the Center for Disease Control Guidelines was the best to discriminate between frail and non-frail • Direct relationship between UPDRS score and walk time but not grip strength
Aithal*	2016	Incidence of fragility fractures in PD	CFS	NR	3.42 (1,7)	• Persons with Fragility Fractures had higher CFS Scores (3.8), the association was 'non-significant' (results not presented) • Frailty scores increased over the 5-year period in both the fracture and non fracture group
Borda*	2019	Examining the association between frailty and incident dementia in persons with PD compared to controls.	Frailty Index	42.2%	NR	• Over 7 years 38.46% developed dementia in the frail population ($p = 0.001$ vs. those without frailty). • In persons with frailty at baseline they have 3.37-fold increased odds of dementia over a 7-year period (OR 3.37; 95% CI 1.30–8.74; $p = 0.012$).
Buchman	2013	The relationship between brain pathology and frailty progression in older adults.	Frailty Phenotype	NR	NR	• Although all patients show progression in frailty over time, having Lewy body pathology or nigral neuronal loss, was associated with a more rapid increase in frailty.
Chen	2018	How brain structural changes correlate with cognitive impairment and frailty in PD	Frailty Phenotype	NR	NR	In persons with frailty and PD there was a significant reduction in grey matter volume
Firat-Ozer*	2018	Identify the prevalence of frailty in PD, describe the relationship between PD severity and frailty; evaluate the TUG as a test of frailty	Frailty Phenotype	Frail 51.5%Pre-frail 36.4%	NR	• The following were associated with frailty: • Female • Depression • Levodopa dose ≥ 400 mg PO/day • Dependency with IADL • TUG > 15.36 s was strongly associated with frailty with 80% sensitivity and 82% specificity
Hippisley-Cox	2017	To develop a definition of frailty which is based on risk of outcomes	Tool Created by Authors	48% mildly frail28% moderately frail16% severely frail	NR	• This study created a new tool to predict mortality as well as developed a new method for classifying frailty based on risk of mortality and unplanned hospital admission. • The reported % of persons who are frail is based on this new definition of frailty
Holland*	2019	Examine the association between falls and frailty in persons with PD	Frailty Index	43.7% pre-frail25.2% frail	NR	• 50% of those who fell were frail ($p < 0.001$ vs prefrail or non-frail) and 17.3% were pre-frail.
Kotani	2020	Testing an assistive lumbar support device for persons with frailty with or without PD	Frailty Phenotype	62.5% prefrail37.5% frail	NR	• At the 1-month follow-up 2 people became pre-frail from frail, 1 remained pre-frail at 3 months. • At the 1-month follow-up 2 people became robust from pre-frail, 1 remained pre-frail at 3 months. • Results were not significant.
Khwaja*	2019	Evaluating whether persons with PD complete advanced care planning documents	NR	NR	NR	In this population of persons with PD in a higher complexity stage, there was documented discussion of disease progression and medication side effects but no discussion of advanced care planning.
Lawson	2020	Aimed to understand the incidence and prevalence of delirium in persons with PD	CFS	NR	Weighted mean CFS 5.7 across all groups	Prevalent and incident delirium cases were associated with more severe PD motor symptoms, frailty, lower GCS and more severe delirium.Mean CFS 5.1 (SD 1.4) in patients with no prevalent deliriumMean CFS 6.8 (SD 0.5) in patients with prevalent delirium ($p < 0.001$) Mean CFS 4.9 (SD 1.4) in patients with no incident deliriumMean CFS 6.3 (SD 1.1) in patients with incident delirium ($p < 0.001$)

(*continued on next page*)

Table 2 (*continued*)

