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Original Research

The interrelationship of frailty, multimorbidity and disability in Parkinson's disease: PRIME-UK cross-sectional study

Emma Tenison [a,b,*], Yoav Ben-Shlomo [a,c], Anahita Nodehi [a], Emily J Henderson [a,b]

[a] Ageing and Movement Research Group, Department of Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, Bristol, BS8 2PS, United Kingdom
[b] Older People's Unit, Royal United Hospitals Bath NHS Foundation Trust, Combe Park, Bath, BA1 3NG, United Kingdom
[c] The National Institute for Health and Care Research Applied Research Collaboration West (NIHR ARC West) at University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

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ABSTRACT

Background: The prevalence of Parkinson's disease rises with age and so patients may also be living with multimorbidity, two or more long-term conditions, and frailty, a loss of physiological reserve. However, these individuals are typically under-represented in clinical research. The aim was to describe the prevalence and interrelationship of frailty, multimorbidity, disability, sarcopenia and polypharmacy in a representative sample of people with parkinsonism recruited to the PRIME-UK cross-sectional study.

Methods: In this single-centre cross-sectional study of people with parkinsonism, we supported the inclusion of typically under-represented groups including those with impaired capacity to consent to the research. Participants, or their representative, completed questionnaires including self-reported comorbidities, medications, a sarcopenia screening tool and measures of frailty and disability. Venn diagrams were used to show the overlap between these domains and a hierarchical cluster analysis was performed to explore clustering.

Results: Only 78 (16.8 %) were categorised as neither frail nor multimorbid nor disabled. Almost all patients living with frailty were additionally living with disability and/or multimorbidity. It was uncommon to have multimorbidity and frailty without disability. Only 6 (1.3 %) had frailty without probable sarcopenia. Individuals clustered into three groups based on co-occurrence of some or all of these five domains.

Conclusions: Amongst a representative sample of people with parkinsonism, there was a high frequency and co-occurrence of pre-frailty/frailty, sarcopenia, multimorbidity, polypharmacy and disability. This has implications for the structuring of health services for people with parkinsonism. There may also be opportunities to intervene to stop or slow the trajectory towards disability.

1. Introduction

Idiopathic Parkinson's disease (PD) is the commonest cause of the symptom complex of parkinsonism which comprises bradykinesia, tremor, rigidity and postural instability [1]. There is a high degree of heterogeneity in the way the disease manifests, partly from variable occurrence of a wide variety of non-motor features [2]. Neurological diseases, including PD, are now the leading cause of disability globally [3]. PD is predominantly a disease of older people and so patients are often also living with multimorbidity and/or frailty [4].

Multimorbidity describes the coexistence of two or more chronic diseases in a person [5] without implying that any single disease has priority over the other coexisting disease [6]. Although multimorbidity does not attribute weight to different illnesses, its impact on an individual's risk profile may be greater than the sum of conditions [7]. A large Scottish cross-sectional study showed that PD patients had a greater number of both physical and mental health comorbidities compared to controls [8] after adjusting for potential confounders, although the burden of comorbidity is low in early disease [9,10]. Comorbidities, as well as progression of PD itself, may prompt addition of medications, which can lead to polypharmacy, commonly defined as five or more different prescribed medications [11].

Frailty is recognised as a syndrome of loss of physiological reserve, conferring vulnerability to negative health outcomes. Frailty can be operationalised using a frailty phenotypic (FP) or frailty index (FI) based approach [12]. The estimated prevalence of frailty in PD varies [13] but

* Corresponding author at: Department of Population Health Sciences, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS.
E-mail address: Emma.Tenison@bristol.ac.uk (E. Tenison).

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has been associated with disability [14], institutionalisation [15] and inpatient mortality [16]. Features of frailty and sarcopenia overlap. Sarcopenia is characterised by low muscle strength with low muscle quality or quantity [17] which is reflected by reduced grip strength in the FP model. Similarly, reduced gait speed can indicate poor physical performance and categorises sarcopenia as severe [17].

Populations recruited into parkinsonism research are often not representative of the population cared for in clinical practice [18–20]. A better understanding of the relationship and potentially synergistic interactions between PD, frailty, sarcopenia, multimorbidity, disability and polypharmacy, studied in a more representative population, offers scope to optimise care and improve outcomes for this high risk patient group.

This paper describes the prevalence and interrelationship of frailty, multimorbidity, disability, sarcopenia and polypharmacy in a representative sample of people with parkinsonism recruited to the PRIME-UK cross-sectional study and explores the clustering of these domains.

