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Cross-Sectional and Prospective Associations between Parkinsonism and Parkinson's Disease with Frailty in Latin America

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Abstract: Background: Little is known about the relationship between parkinsonism or Parkinson's disease (PD) and frailty in Latin America.

Objective: The study aimed to determine the cross-sectional and prospective associations between parkinsonism and PD with frailty in a large multi-country cohort in Latin America. Frailty was assessed using three different models to explore which definitions are more appropriate to screen for frailty in a PD population.

Methods: 12,865 older adults (aged ≥65 years) from the 10/66 population-based cohort study in six Latin American countries were analyzed. Logistic regression models assessed the cross-sectional association between parkinsonism/PD with baseline frailty. Individual country analyses were combined via fixed-effect meta-analysis. In non-frail participants who were followed up for 4 years, Cox proportional hazards regression models assessed the prospective association between parkinsonism/PD with incident frailty accounting for competing risk of mortality.

Results: At baseline, the prevalence of parkinsonism and PD was 7% and 2%, respectively, and the prevalence of frailty varied across the three models with rates of 18% for frailty phenotype, 20% for frailty index and 30% for multidimensional frailty model. PD was associated with baseline and incident frailty after accounting for age, sex, and education: odds ratios and 95% confidence intervals (95% CI) for frailty were 2.49 (95% CIs 1.87–3.31), 2.42 (95% CIs 1.80–3.25), and 1.57 (95% CIs 1.16–2.21), and cause-specific hazard ratios were 1.66 (95% CIs 1.07–2.56), 1.78 (95% CIs 1.05–3.03), and 1.58 (95% CIs 0.91–2.74). Similar results were found for parkinsonism.

Conclusion: Parkinsonism and PD were cross-sectionally and prospectively associated with frailty in Latin America. Routine screening for frailty in PD patients may aid earlier detection of those at greater risk of adverse outcomes.

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Parkinson's disease (PD) and frailty are both highly prevalent in older people and projected to increase significantly with population aging.[1] PD is a neurological disorder that affects around 8.5 million people worldwide[2] and frailty, a state of increased vulnerability to stressors, affects approximately 12–24% of adults aged ≥50 years.[3] A systematic review of high-income countries found that frailty was present in 30% to 67% of people with PD.[4] Since PD and frailty are associated with substantial health and socioeconomic burden, understanding their relationship is relevant to public health policies concerning older people.

PD and frailty share common features, but their precise relationship is unknown. PD is a neurodegenerative disorder resulting in motor (eg, tremor, rigidity, and slowness) and nonmotor (eg, cognitive decline, depression, and pain) symptoms.[5] Frailty is associated with a cumulative dysfunction in multiple physiological systems, resulting in a range of symptoms like slow gait, falls, and poorer cognitive performance.[6] Both PD and frailty develop over a long time and slowly result in disability, comorbidities, and adverse outcomes for the diagnosed individual.[7–9] As PD and frailty overlap in prevalence, risk factors, and symptoms, involving similar hypothesized mechanisms such as age-related biological processes like chronic inflammation and mitochondrial disruption,[5,6] studying their relationship is challenging and has resulted in a gap in the literature.[10] In addition, there is wide variability across studies in the criteria used to assess frailty, including the frailty phenotype,[11] multidimensional frailty,[12] and frailty index.[13] This diversity not only poses challenges when attempting to evaluate cross-population differences, but there is also uncertainty about which criteria is most appropriate to screen for frailty in PD patients. For example, certain frailty criteria depend heavily on motor features (thus overlap with PD symptoms) and may be less suitable in the context of PD, potentially leading to overdiagnosis.

At present, there is a limited number of studies in the literature evaluating the relationship between parkinsonism, PD, and frailty. The existing literature is also based on small sample sizes[14–17] and generally a cross-sectional design conducted in high-income countries.[4,18] Large longitudinal cohort studies investigating the onset and progression of PD and frailty are lacking and would help inform whether one precedes the other. Understanding this relationship may provide clues about the shared pathogenesis and inform whether current medical practices should be adapted. Additionally, research conducted in low- and middle-income countries (LMICs) such as those in Latin America is currently lacking. A systematic PubMed search revealed that there are no available community-based studies assessing the associations between Parkinsonism and Parkinson's Disease with frailty in Latin American countries. This underscores a significant research gap in understanding frailty among PD patients in this region, highlighting the need for large-scale studies to better inform healthcare strategies and improve patient outcomes. Thus, the study aimed to determine the cross-sectional and prospective associations between parkinsonism and PD with frailty in a large multi-country cohort in Latin America. In addition, we assess frailty using three different models to explore which definitions are more appropriate to screen for frailty in a PD population.