Author	Year	Primary Study Objective	Frailty Measure	Proportion with Frailty	Mean or Median Frailty Score	Reported Frailty Related Outcomes
Lee*	2018	Focused on understanding the prevalence of frailty in inpatients of an acute geriatric ward, as well as the effect of frailty on discharge.	CFS + Edmonton Frailty Scale	NR	NR	In the frail group as measured by the CFS, there were more persons with PD (p = 0.03)
Lin	2019	To identify the relationship between cognitive function and physical frailty in patients with PD	Frailty Phenotype	38.2% frail	NR	• UPDRS scores and levodopa doses were significantly associated with frailty • Risk factors for frailty included age, UPDRS stage, H + Y Score, neuropsychological assessment covering 5 cognitive domains.
McManus*	2019	To assess if the UPDRS and a digital motor test can detect improvement with an exercise intervention	QTUG Frailty Index (%)	35.3% frail	35.32+/-25.07	QTUG Frailty Index (%) was 21.18 (+/-16.35) post-intervention (p < 0.01)
Mohamed*	2016	Examined the mortality of persons with PD after a hospital admission	CFS	NR	NR	• Average frailty score was higher for those who died (6) than those who lived (4.84)
Peball		Screened persons with PD for sarcopenia and frailty to look at association with other conditions of aging, and quality of life	CFS	22.2% frail	3.8 (1.7)	
	2018			35.6% frail	3.1 (1.6)	Frailty was associated with: • Motor Impairment • PD and PD Duration • H + Y Score • Falls • Care needsQuality of life
Roberts *	2010	To establish normative values for grip strength in different groups of older adults	Grip strength & Strawbridge frailty questionnaire	56% frail	NR	Frailty was found in 56% of persons in a PD clinic, which was a similar proportion to those in in-patient rehab, out-patient rehab and less than those in LTC.
Roland	2012	Aimed at understanding how physical activity impacts frailty	Frailty phenotype	46.7% prefrail 26.7% frail	NR	• No physical activity variables were significantly associated with frailty in female persons with PD
Roland	2012	To understand the characteristics that contribute to frailty in female persons with PD	Frailty phenotype	47.1% prefrail 29.4% frail	NR	• Total daily levodopa dose was associated with frailty.(p = 0.01) • Neither PD duration (p = 0.23) nor PD severity (p = 0.08) was associated with frailty
Roland	2012	Focused on which aspects of frailty and quality of life help to discriminate in persons with PD	Frailty phenotype	65.5% prefrail 3.4% frail	NR	• PD disease severity, exhaustion and poor quality of life were associated with frailty. • Frailty was more common in women than men (OR 9.78; 95% CI 1.0, 93.5).
Roland	2014	Determine whether muscle activity can be used to identify frailty phenotypes in females with PD	Frailty phenotype	46.2% prefrail 23.1% frail	NR	• Decreased number of EMG muscle gaps and greater EMG burst duration in frail females with PD compared to non-frail females with PD
Smith*	2019	Examine the prevalence of frailty and associated factors in persons with PD	Frailty Phenotype	58% prefrail26% frail	NR	Several factors were associated with frailty: • High depression scores (OR 1.12; 95% CI 1.01,1.24) • High UPDRS (OR 1.02; 95% CI 1.01,1.03) • Female were associated with frailty (OR 3.10; 95% CI 1.53,6.26)
Tan	2018	Looked at sarcopenia, body composition, and frailty in persons with PD.	Frailty Phenotype + Frailty Index	69.4% frail using FI27.9% frail using FP	NR	• Increased motor symptoms (OR 1.09, p = 0.013) was associated with frailty, when measured by the phenotype. • When using the frailty index age was associated with frailty (OR 1.15, p = 0.01) as was sarcopenia (OR1.16, p = 0.038)
Tom	2013	Examined whether frailty increased the risk of fractures in older women.	Frailty Phenotype	19.1% prefrail 63.3% frail	NR	• Data cane from the Global Longitudinal study of Osteoporosis in Women (GLOW) • FP associated with risk of fracture, disability and falls in women > 55 years
Torsney	2018	To see if frailty was a predictor of mortality and other hospital outcomes in persons with PD in hospital	CFS	vulnerable 9.4% mildly frailty 17.3% moderate frailty 33.3% severe frailty 24.9%v. severe frailty 5.6%	Median CFS 6.0 Mean CFS 5.9 (SD1.4)	• Overall prevalence of frailty was 57% • Frailty predicts mortality for severe + very severe frailty, OR 8.1 (95% CI 1,63.5).
Wang	2019	To examine body composition as it relates to disease severity in persons with PD	Frailty Phenotype + Taiwan International Physical Activity Questionnaire Short Form	NR	NR	• Increased fat content of muscles is associated with frailty and disease severity. • The poorer muscle integrity was associated with higher weakness and exhaustion scores.