2. Methods

2.1. Study procedures

The protocol for the PRIME-UK cross-sectional study has been published previously [21] and the study was approved by the London-Brighton & Sussex Research Ethics Committee (REC) on 27 July 2020; REC reference 20/LO/0890. This was a single-centre study in which patients with parkinsonism, including idiopathic PD as well as related conditions such as progressive supranuclear palsy, in the Royal United Hospital Bath catchment area were screened and invited by post to participate. Effort was made to support the inclusion of groups who are typically under-represented in research. Patients who did not initially respond were telephoned to discuss the study, and supported to take part, including assessment of mental capacity. Willing patients signed a written consent form. For patients lacking capacity to consent to research, a personal consultee advised on their prior wishes and signed a consultee declaration if it was felt they would have consented when capacitous. Recruited participants completed a questionnaire booklet at home on one occasion. For participants lacking capacity to consent, the consultee or another friend/relative completed a shorter, bespoke questionnaire booklet on their behalf, acting as their 'representative'. This shorter representative-completed questionnaire booklet did not include questionnaires which were unsuitable for completion by a representative, such as those assessing non-motor/autonomic symptom burden, freezing of gait, health-related quality of life and activation level, but instead included measures of functional ability and neuropsychiatric symptoms which have been validated for proxy completion. The variables described here were included in both the full patient-completed and shorter representative-completed booklets.

2.2. Derivation of variables

Comorbidity count was the sum of the number of chronic condition categories selected by the participant from the 20 categories specified by Fortin et al. [22]. The minimum count was 0 since parkinsonism was not included in these categories. A count of two or more indicated multimorbidity.

An overall count of medications was generated by summing the number of distinct pharmacologically active agents. Five or more medications per day indicated polypharmacy. A variable was also generated to indicate five or more medications, excluding medication for motor symptoms of Parkinson's. Parkinson's Disease (PD) medication was classified into drug classes and a count of the number of PD drug classes was generated. The total levodopa equivalent daily dose (LEDD) was calculated using published conversion formulae [23,24]. Participants were categorised into those taking fewer than five versus five or more doses of levodopa per day, as per the 5–2–1 criteria proposed by a Delphi panel to identify patients with advanced PD [25]. The Survey of Health, Ageing and Retirement in Europe-Frailty Index 75+ (SHARE-FI75+) total score (between 0 and 1) was calculated for males and females using the formula specified by the authors [26] and categorised as non-frail (0–0.24999), pre-frail (0.25- 0.74999)or frail (0.75–1). The formula incorporates the self-reported answers to questions about fatigue, weakness, appetite, slowness/gait and physical activity, and applies an age adjustment [26].

The five components of SARC-F, each varying from 0–2 were summed to generate a score between 0–10. A binary outcome was generated (score < 4 or ≥ 4) since a score of four or more is predictive of sarcopenia [27].

A dichotomised variable was generated to indicate whether a participant was physically disabled or not, based on the activities of daily living (ADL) domain of the Parkinson's Disease Questionnaire-39 [28], for participants who completed a full patient questionnaire booklet, and the Bristol Activities of Daily Living Scale [29] for participants whose questionnaire booklet was representative-completed. Similar to the approach used by Fried et al. in which disability was defined as impairment in one or more ADLs [30], physical disability was assumed to be present if the participant answered that they 'often' or 'always' had difficulty with any of the 6 tasks specified within the PDQ-39 or if the representative answered that the participant was unable to do any of the 20 activities of daily living listed.

2.3. Statistical analysis

Stata 17 was used for data cleaning and analysis. Venn diagrams, generated in R studio, were used to show how frailty/pre-frailty, multimorbidity, disability, sarcopenia and polypharmacy overlapped in individuals with complete data for the relevant variables, with a heat map to reflect the frequency. 95 % confidence intervals were calculated for these proportions.

Additionally, a dissimilarity matrix was generated, and hierarchical complete linkage clustering was performed [31] to show how individuals clustered based on the presence or absence of frailty, disability, multimorbidity, sarcopenia and polypharmacy, as shown in a dendrogram. The characteristics of participants in the three clusters were compared using the Kruskal-Wallis rank test for continuous variables and Pearson's chi-squared test for categorical variables. Hierarchical clustering was also used to visualise how the variables clustered.