Methods

The study was reported according to the STROBE checklist for cohort studies (Table S1).[19]

Data Source

The present study analyzed data from the 10/66 Dementia Research Group population-based cohort study.[20] The 10/66 cohort included older adults (aged ≥65 years) from 10 LMICs across India, China, Africa, and Latin America.[21] The six Latin American countries (Cuba, Dominican Republic, Puerto Rico, Venezuela, Mexico, and Peru) were included in the present analysis. All countries included data from urban areas only except for Mexico and Peru, which included separate urban and rural catchment sites.[21] The rural sites were remote areas with low population density and an agricultural lifestyle, whilst urban sites were areas with low or mixed socioeconomic status households.[21] Catchment areas were chosen based on their accessibility and relationship with local research groups and stakeholders.[20] Eligible participants were identified by door-knocking all households in the catchment area.[20]

The baseline phase data was collected between 2003 and 2007 (between 2006 and 2008 in Puerto Rico)[20] and the incidence phase data was collected between 2007 and 2011, approximately 4 years after.[20,21] The response rates for the baseline surveys across study sites ranged from 74% to 98%.[21] During the baseline and incidence survey, all participants underwent a full interview including physical and biological assessments.[21]

Study Sample

The 10/66 study includes 12,865 participants from Latin America: Cuba (n = 2944), Dominican Republic (n = 2011), Peru (n = 1933), Venezuela (n = 1965), Mexico (n = 2003), and Puerto Rico (n = 2009). The present study involved two different analytical cohorts. First, the cross-sectional analyses included the 12,865 baseline participants; and second, the prospective analyses included participants who: (1) were followed or whose vital status was ascertained; (2) had complete data (excluding missing observations on frailty-related variables during follow-up for prospective analysis) to assess PD and frailty; and (3) were not considered frail at baseline. The baseline characteristics of the total Latin American cohort according to follow-up status were compared.

Measures

The 10/66 population-based cohort study was designed to investigate the epidemiology and impact of dementia in LMICs.[21] Accordingly, the survey involved a comprehensive assessment of a wide range of health-related aspects including information on demographics, chronic diseases, disability, health service utilization, and socioeconomic status by trained research staff using standardized study protocols. Every site had a project coordinator and between four and 10 interviewers who were generally healthcare personnel (graduate physicians, primary care providers, geriatricians, specialists in internal medicine and registered

nurses). For the Cuba and Mexico sites, only medical doctors administered the interview. All interviewers and field examiners (4–9 per country) received uniform and standardized training, including (1) study protocol and procedures, (2) standard structured interview techniques, and (3) a two-day specific training for structured clinical assessment and neurological/physical examination including collecting other frailty-related measures. Interviewers and field examiners were regularly monitored and supervised to ensure uniform data collection and procedures. Additionally, the interviewers from the first wave also conducted the second wave. Full details of these protocols and procedures are available elsewhere[20,21] and the relevant variables for this paper are described below.

Definition of Parkinsonism and Parkinson's Disease

All participants underwent a comprehensive assessment, including a structured interview, a physical and neurological examination, and an informant interview.[21] The interviewers selected key informants, usually co-residents, family members, or caregivers, who were considered to be the most knowledgeable about the current circumstances of the older person.[20] This comprehensive interview obtained data on self-reported chronic diseases (eg, stroke) and neurological symptoms (eg, tremor), which permitted the diagnosis of parkinsonism and PD using an algorithm based on current clinical criteria.[22,23]

Parkinsonism and PD was defined according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria (Table S2).[24] First, parkinsonism was diagnosed as the presence of bradykinesia (slowness of voluntary movement with progressive difficulty performing repetitive actions) and at least one of the following: rest tremor, muscular rigidity, or postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. Subsequently, PD was diagnosed when there was at least three supportive criteria (eg, rest tremor, progressive disorder, and asymmetry) that favored a PD diagnosis and no red flags (eg, repeated strokes, supranuclear gaze palsy, cerebellar signs, cerebral tumor, and severe autonomic involvement) that argued against a PD diagnosis.[24,25] This diagnostic algorithm has been recommended for use in epidemiological studies.[26] The sensitivity (94% for parkinsonism and 86% for PD) and specificity (97% for parkinsonism and 99% for PD) of this diagnostic algorithm was estimated in the Cuba sample using clinical diagnoses by two neurologists as the reference standard.[22]