Table 2 (*continued*)

Author	Year	Primary Study Objective	Frailty Measure	Proportion with Frailty	Mean or Median Frailty Score	Reported Frailty Related Outcomes
Wei*	2019	To evaluate sarcopenia, body fat and frailty in persons with PD	Frailty Phenotype + Frailty Index	63.6% frail (phenotype) 78.8% frail (index)	Mean number of FP deficits 2.7 (SD 1.3)Mean FI 0.3 (SD 0.1)	• Patients had a higher prevalence of sarcopenia (30.3% versus 7.4%, p = 0.049) • Patients had a higher prevalence of frailty than controls • 63.6% versus 11.1%, p < 0.001 using the frailty phenotype • 78.8% versus 18.5%; p < 0.001 using the frailty index)
Wells*	2019	Examine the prevalence of atrial fibrillation and its affect on cognition in persons with PD	Clinical Frailty Scale	NR	6.7 (1.3)	• Prevalence of AF in PD patients is higher than the general population
Williams*	2016	Evaluate the effectiveness of delivering specialist care is in LTC for persons with PD	Clinical Frailty Scale	NR	7.04 (Range 6–8)	• Care provided in the LTC provided a 'better subjective experience' for frail patients.

* Abstract only. PD Parkinson's disease; SD standard deviation; CFS Clinical Frailty Scale; NR not reported; FP Frailty phenotype; FI frailty index; UPDRS Unified Parkinson's disease Rating Scale; US United States; UK United Kingdom; OR odds ratio; CI Confidence Interval; IADL instrumental activities of daily living; GCS Glasgow Coma Scale; H & Y Hoehn and Yahr scale; TUG Timed up and go; LTC long-term care; AF atrial fibrillation

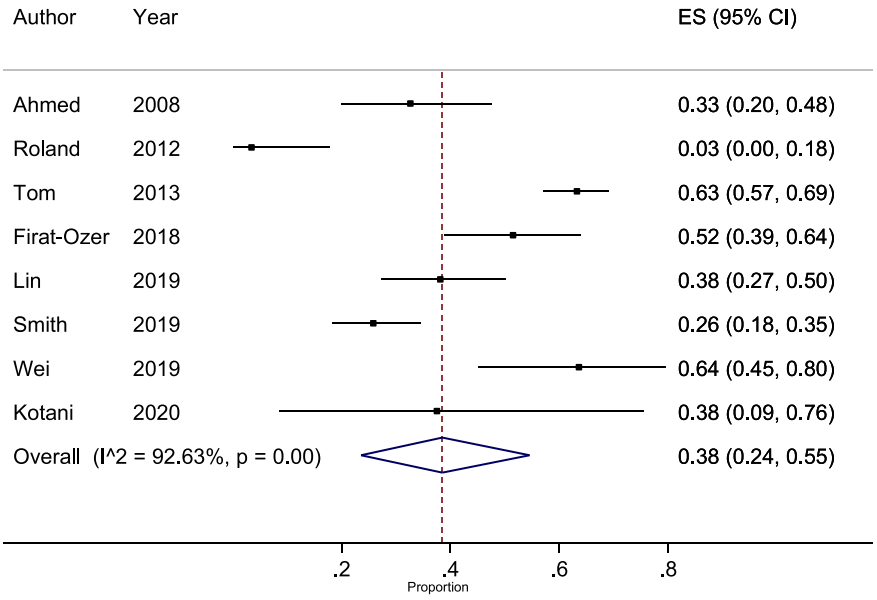

Fig. 2. Forrest Plot. The prevalence of frailty in PD using random effects *meta*-analysis and the frailty phenotype.

ated with frailty. Ascertainment of frailty was most often through independent blind assessment. The majority of studies made no statement on loss-to-follow-up, or loss to follow-up was >5%.

Fourteen cross-sectional studies were included all of which enrolled PD patients either from a selected group, or a somewhat representative sample of PD patients. Sample size calculations were not provided or justified in any of the studies. Half (7/14) of the studies ascertained PD through secure record, the remainder provided no description of PD ascertainment. None of the studies controlled for other risk factors for frailty. Frailty was ascertained through record linkage in 4/14 studies, by independent blind assessment in 5/14 studies, and no description was provided in the remainder.