3. Results

3.1. Patient characteristics

The flowchart of patients screened, invited and recruited to the study has been published previously [32]. Of 477 study participants who returned partially/fully completed questionnaires, 412 (86.4 %) participants had a self/representative-reported diagnosis of PD, 27 (5.7 %) PD dementia or Dementia with Lewy Bodies and 38 (8.0 %) had another form of parkinsonism or did not know the type. Table 1 displays the clinical characteristics of participants, including those requiring a representative to complete questionnaires on their behalf ($n = 32$), together with the completeness of data for each measure (97 % and above for the variables reported here). Mean frailty score was 0.49 (SD 0.33), median 0.49 (*IQR 0.18; 0.82)*), ranging from 0 to 1. Table S1 displays median frailty score by gender and age group. 133 (28.2 %) participants were categorised as frail, 245 (52.7 %) had a SARC-F score consistent with possible sarcopenia. 289 (61.8 %) were classified as disabled. 309 (64.9 %) were multimorbid. Table S2 displays the frequency of self-reported chronic conditions / categories.

3.2. Medication use including for motor symptom of Parkinson's

301 patients (63.1 %) were prescribed five or more medications

Table 1
Clinical characteristics of patient participants.

Characteristic / measure	N (%)	Number (%) of 477 patient participants who had data for measure
Gender		
Male	310 (65.0)	477 (100%)
Female	167 (35.0)	
Diagnosis		
Parkinson's disease	412 (86.4)	467 (98%*)
Parkinson's disease dementia	10 (2.1)	
Dementia with Lewy Bodies	17 (3.6)	
Progressive supranuclear palsy	12 (2.5)	
Multiple system atrophy	6 (1.3)	
Vascular parkinsonism	10 (2.1)	
Age group		
40-59	21 (4.4)	477 (100%)
60-64	29 (6.1)	
65-69	59 (12.4)	
70-74	102 (21.4)	
75-79	113 (23.7)	
80-84	79 (16.6)	
85-89	62 (13.0)	
90+	12 (2.5)	
Disease duration (years)		
< 2 years	79 (16.6)	477 (100%)
2-5 years	142 (29.8)	
5-10 years	154 (32.3)	
10-20 years	88 (18.5)	
20+ years	14 (2.9)	
Frailty (SHARE-FI 75+)		
Non-frail	142 (30.2)	471 (99%)
Pre-frail	196 (41.6)	
Frail	133 (28.2)	
Number of comorbidities		
0	52 (10.9)	476 (99.8%)
1	115 (24.2)	
2	97 (20.4)	
3	92 (19.3)	
4	54 (11.3)	
5+	66 (13.9)	
Sarcopenia		
Score <4	220 (47.3)	465 (97%)
Score ≥ 4 (possible sarcopenia)	245 (52.7)	
Disability		
No	179 (38.3)	468 (98%)
Yes	289 (61.8)	
Number of prescribed medications		
<5 medications	176 (36.9)	477 (100%)
≥5 medications	301 (63.1)	

* Not including the 10 individuals who selected 'don't know'.

overall and 211 patients (44.2 %) were prescribed five or medications excluding medication for motor symptoms of Parkinson's. The three most commonly prescribed non-PD medications were vitamin D (with/without calcium), atorvastatin and omeprazole (Table S3). Prescribed medication for PD, including device-aided therapy, is summarised in Table S4. Of the 441 patients taking levodopa, 193 (43.8 %) were prescribed five or more doses per day (Table S4). Median LEDD was 505 mg, ranging from 0 to 2443 mg. 18 (3.8 %) of participants used a device-aided therapy, including subcutaneous apomorphine, levodopa-carbidopa intestinal gel or deep brain stimulator (Table S4). 24 (5.0 %) of participants were on no Parkinson's medications, of whom 12 (50.0 %) reported that they had an atypical parkinsonian syndrome or vascular parkinsonism. 70 (14.7 %) were on three or more classes of PD medication. 441 (92.5 %) of patients were prescribed levodopa, 145 (30.4 %) a dopamine agonist, not including apomorphine, 60 (12.6 %) a COMT inhibitor and 81 (17.0 %) a MAO-B inhibitor.

3.3. Interrelationship of frailty, disability and multimorbidity

Of 465 patient participants with complete data for frailty, multimorbidity and disability, 78 (16.8 %; 95 % CI 13.5- 20.5 %) were categorised as neither frail nor multimorbid nor disabled (Fig. 1A). Whilst all three clinical entities were observed in isolation, all except 3 of 132 patients with frailty (2.3 %; 95 % CI 0.5- 6.5 %) were additionally living with disability and/or multimorbidity and all except 11 of 132 participants with frailty (8.3 %; 95 % CI 4.2- 14.4 %) were categorised as disabled. Only 52 participants (11.2 %; 95 % CI 8.5- 14.4 %) were categorised as disabled, without co-existing frailty or multimorbidity. The most common overlaps observed were the co-occurrence of frailty, disability and multimorbidity in 92 out of 465 (19.8 %; 95 % CI 16.3- 23.7 %) and multimorbidity together with disability, but without frailty in 114 out of 465 (24.5 %; 20.7- 28.7 %). When frailty was broadened to include those categorised as pre-frail, the largest group were those categorised as being frail/pre-frail, along with multimorbidity and disability (Fig. 1B).