Definition of Frailty

Frailty was defined using three different models: frailty phenotype (FP),[11] multidimensional frailty (MF),[12] and frailty index (FI).[27] The original FP definition involves five components (exhaustion, weight loss, slow walking speed, low energy expenditure, and grip strength). In the absence of grip strength data in the 10/66 survey, a modified FP measure including four components was used.[28–31] The MF approach developed in the Alameda County study comprises 16 self-reported items grouped into four domains (physical, nutrition, cognitive, and sensory).[12] This approach has also been operationalized in the 10/66 study previously.[28,31,32] Frailty definitions, however, often include motor symptoms that overlap with PD. For instance, the FP and MF definition involves slow walking speed, a motor feature of PD, which means that this definition may over-diagnose frailty in a PD population by attributing their slow walking to frailty rather than their PD. Thus, an alternative frailty definition that can exclude motor features was used for comparison. The FI defines frailty as the accumulation of deficits, which are symptoms, signs, diseases, and disabilities.[13] The FI score, a ratio between 0 to 1, is calculated as the number of deficits present as a proportion of the total deficits considered, usually more than 20 to 30. The FI was operationalized in the 10/66 survey using 23 deficits, which excluded any variables that may overlap with symptoms of parkinsonism or PD, such as slow gait and difficulty walking. The definition of each frailty measure in 10/66 is described in detail in Table S3. Frail participants were defined as having ≥2 criteria of the FP or MF and an FI score ≥0.25.

Covariates

The following covariates were included in the analysis: age (years), sex (male or female), and educational level (none, did not complete primary, completed primary, secondary, or tertiary education).

Statistical Analysis

The present study used the 10/66 baseline and incidence phase data. The baseline characteristics of participants were reported overall and for individual countries, and by the incident frailty status. The prevalence of frailty by parkinsonism and PD status at baseline was calculated. The overlap in frailty participants by the three different frailty definitions was also illustrated using a Venn diagram.

Logistic regression models were used to assess the cross-sectional associations between parkinsonism or PD and frailty at baseline. Models were fitted separately for each country and combined via a fixed effect meta-analysis, estimating the magnitude of heterogeneity using Higgins I^2 statistic. Cox proportional hazards models were used to assess the prospective associations between parkinsonism or PD and incident frailty. Models were not fitted separately for individual countries in the prospective analyses due to smaller numbers. The proportional hazards assumption for the Cox regression models was tested and violation of the assumption was accounted for by stratifying models.[33,34] To account for the competing risk of death, we estimated cause-specific hazard ratios (HRs) and their 95% confidence intervals (CIs).[35] Participants were censored at the date of event, the date of death, or the last date of follow-up. The date of onset of frailty was assigned as the midpoint between the baseline and follow-up interview. As sensitivity analyses, different dates of onset of frailty were assigned. All analyses were conducted separately for each frailty definition and models were adjusted for age, sex, and education level.

Missing data were imputed for the baseline cross-sectional analyses. The proportion of participants with missing values in key demographic, parkinsonism, PD, and frailty-related variables were recorded (Table S5). Multiple imputation (MI) by Chained Equations was used to impute missing data.[36,37] We carried out five imputations with 10 iterations.[38] The following variables were included in the imputation model: country, age, sex, number of assets, number of physical illnesses, marital status, education level, care need, and all the variables used to define parkinsonism, PD, and frailty (Table S4). MI was not carried out for the prospective analyses due to the requirement of selecting participants by their frailty status, which is missing for some, for their inclusion in the analytical cohort.

All analyses were carried out in R version 4.2.2.

Results

Cohort Characteristics

The 10/66 cohort included 12,865 participants aged ≥65 years living in Latin America. At baseline, the mean age (SD) of the cohort was 74.7 (7.24) years and 36% were males (Table S5). Most participants were married or cohabiting (45%), had at least some level of primary education (90%), had one or two illnesses (43%), and were not dependent (87%). The prevalence of parkinsonism and PD was 7% (n = 934) and 2% (n = 230), respectively, and the prevalence of frailty was 18% (n = 2293), 30% (n = 3958), and 20% (n = 2520) according to the FP, MF, and FI definitions, respectively. The prevalence of frailty after imputation of missing data was 20% (n = 2546), 33% (n = 4267), 20% (n = 2617), respectively, and there was limited overlap in frailty by the different definitions (Fig. S1). Approximately 1 in 5 frail participants were considered frail by all three definitions and 1 in 2 frail participants were considered frail by only one definition.

The number of participants included in each country ranged from 1933 (Peru) to 2944 (Cuba). Demographic factors were largely similar across countries but there was some variation in clinical factors. For instance, the prevalence of parkinsonism ranged from 4.5% (Venezuela) to 10% (Dominican Republic) and the prevalence of PD ranged from 1.2% (Puerto Rico) to 2.6% (Cuba). Missingness in parkinsonism and PD was highest in Venezuela and Puerto Rico. The prevalence of frailty also varied between 11% to 36% (FP), 20% to 50% (MF), and 14% to 25% (FI) across countries.

The flow diagram of the study participants for the present study is shown in Fig. S2 and the baseline characteristics of participants who were lost to follow-up and followed-up (or deceased) at the incidence phase were compared (Fig. S6). Participants who were followed-up or deceased at incidence phase were more likely to be married/cohabiting (46% vs 43%, $P = 0.001$), have incomplete primary education (40% vs 34%, $P < 0.001$), no illnesses (38% vs 43%, $P < 0.001$), and more dependence (6.0% vs 5.7%, $P < 0.001$) than those lost to follow-up.