Six case-control studies were included. Five independently validated the PD case definition. Four had potential for selection bias of cases. Four enrolled community controls and two enrolled hospital controls. All controlled for age and sex. All 6 studies ascertained frailty through secure record.

3.5. Frailty prevalence

Eight studies were included in *meta*-analysis using the frailty phenotype [17,20,22,24,25,27–29]. The prevalence using the FP ranged from 0.03 to 0.64 across included studies. The pooled prevalence of frailty in persons with PD using the frailty phenotype was 38% (95% Confidence Interval [CI] 24% to 55%) (Fig. 2). Heterogeneity as measured by the I^2 was 92.6%, which is high and was significant (p < 0.01). We were unable to do subgroup analyses or *meta*-regression as there were too few studies. There was insufficient data to perform *meta*-analysis of frailty prevalence using the CFS or FI. However, the mean CFS ranged from 3.4 to 7.0 and the proportion of PD patients who were frail determined by the FI ranged from 25.2 to 78.8%. For reference, a mean CFS score of 3 equates to someone who is managing well, whereas a CFS score of 7 equates to someone who is severely frail and is completely dependent on others for personal care (https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html).

3.6. Q mortality risk prediction

Two prediction equations categorized patients into severely-frail, moderately-frail, mildly-frail and fit categories [40]. Sixteen percent of PD patients were severely frail, 28% were moderately frail, 48% were mildly frail, and only 8% were categorized as fit [40].

3.7. Association between frailty and PD characteristics

Female gender (OR 11.77; 95% CI 1.01–142.91), depression (OR 12.56; 95% CI 1.01–162. 83), and dependency in instrumental activities of daily living (IADLs) (OR 339.18; 95% CI 9.95–11558.97) were significantly associated with frailty [20]. Another study reported similar associations between female gender (OR 3.10; 95% CI 1.53–6.26) and depression (OR 1.12; 95% CI 1.01–1.24) and frailty in a U.K. study [28] .

United Parkinson's disease rating scale (UPDRS) scores were higher for patients who were identified as frail compared to those who were not frail [17,28]. The number of components of the frailty phenotype that were present directly related to the UPDRS scores ($r = 0.39$; $p = 0.005$) [17].

Frailty is associated with longer disease duration, higher motor impairment (UPDRS score), higher Hoehn and Yahr (H&Y) stages, and non-tremor dominant PD (postural instability/gait difficulty dominant phenotype) [25,28,31]. Similarly, Tan et al reported an association between worse PD motor severity score (based on the modified UPDRS) and frailty phenotype (adjusted odds ratio [OR] 1.09; $p = 0.013$) [19]. In the same study, utilizing the frailty index, increasing age was the only factor associated with higher frailty index (adjusted OR 1.15; $p = 0.01$) [19]. Higher daily dose of levodopa carbidopa has been also shown to be associated with frailty [25]. Findings reported in a conference abstract found that frailty was positively associated with levodopa dose ≥400 mg (OR 26.78; 95% CI 1.34–535.45) [20].

3.8. Associations between frailty and adverse outcomes in PD patients

Frailty was associated with recurrent falls [31,38], cognitive impairment, dementia, orthostatic hypotension, fatigue, hallucinations, nursing home placement, dependency in activities of daily living and Parkinson's disease questionnaire-8 summary index [31]. In a Norwegian PD study, the odds of dementia development over 7 years of follow-up was 3-fold higher for individuals who were frail at baseline, compared to those who were not frail at baseline (OR 3.37; 95% CI 1.30–8.74; $p = 0.012$) [37]. In a Taiwanese study of 76 patients with PD, frailty phenotype was associated with worse scores on neuropsychological assessments of attention, executive function, memory, speech, language, and visuospatial function [25]. A U.K. inpatient study found that PD patients who developed delirium were more likely to be frail [14].