3.4. Interrelationship of frailty, polypharmacy and multimorbidity

Fig. 2A shows the interrelationship between frailty, polypharmacy and multimorbidity. The most common overlap was between multimorbidity and polypharmacy, in 153 out of 471 (32.5 %; 95 % CI 28.3- 36.9 %) participants, followed by the co-occurrence of frailty, multimorbidity and polypharmacy in 86 (18.3 %; 14.9- 22.0 %) participants. Only 18 (3.8 %; 95 % CI 2.3- 6.0 %) had frailty in isolation. When the frailty category was broadened to include those with pre-frailty, many of those previously categorised as having multimorbidity and polypharmacy without frailty had all three clinical entities. Only 58 out of 471 participants with parkinsonism (12.3 %; 95 % CI 9.5- 15.6 %) were on fewer than five medications and not classified as frail/pre-frail or multimorbid (Fig. 2B). When considering only non-PD medications, the most common overlap was still between multimorbidity and non-PD polypharmacy without frailty (Fig. S1A), whilst 162 (34.4 %; 95 % CI 30.1- 38.9 %) patients were classified as frail/pre-frail, multimorbid and on five or more non-PD medications (Fig. S1B).

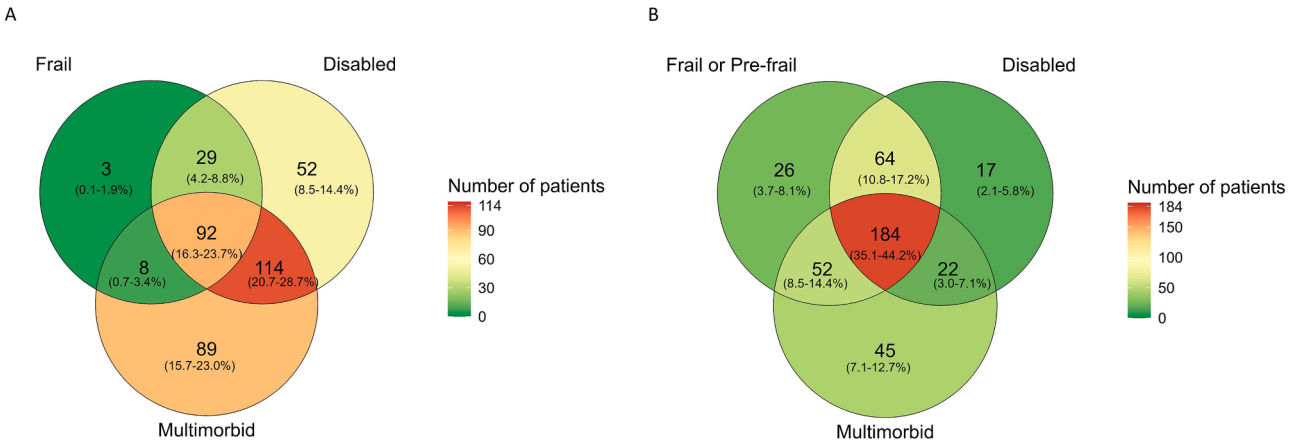

Fig. 1. The prevalence and overlap of A) frailty, multimorbidity and disability and B) frailty/pre-frailty, multimorbidity and disability amongst $n = 465$ patient participants with complete data for these domains, displayed as number (95 % confidence interval for the proportion) of patients. A: 78 (13.5- 20.5 %) individuals were neither frail nor multimorbid nor disabled. B: 55 (9.0- 15.1 %) individuals were neither frail or pre-frail nor multimorbid nor disabled.