Table 1 shows the prevalence of frailty by parkinsonism and PD status at baseline. The reported prevalence is the mean value of results from the five imputed datasets (individual results are shown in Table S7). The prevalence of frailty was approximately 2-fold higher in participants living with parkinsonism or PD than in those without regardless of the frailty definition used. Frailty prevalence was highest using the MF definition (59% in PD; 70% in parkinsonism) and lowest using the FI definition (32% in PD; 49% in parkinsonism).

The baseline characteristics of non-frail participants varied by their incident frailty status (Table 2). Regardless of the frailty definition, non-frail participants who became frail at follow-up were older, females, never married or widowed, have no formal education, fewer number of assets, more illnesses, and were more dependent at baseline than those who remained non-frail. Participants who became frail were also more likely to be parkinsonism or PD cases at baseline.

Cross-Sectional Associations between Parkinsonism, Parkinson's Disease, and Frailty

In logistic regression models, parkinsonism (Fig. 1) and PD (Fig. 2) were associated with frailty after adjustment for age, sex, and education level. The ORs (95% CIs) for frailty in parkinsonism cases were 3.53 (95% CIs 3.05–4.08) (FP), 3.64 (95% CIs 3.12–4.25)

TABLE 1 *Prevalence of frailty by parkinsonism and Parkinson's disease status at baseline*

	Frailty phenotype		Multidimensional frailty		Frailty index	
	Non-frail	Frail	Non-frail	Frail	Non-frail	Frail
Parkinsonism						
No	9436 (82.2%)	2046 (17.8%)	8236 (70.1%)	3508 (29.9%)	9673 (82.4%)	2072 (17.6%)
Yes	561 (52.7%)	504 (47.3%)	352 (31.5%)	765 (68.5%)	574 (51.2%)	547 (48.8%)
Parkinson's disease						
No	9849 (80.1%)	2447 (19.9%)	8482 (67.3%)	4120 (32.7%)	10,070 (79.9%)	2534 (20.1%)
Yes	148 (59.2%)	102 (40.8%)	107 (41.2%)	153 (58.8%)	176 (67.7%)	84 (32.3%)

Note: Counts represent mean value of counts from five imputed datasets. The individual count from each imputed dataset can be found in Table S4. Row percentages are reported.

TABLE 2 *Cohort characteristics at baseline by incident frailty status*

	Frailty Phenotype			Multidimensional Frailty			Frailty Index		
N (%)	**Non-frail**	**Frail**	***P*-value**	**Non-frail**	**Frail**	***P*-value**	**Non-frail**	**Frail**	***P*-value**
Total	4642	993		4584	681		5498	501	
Age mean (SD)	72.69 (5.93)	74.79 (6.70)	<0.001	72.01 (5.59)	76.00 (6.35)	<0.001	72.76 (6.00)	76.56 (7.21)	<0.001
Male sex	1771 (38.2)	286 (28.8)	<0.001	1708 (37.3)	214 (31.4)	0.004	1951 (35.5)	167 (33.3)	0.358
Marital status			<0.001			<0.001			<0.001
Never married	345 (7.4)	49 (4.9)		337 (7.4)	44 (6.5)		410 (7.5)	42 (8.4)	
Married/cohabiting	2430 (52.4)	458 (46.2)		2474 (54.1)	295 (43.4)		2829 (51.6)	196 (39.1)	
Widowed	1287 (27.8)	383 (38.6)		1200 (26.2)	267 (39.3)		1570 (28.6)	208 (41.5)	
Divorced/ separated	571 (12.3)	101 (10.2)		562 (12.3)	74 (10.9)		676 (12.3)	55 (11.0)	
Education level			<0.001			<0.001			<0.001
None	424 (9.2)	157 (15.8)		300 (6.6)	125 (18.4)	72 (3.6)	478 (8.7)	109 (21.8)	
Some, did not complete primary	1180 (25.5)	317 (32.0)		1044 (22.8)	230 (33.8)		1407 (25.7)	180 (35.9)	
Completed primary	1381 (29.8)	243 (24.5)		1418 (31.0)	161 (23.6)		1657 (30.2)	130 (25.9)	
Completed secondary	993 (21.4)	168 (16.9)		1087 (23.8)	101 (14.8)		1163 (21.2)	50 (10.0)	
Tertiary (college)	654 (14.1)	107 (10.8)		721 (15.8)	64 (9.4)		779 (14.2)	32 (6.4)	
Number of assets			<0.001			<0.001			<0.001
1st quartile – least assets	660 (14.2)	193 (19.5)		560 (12.2)	135 (19.9)		734 (13.4)	113 (22.6)	
2nd quartile	1642 (35.4)	334 (33.7)		1632 (35.6)	232 (34.2)		2024 (36.9)	180 (36.0)	
3rd quartile	1288 (27.8)	297 (30.0)		1325 (28.9)	201 (29.6)		1519 (27.7)	118 (23.6)	
4th quartile – most assets	1048 (22.6)	167 (16.9)		1062 (23.2)	111 (16.3)		1214 (22.1)	89 (17.8)	
Number of illnesses			<0.001			0.548			<0.001
No illnesses	2184 (47.0)	341 (34.3)		2351 (51.3)	348 (51.1)		2611 (47.5)	177 (35.3)	
One to two illnesses	1968 (42.4)	455 (45.8)		1794 (39.1)	259 (38.0)		2428 (44.2)	243 (48.5)	
Three or more illnesses	490 (10.6)	197 (19.8)		439 (9.6)	74 (10.9)		459 (8.3)	81 (16.2)	
Dependency (need for care)			<0.001			<0.001			<0.001
Much of the time	27 (0.6)	15 (1.5)		24 (0.5)	14 (2.1)		31 (0.6)	13 (2.7)	
Some of the time	76 (1.7)	41 (4.2)		59 (1.3)	43 (6.5)		90 (1.7)	24 (4.9)	
Does not need care	4367 (97.7)	913 (94.2)		4346 (98.1)	607 (91.4)		5181 (97.7)	451 (92.4)	
Parkinsonism	159 (3.4)	86 (8.7)	<0.001	132 (2.9)	61 (9.0)	<0.001	208 (3.8)	51 (10.2)	<0.001
Parkinson's disease	44 (0.9)	21 (2.1)	0.003	49 (1.1)	14 (2.1)	0.043	66 (1.2)	13 (2.6)	0.016