Utilizing the CFS in inpatients, frailty was shown to be an independent predictor of inpatient mortality with an odds ratio for severely/very severely frail (i.e. CFS score of 7 +) of 8.1 (95% CI 1.0–63.5) [13]. In the same study, CFS did not predict other outcomes investigated including death within 30 days of discharge, new institutionalization, length of stay ≥ 7 days or readmission to the same hospital within 30 days [13]. In a study of 41 patients with PD admitted to hospital with a mean age of 78 years, 37% died within 18 months of the index admission [35]. Patients who died during follow-up had an average CFS score of 6 compared to 4.8 for patients who survived [35].

In an imaging study, fat content on magnetic resonance imaging was higher in PD patients with frailty, than in those who were not frail [26]. Specifically, fat content in the thigh was associated with weakness and exhaustion, two components of the frailty phenotype [26]. Similarly, higher frailty index has been associated with sarcopenia in persons with PD [19]. In a study of PD patients and spouse/sibling controls, persons with PD had greater prevalence of sarcopenia than controls (30.3% versus 7.4%; $p = 0.049$) [27].

3.9. Exercise interventions in PD patients with frailty

In 8 frail and pre-frail PD patients, core exercise training using an assistive lumbar support worn during exercise for five consecutive days resulted in improvements in timed 10-meter walk, step-length, timed up and go (TUG) and chair stands in 30 s [24]. The timed 10-meter walk improved from 15.3 s at baseline to 9.6 s at the end of the intervention with the improvement maintained at 3-months (10.4 s) [24]. Step-length improved from 0.37 m to 0.51 m at the end of the intervention, as did TUG (17.7 s at baseline, 14.0 s at the end of the intervention), and chair stands in 30 s (4 at baseline, 6.5 at the end of the intervention) [24].

In the second exercise intervention study, 18 patients with PD participated in exercise classes three times per week for 12-weeks [39]. The classes included Tai Chi, rhythmic cycling (spinning) and strength and conditioning circuit classes [39]. Between baseline and the end of the 12-week exercise intervention, the quantitative timed up and go frailty index (QTUG FI) improved [39].

3.10. Frailty and brain pathology

In a study of nearly 800 individuals in the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) cohort studies, authors investigated the association between brain pathology and frailty [41]. Macroinfacts, Alzheimer disease pathology, Lewy Body Disease pathology and nigral neuronal loss (the latter two found in PD) were associated with more rapid progression of frailty [41]. Nigral neuronal loss was independently associated with frailty progression, but Lewy Body pathology was not [41]. Additionally, patients with nigral neuronal loss and dementia showed a more rapid frailty progression than patients with nigral neuronal loss without dementia [41]. Nigral neuronal loss was associated with rate of decline in grip strength and walking speed, but not with rate of change in body mass index (BMI) or fatigue [41].

4. Discussion

The current knowledge of frailty in persons living with PD is limited. Interestingly, 40% of included studies were published in 2019–2020, signifying a growing interest in the synergistic relationship between the two conditions. Similarly, one-half were published as abstracts-only, reflecting a domain in its infancy. We performed a systematic review and *meta*-analysis to determine the prevalence, associations and outcomes associated with frailty in persons living with PD.

Twenty-five studies enrolled community-dwelling participants with five studies in the inpatient setting. Community-dwelling participants are likely fitter and less frail than persons admitted to hospital or communal settings. Frailty assessments performed in hospital likely overestimate frailty prevalence, however, provide outcome data such as inpatient mortality and length of stay. Additionally, the mean age of PD participants ranged from 63 to 83 years, as such comment on the prevalence, associations and outcomes of frailty in a younger PD population cannot be made. Despite this limitation, frailty is not exclusive to older age groups and there would likely be benefit to identification and management of frailty in younger persons with PD. That being said, a recent review of frailty screening in populations <60 years determined that further study is needed around the validity of frailty screening measures, and the utility of identifying frailty in younger age groups [42].

Studies originated from around the globe, with 16 studies from Europe, 6 each from North America and Asia and 1 each from Australia

and internationally. The generalizability of these findings to resource-poor settings is limited.