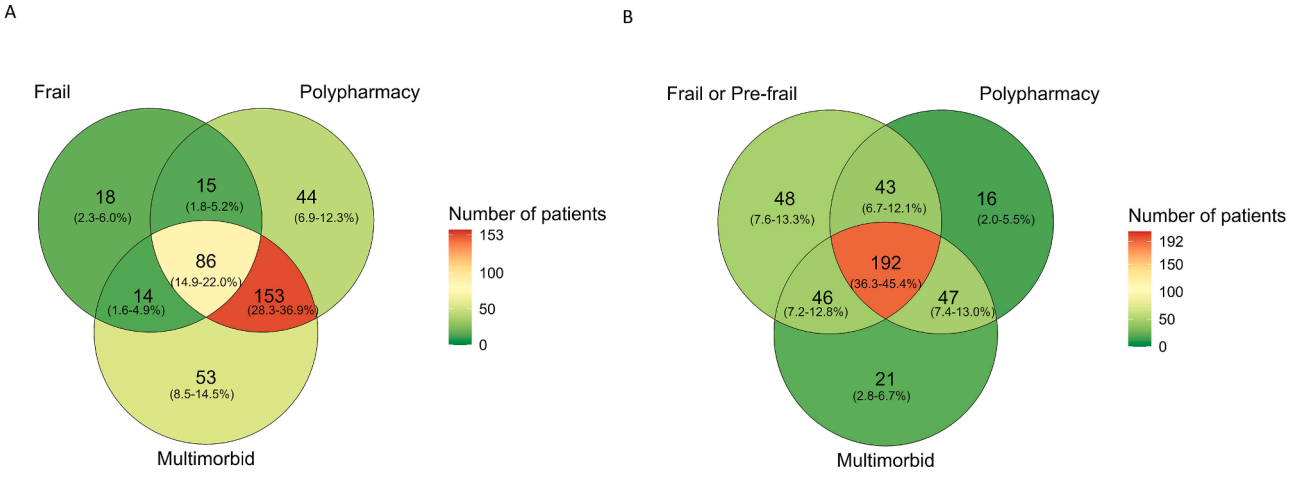

Fig. 2. The prevalence and overlap of A) frailty, multimorbidity, polypharmacy and B) frailty-pre-frailty, multimorbidity, polypharmacy amongst $n = 471$ patient participants with complete data for these domains, displayed as number (95 % confidence interval for the proportion). A: 88 (15.3- 22.5 %) individuals were neither frail nor multimorbid nor on ≥5 medications. B: 58 (9.5- 15.6 %) individuals were neither frail/pre-frail nor multimorbid nor on ≥5 medications.

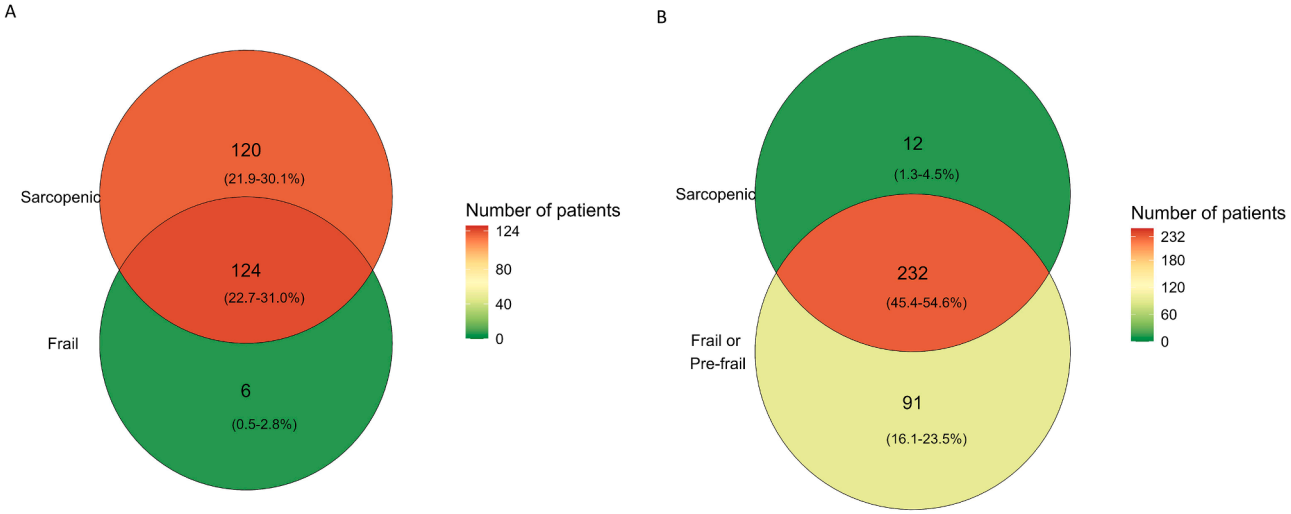

Fig. 3. The overlap between A) frailty and sarcopenia and B) frailty/pre-frailty and sarcopenia amongst $n = 464$ patient participants with complete data for these domains, displayed as number (95 % confidence interval for the proportion) of patients. A: 214 (41.5- 50.8 %) individuals were neither frail nor sarcopenic. B: 129 (23.8- 32.1 %) individuals were neither frail/pre-frail nor sarcopenic.