(MF), and 3.00 (95% CIs 2.59–3.46) (FI). Individual country analyses generally reported weaker associations in Mexico and stronger associations in Dominican Republic. The ORs (95% CIs) for frailty in PD cases were 2.49 (95% CIs 1.87–3.31) (FP), 2.42 (95% CIs 1.80–3.25) (MF), and 1.57 (95% CIs 1.16–2.21) (FI). Individual country analyses generally reported consistent associations by country. The corresponding results using complete cases are shown in Fig. S3 (parkinsonism) and Fig. S4 (PD), which were similar to the multiple imputation results.

Prospective Associations between Parkinsonism, Parkinson's Disease, and Frailty

In Cox proportional hazards models, both parkinsonism and PD at baseline were associated with incident frailty after adjustment for age and sex and stratification by education level (Table 3). Among non-frail participants who were alive, parkinsonism was associated with a

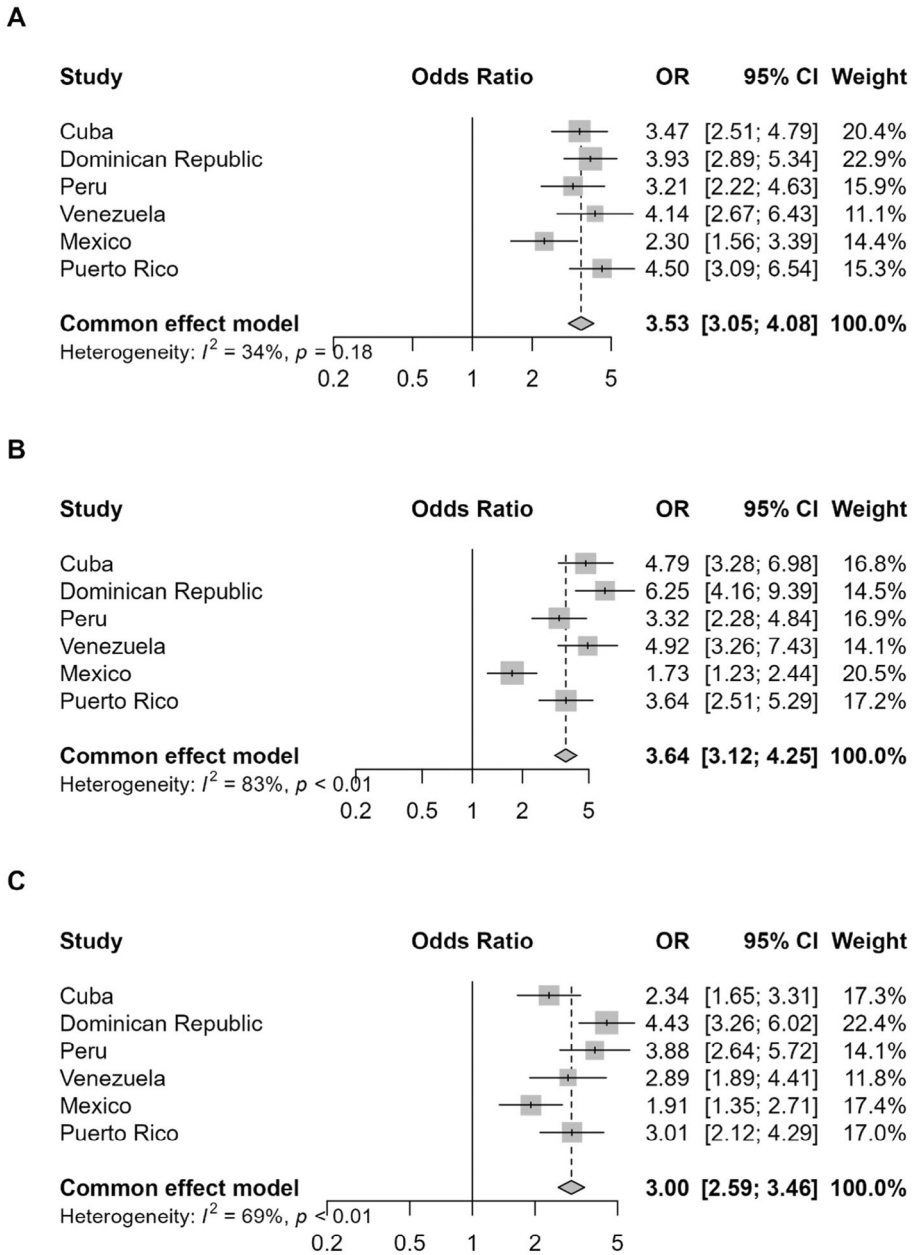

Figure 1. Odds ratios (95% CIs) of the cross-sectional association between parkinsonism and frailty according to the frailty phenotype (A), multidimensional frailty (B), and frailty index (C) Logistic regression models were adjusted for age, sex, and education. Models were fitted separately for each country and combined via a fixed effect meta-analysis.

higher rate of incident frailty. Cause-specific HRs (95% CIs) were 1.75 (95% CIs 1.40–2.20) (FP), 2.09 (95% CIs 1.60–2.73) (MF), and 1.63 (95% CIs 1.21–2.19) (FI). Similarly, PD was associated with a higher rate of incident frailty, though associations were not statistically significant when the FI definition was used. The cause-specific HRs (95% CIs) were 1.66 (95% CIs 1.07–2.56) (FP), 1.78 (95% CIs 1.05–3.03) (MF), and 1.58 (95% CIs 0.91–2.74) (FI). The sensitivity analyses using varying dates of onset of frailty showed similar results that were directionally consistent with the main findings (Table S8).

Discussion

Summary of Findings and Comparison with Previous Literature

We show that frailty is highly common in parkinsonism and PD in Hispanic older adults, its prevalence ranging from 47% to 69% and