There are many frailty screening methods available and within the PD population three were most commonly employed. Fifteen studies reported using the frailty phenotype, 9 studies used the clinical frailty scale, 4 used the frailty index, 5 used alternative frailty screening measures, or created novel tools. The variability in frailty screening tools creates tremendous difficulty in comparing prevalence, associations and outcomes across studies. The most frequently employed screening tool, the frailty phenotype, includes 5 measured variables, which may be affected by the manifestations of PD (i.e. grip strength, slow walking speed, unintentional weight loss, self-reported exhaustion and low physical function). The original Cardiovascular Health Study cohort in which the frailty phenotype was developed excluded persons with PD [5]. The overlap in the manifestations of frailty and PD may lead to misclassification of persons with PD as frail, when indeed they are not. Studies are required to determine whether an alternative frailty screening measure better identifies frailty in PD.

The prevalence of frailty in PD using random effects *meta*-analysis and the frailty phenotype was 0.38 (95% CI 0.24–0.55) [17,20,22,24,25,27–29]. The heterogeneity of included studies was high and significant (I^2 = 92.6%, p < 0.01) likely a reflection of both clinical and methodological heterogeneity of the included studies, including, sample compositions, age, gender, duration and severity of PD and methodological specifics including features of the study design and the performance of the frailty phenotype evaluation. Interestingly one study had a low prevalence of frailty at 3.4%, however other studies ranged from 26% to 64%. This study enrolled 29 community participants (41% female, mean age 66 years) who were able to ambulate independently, were cognitively intact, had a mean PD disease duration of 7.2 years, and had a mean H & Y score of 2. This younger sample, with lesser disease burden may be less frail for these precise reasons. Overall, there appears to be a high proportion of persons with PD experiencing frailty; however, due to the high heterogeneity and few studies, precluding further subgroup exploration, this pooled estimate must be interpreted with caution.

Utilizing the frailty index the estimated prevalence of frailty ranged from 25.2 to 78.8% [19,27,37,38]. This in contrast to Canadian community-dwellers without PD in which the estimated prevalence utilizing the FI was 20.2% [4]. In the present study, the range of CFS scores in PD patients was 3.4 to 7.0. The imprecision of these estimates, employing either the FI or CFS, is a reflection of the heterogeneity of the included studies, including both clinical and methodological heterogeneity.

Our results, that frailty in PD is associated with adverse outcomes are unsurprising given the impact of frailty in the general population. We found that frailty in PD is associated with dementia [37], recurrent falls [31,38], cognitive impairment [25], orthostatic hypotension, fatigue, hallucinations, nursing home placement, dependency in activities of daily living [31], delirium [14], and inpatient mortality [13]. We propose that clinicians should routinely screen for frailty in patients with PD, and that interventions to prevent and/or ameliorate these adverse outcomes should include: falls risk assessment, screening for cognitive impairment, orthostatic hypotension screening and management; screening for non-motor symptoms of PD such as fatigue and hallucinations and monitoring of functional status.

We found that several PD characteristics were associated with frailty status. These included: longer disease duration, greater motor impairment, higher Hoehn and Yahr (H&Y) stages, and non-tremor dominant PD (postural instability/gait difficulty dominant phenotype) [25,28,31]. Similarly, Tan et al reported an association between worse PD motor severity score [19]. This knowledge will assist clinicians caring for patients with PD so that frailty screening may focus on patients of longer disease duration, higher motor impairment, and non-tremor dominant (i.e. postural instability/gait difficulty dominant) phenotypes. This knowledge will help to direct resources and more easily identify PD patients living with frailty.

We found two interventions studies, involving exercise [24,39]. Further intervention studies are needed to guide clinicians caring for patients with PD living with frailty.

5. Conclusion

Frailty and PD are both common conditions, with approximately 38% of patients with PD identified as frail by the frailty phenotype. There is no universally employed screening tool for frailty in PD and further studies are needed to determine the best method for identifying frailty. Regardless of how it is identified, the importance of identification of frailty in PD is clear. Frailty in PD is associated with a number of adverse outcomes, many of which may be targets of treatment. Frailty in PD is associated with certain PD-specific characteristics, such as motor severity and disease duration, and this knowledge may assist clinicians in anticipating the robustness of such patients.

5.1. Limitations

The small number of included studies, 40% of which were abstracts only, as well as the heterogeneity in clinical and methodological study characteristics are limitations of the study. Further large, longitudinal studies are needed to investigate the associations between frailty and PD, as well as interventional studies, to guide clinicians caring for this vulnerable group of older adults.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2021.100095.

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