3.5. Interrelationship of frailty and sarcopenia

214 out of 464 (46.1 %; 95 % CI 41.5- 50.8 %) were categorised as non-frail, together with a SARC-F score not suggesting sarcopenia (Fig. 3A). 120 patients were categorised as non-frail but with a SARC-F score predictive of sarcopenia (25.9 %; 95 % CI 21.9- 30.1 %) and a similar number (124) as frail with likely co-existing sarcopenia (26.7 %; 95 % CI 22.7- 31.0 %). However, the occurrence of frailty without probable sarcopenia was observed in only 6 participants (1.3 %; 95 % CI 0.5- 2.8 %). Broadening the frailty category to also include those who were pre-frail, demonstrated that most of those categorised as probably sarcopenic but non-frail were classified as pre-frail: coexisting frailty/pre-frailty and likely sarcopenia affected 232 out of 464 individuals (50 %; 95 % CI 45.4- 54.6 %) (Fig. 3B).

3.6. Clustering of individuals and variables

The dendrogram (Figure S2) revealed that individuals ($n = 458$ with complete data) clustered into three groups based on the five variables: (i) 'Multimorbid-Multimedication (Frailty resilient)' group ($n = 236$), in which 122 (51.7 %) individuals had polypharmacy, 133 (56.4 %) multimorbidity, 71 (30.1 %) disability, whilst only 25 (10.6 %) and 0 (0 %) met criteria for probable sarcopenia and frailty respectively (Table 2); (ii) 'Disabled and Complex' group ($n = 209$), in which 100 % had sarcopenia and disability, around three quarters polypharmacy and comorbidity and 116 (55.5 %) were frail; (iii) a small 'Frail (Disability-Resilient)' group ($n = 13$), in which 100 % were frail, of whom 9 (69.2 %), 8 (61.5 %) and 7 (53.8 %) had multimorbidity, polypharmacy or probable sarcopenia respectively, but only 3 (23.1 %) were disabled. Table S5 shows the clinical characteristics of participants in each cluster. There is strong evidence that the three clusters differed in terms of age, gender, duration of parkinsonism and LEDD. Participants categorised as 'multimorbid-multimedication (frailty-resilient)' appeared to be somewhat younger than those categorised as 'frail (disability-resilient)'. A smaller proportion of the 'Disabled and complex' group (56.0 % versus 72.9 % of the 'Multimorbid-multimedication' group and 61.5 %of the 'Frail (disability-resilient)' group) were male and they had a slightly longer mean duration of parkinsonism. The dendrogram (Fig. S3) resulting from the hierarchical clustering, which used a matching measure to cluster by variables, indicated that sarcopenia and disability showed the greatest similarity (dissimilarity measure closest to zero), followed by multimorbidity and polypharmacy. Frailty was more closely related to sarcopenia and disability than was multimorbidity/polypharmacy.

4. Discussion

In this study, 28.2 % of patients were classified as frail and a further 41.6 % as pre-frail. This is higher than the proportion of individuals classified as frail (17.5 % of females and 12.2 % of males) according to SHARE-FI75+ in the SHARE cohort, a general population of older adults, with a slightly higher mean age (81.1 years in females; 80.4 years in males) than PRIME-UK cross-sectional participants [26]. It is also higher than the prevalence of frailty (14 %) found in over 5000 participants of the English Longitudinal Study of Ageing [33], albeit defined according to the original Fried phenotype criteria, not SHARE-FI75+. This finding aligns with existing studies suggesting that the frequency of frailty is higher in PD patients than non-PD populations comparable in terms of age and sex [15,34]. The frequency obtained in the PRIME-UK cross-sectional study lies within but towards the lower end of the 95 % CI (24 to 55 %) obtained in a recent meta-analysis [13]. This may be explained by differences between the Fried frailty phenotype and SHARE-FI75+, including the latter measuring weakness and slowness by self-reported functional limitation. Indeed, the SHARE--FI75+ authors acknowledge it may capture people at a later stage on the trajectory from frailty to disability and suggest that it may be more suitable to assess, rather than to screen for, frailty [26].