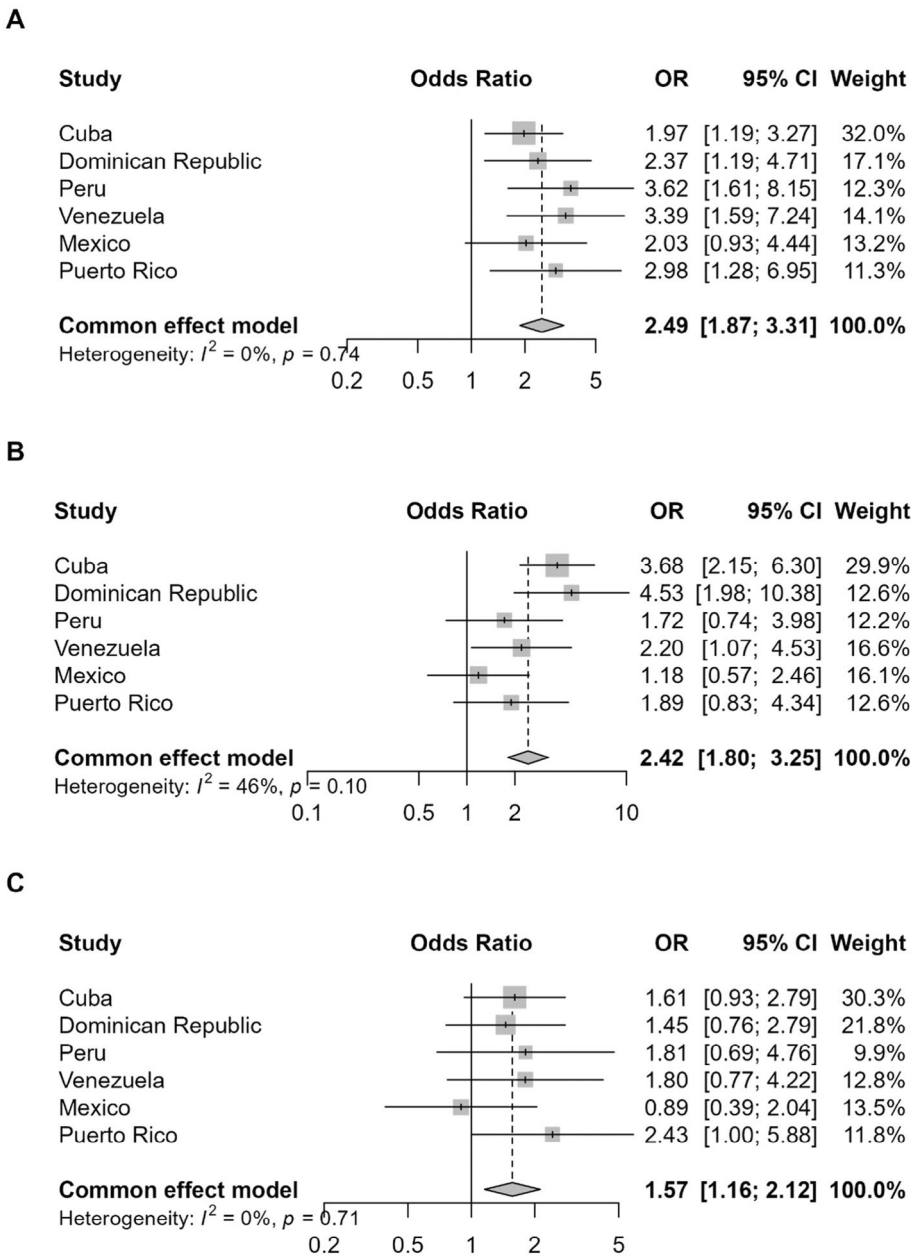

Figure 2. Odds ratios (95% CIs) of the cross-sectional association between PD and frailty according to the frailty phenotype (A), multidimensional frailty (B), and frailty index (C) Logistic regression models were adjusted for age, sex, and education. Models were fitted separately for each country and combined via a fixed effect meta-analysis.

32% to 59%, respectively, depending on the frailty definition. Previous studies have also reported that frailty is common in PD. For example, the prevalence of frailty was 55% (using the FI) in 62,786 participants from a claims-based US cohort[39] and 36% (using the Clinical Frailty Scale of the Canadian Study of Health and Aging) in 104 PD patients from a tertiary center in Austria.[40] However, little longitudinal evidence has been reported on PD and incident frailty. To our knowledge, this is the first large prospective study investigating the association between PD and the incidence of frailty in Latin America.

We found that parkinsonism and PD was associated with frailty both cross-sectionally and prospectively. Among older adults living in Latin America, people living with PD had 1.6- to 2.5-fold higher likelihood of being frail and 1.6- to 1.8-fold higher risk of developing incident frailty compared to non-cases, which were independent of basic demographic factors. The precise mechanism by which parkinsonism and PD may be linked to frailty is unknown. The hypothesized pathogenesis of PD and frailty, while uncertain, is believed to involve similar age-related

TABLE 3 *Cause-specific hazard ratios (95% CIs) of the prospective association between parkinsonism and Parkinson's disease and incident frailty*

	Frailty phenotype HR (95% CIs)	Multidimensional frailty HR (95% CIs)	Frailty index HR (95% CIs)
Parkinsonism			
Crude model	2.04 (1.64–2.55)	2.75 (2.12–3.58)	2.24 (1.67–2.99)
Adjusted model	1.75 (1.40–2.20)	2.09 (1.60–2.73)	1.63 (1.21–2.19)
Parkinson's disease			
Crude model	1.81 (1.17–2.79)	1.88 (1.11–3.19)	1.84 (1.06–3.19)
Adjusted model	1.66 (1.07–2.56)	1.78 (1.05–3.03)	1.58 (0.91–2.74)

Note: Cox regression models were adjusted for age and sex and stratified by education.

cellular pathways like inflammation, mitochondrial dysfunction, and impaired insulin signaling.[9] Importantly, our study assessed different definitions of frailty given the lack of consensus on the optimum tool to screen for frailty in PD. We found varying levels of frailty prevalence among PD cases depending on the frailty definition used with the highest prevalence found using the multidimensional frailty and the lowest using the frailty index. Similarly, the positive associations between parkinsonism and PD with frailty were also generally strongest using the multidimensional frailty and weakest using the frailty index. This may be explained by the fact that the multidimensional frailty measure is completely composed of motor (slow walking speed) or non-motor (cognitive, sensory, and nutritional deficiency) symptoms of PD. For example, hearing impairment is commonly observed in PD and may be associated with dopamine depletion that occurs in the development of PD.[41] Also, the nature of the disease, such as rigidity and tremor, means that people living with PD are less able to shop, cook, and feed independently, which increases their risk of malnutrition.[42] Thus, the large overlap in MF components and PD symptoms (ie, circularity) may have resulted in the over-diagnosis of frailty. Conversely, the FI operationalized in the present study excluded motor symptoms and included a wider range of signs and symptoms unrelated to PD, which may explain the lower prevalence of frailty among PD cases using this definition. However, a previous study including 1765 participants from the Hellenic Longitudinal Investigation of Aging and Diet found that the likelihood of PD was higher in those who were frail defined by the FI OR (95% CIs) 12.16 (95% CIs 5.46–27.09) than FP OR 4.09 (95% CIs 1.43–10.89),[43] which may reflect the inclusion of motor-symptoms in this particular FI. This variation in frailty prevalence in PD depending on the frailty tool have been reported previously[18] and highlights the need to determine which is the optimum tool to screen for frailty in PD.