52.7 % had a SARC-F score of four or more, indicative of possible sarcopenia. This is in keeping with a cross-sectional study in which 55.8 % (95 % CI: 46.2- 64.9 %) of PD patients had a SARC-F score of four or more, compared to 8.2 % (5.7- 11.7 %) of non-PD controls [15]. SARC-F does not include a formal assessment of muscle strength, so cannot be used to confirm a diagnosis of sarcopenia according to the revised European consensus guidelines [35]. A systematic review and meta-analysis found that SARC-F had low to moderate sensitivity (28.9–55.3 % depending on the sarcopenia definition) and moderate to high specificity (68.9- 88.9 %) [36]. The high specificity means that there should be few people without sarcopenia incorrectly categorised on SARC-F as possible sarcopenia. However, the low sensitivity may mean that some people with sarcopenia (based on muscle strength, quality and quantity) are not captured by SARC-F. Nonetheless there is utility, particularly in an older population, of excluding sarcopenia in those without the condition, since this avoids the burden of unnecessary tests and interventions, whilst being simple to implement widely, thus raising awareness of the concept and addressing an unmet need [37].

Of 465 participants with data for disability, frailty and multimorbidity, 387 were disabled and/or frail and/or multimorbid. Of these patients, 24 % had all three conditions, 29 % multimorbidity with disability and 23 % multimorbidity without frailty or disability. It was uncommon to have frailty alone or multimorbidity and frailty without disability. These results support the notion that frailty, multimorbidity and disability are distinct but overlapping concepts, and that they are causally related [30]. Fried et al. suggested that comorbidity may contribute to the development of frailty [30]; the finding in PRIME-UK that 100 out of 132 who were frail (76 %) had multimorbidity would support this. Of 287 PRIME-UK participants classified as disabled, 235 (82 %) were also frail and/or multimorbid, consistent with the theory that development of disability may be triggered by frailty and/or multimorbidity. Fried et al. also hypothesised that disability and frailty may worsen comorbidity, for example by negatively impacting activity levels [30]. Multimorbidity is associated with functional impairment, but is also predictive of future decline in function, with a steeper decline noted with greater number and severity of morbidities [38]. This relationship may be bidirectional with worsening functional status contributing to increased multimorbidity [38].

Of 298 PRIME-UK participants (63 % of the total) who met the criteria for polypharmacy, 239 (80 %) had co-existing multimorbidity; these variables clustered together (Fig. S2). Multimorbidity is a driver of

Table 2
Frequency (%) who are positive for each of the 5 variables in the cluster analysis for 458 participants with complete data for all five variables.

Groups ($n = 458$)	**Variables**				
	Frailty	**Sarcopenia**	**Polypharmacy**	**Multimorbidity**	**Disability**
(i) Multimorbid-Multimedication (Frailty-resilient) ($n = 236$)	0 (0.0 %)	25 (10.6 %)	122 (51.7 %)	133 (56.4 %)	71 (30.1 %)
(ii) Disabled and complex ($n = 209$)	116 (55.5 %)	209 (100 %)	159 (76.1 %)	155 (74.2 %)	209 (100 %)
(iii) Frail (Disability-resilient) ($n = 13$)	13 (100 %)	7 (53.8 %)	8 (61.5 %)	9 (69.2 %)	3 (23.1 %)

polypharmacy [39] and a risk factor for hospital admission and mortality, in part due to the increased risk of adverse events and drug interactions [40]. Whilst not all polypharmacy is inappropriate [40], taking multiple medications contributes to treatment burden in patients with parkinsonism [41], providing a further rationale to address polypharmacy.

There was considerable overlap between frailty and sarcopenia and only 6 out of 464 participants (1.3 %) with data for both measures were classified as frail without probable sarcopenia. This is unsurprising since the SHARE-FI75+ criteria include self-reported weakness, and low muscle strength is key to the definition of sarcopenia. Slow walking speed, captured in SHARE-FI75+, suggests low physical performance, which is a marker of severe sarcopenia [26,35]. Weight loss, also captured within both Fried's frailty phenotype and SHARE-FI75+, may reflect sarcopenia [35]. Sarcopenia, a disease of muscle failure [42], is recognised to contribute to the development of physical impairment which is one aspect of the multidimensional geriatric syndrome known as frailty [35]. 26 % of participants were classified as having sarcopenia without frailty yet, when frailty and pre-frailty were combined, only 12 out of 464 patients (3 %) were classified as having sarcopenia alone. This supports the theory that sarcopenia, by contributing to physical decline, contributes to the trajectory from pre-frailty to frailty.

The cluster analysis demonstrated three groups of individuals: a group who were younger on average, in whom a high proportion had multimorbidity and polypharmacy, some of whom were also disabled, but generally not sarcopenic or frail who we termed 'Multimorbid-Multimedication (Frailty resilient)'; a large 'Disabled and Complex' group, with a higher proportion of females and longer mean disease duration, in which all individuals were disabled with a high proportion positive for all five variables; and a small 'Frail (Disability-Resilient)' group in which a relatively low proportion were disabled despite high levels of frailty and multimorbidity. This suggests that disability may result from multimorbidity or frailty, either alone or in combination, whilst a small proportion of individuals may be 'disability-resilient' despite living with multimorbidity and frailty. Understanding the reason (s) for this resilience, if modifiable, may result in future interventions.

A strength of this study is that it was designed with inclusivity at its core in terms of the eligibility criteria and by specifically targeting and supporting under-represented groups to take part [32]. This large and representative sample, which included those with frailty, cognitive impairment or living in a care home, makes the findings more generalisable to the UK parkinsonism population seen in clinical practice.

There are some limitations. This was a cross-sectional study and so we were unable to analyse longitudinally how, for example, sarcopenia may contribute to frailty and then to development of disability. We conducted this study in a single region which we acknowledge does not reflect the ethnic diversity of the UK overall [32]. However, multicentre recruitment would have precluded us from proactively supporting involvement of frailer individuals and those with impaired capacity to consent, who were a key focus of this research. Whilst routinely collected, national electronic health record data can be used to research large, representative samples, such datasets would not have allowed us to capture sarcopenia, disability or the frailty phenotype. Due to a lack of measures which are feasible and validated for proxy report, a recognised barrier to inclusion of adults with impaired capacity to consent [20], some traditionally patient-reported questionnaires (e.g. to assess frailty) were pragmatically included within the representative-completed booklet. Fortin et al's self-reported research tool, which aims to present conditions in an understandable way for patients [22], was chosen to quantify number of long-term conditions since measures of comorbidity requiring interview administration or reference to health records were not feasible. The Fortin et al. list does not include neurological conditions such as parkinsonism and, if this is counted, almost 90 % of participants would be categorised as multimorbid. It is a simple count so does not account for a condition's severity, unlike a tool such as the Cumulative Illness Rating Scale [43], which is a potential limitation. The approach used to define polypharmacy did not account for whether prescribed medications were appropriate or being taken [44]. Dichotomisation of disability may be an over-simplification since the functional status of individuals with parkinsonism varies from completely unimpaired through to significant loss of independence and, amongst individuals with the same self-reported level of disability, wide variation has been shown in both PD severity and quality of life [45]. There are also limitations to using a self-reported or proxy-reported measure of disability as disagreement has been noted between subjective versus objective disability measurement [45]. Furthermore, because this study did not incorporate in-person assessment, including measures such as the Movement Disorder Society-Unified Parkinson's Disease Rating Scale [46], it was not possible to explore the frequency of frailty, multimorbidity, sarcopenia, polypharmacy and disability according to parkinsonism severity or motor subtype. Additionally, SHARE-FI75+ was selected rather than SHARE-FI because it did not require assessment of handgrip strength; however, we acknowledge that SHARE-FI 75+ was developed and validated in individuals aged 75 years and over, whilst our study also included patients under 75 years, which is a potential limitation.

The finding that a large proportion of PRIME-UK participants were pre-frail/frail and/or multimorbid has implications for clinical care since these individuals can be more challenging to care for and tend to have high healthcare use [47]. It also has implications for how we structure health services for people with parkinsonism so that they are appropriate for those with multiple long-term conditions, rather than overly focused on single diseases. The considerable overlap of multimorbidity with polypharmacy highlights that medication review, accounting for patients' goals and priorities, should be embedded into parkinsonism care. Since frailty is considered to be a dynamic state in which individuals can transition to an improved, as well as more advanced, frailty state [4,12] and it may also be possible to prevent, delay or reverse sarcopenia [35], detection of sarcopenia, pre-frailty or frailty may offer opportunities to intervene to stop or slow the progression towards disability and dependency [30]. Additionally, although frailty, multimorbidity and disability overlap, they appear to be distinct concepts so should all be considered by researchers studying older adults [48].

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CRediT authorship contribution statement

Emma Tenison: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yoav Ben-Shlomo:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Anahita Nodehi:** Writing – review & editing, Visualization, Formal analysis. **Emily J Henderson:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2025.100073.

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