Implications for Clinical Practice and Research

Frailty in PD patients may lead to a higher risk of mortality, hospitalization, emergency department visits, and falls compared to non-frail PD patients.[39] Frailty in newly diagnosed PD patients has also shown to increase the risk of dementia after 3 years,[16] which may result in poorer quality of life and increased caregiver burden and healthcare costs that PD patients are already susceptible to. Thus, screening for frailty in PD from the earliest clinical stages may help identify those at greater risk of adverse outcomes and need for earlier intervention, such as prevention of falls and more frequent assessment of dependency. However, exactly how frailty screening in PD will look like in practice is uncertain given the lack of consensus on the optimum tool to assess for frailty. Currently, the most common tool to screen for frailty in PD is the frailty phenotype[4] but our findings showed large variation in the classification of frailty and little overlap between different frailty tools. Thus, different sets of individuals will be classed as frail depending on the frailty tool (those based on physical components may over-diagnose frailty), which will affect who will receive necessary intervention. Further research is therefore needed to determine which is the optimum tool to assess frailty. For example, future studies comparing the risk of outcomes and the longitudinal risk factors of frail PD patients may provide insight as to which frailty tool is most appropriate to screen PD patients. Although still preliminary, our study suggests that frailty models excluding motor features may offer distinct advantages by identifying a subgroup of PD cases with frailty without over-diagnosing due to overlapping signs.

Strengths and Limitations

Our study has several strengths. First, there are few longitudinal studies investigating the relationship between PD and frailty, thus we provide firsthand evidence on the prospective association between PD and incident frailty. Second, the large sample size using an understudied population increases the significance of our findings. Third, multiple imputation was used in the cross-sectional analyses: the inclusion of many participants who would have been excluded due to missing data increases the credibility of our results. Fourth, despite the consistent training provided to all the research staff, including video training materials for local centers and regular supervision of field interviews, cross-site variability may still occur which is a common challenge in large multicenter, multicounty studies. Fifth, PD is relatively uncommon, and even studies of large populations will find relatively few cases. In addition, our study previously reported a high number of underdiagnosed cases,[22] with limited number having

a previous diagnosis of PD and on treatment. As a result, our study did not assess PD severity and treatment and its potential impact on frailty. It's possible that more advanced PD subgroups with higher reduced mobility due to impaired gait and balance will have a higher frequency of frailty. Moving forward controlling for such factors or using frailty measures less reliant on motor futures will be key to better assessing PD-frailty phenotypes. Sixth, the adapted FI has been previously validated in various populations; however, it has not been specifically validated for use in Latinos with PD populations. The importance of its identification is apparent given the high prevalence and the association between frailty and adverse outcomes in persons with PD. This limitation is not unique to our study; it applies to all frailty measures, as none have been explicitly validated for PD.[44] This highlights a common challenge in the field and underscores the need for further validation studies. Lastly, given the lack of consensus on the optimum instrument to measure frailty in PD patients, we reported our analyses using several frailty instruments, providing a range of estimations that takes into account the overlap in symptoms between frailty and PD. Our study also has several limitations. First, most of the frailty components were based on self-reported data, which may have introduced reporting bias. Second, key covariates were not adjusted for in the statistical models like the number of prior illnesses as this would have resulted in overadjustment (FI includes several diseases as deficits); thus, associations may have been over-estimated. Third, the prospective analysis used complete cases and the exclusion of participants may have introduced bias if data were not missing at random. For example, more frail participants may have been excluded if they were too weak to carry out tests, which may have resulted in fewer frail cases and an underestimation of results. Lastly, given the relatively short follow-up period and the observational nature of the study, the causal nature of the relationship cannot be inferred.

We found significant associations between parkinsonism and PD with the prevalence and incidence of frailty over 4 years of follow-up in older adults living in Latin America. Integrating frailty assessment into the management of PD may help identify older adults at greater risk of adverse outcomes and requiring alternative interventions.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

DJK: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
NK: 1B, 1C, 2A, 2B, 2C, 3B.
JLR: 2C, 3B.
MJ: 2C, 3B.
ARS: 2C, 3B.
IA: 2C, 3B.
ALS: 2C, 3B.
DA: 2C, 3B.
IJV: 2C, 3B.
MG: 2C, 3B.
AS: 2C, 3B.
NDS: 2C, 3B.
RLC: 2C, 3B.
HH: 2C, 3B.
CT: 2C, 3B.
JLG: 1A, 1B, 2A, 2C, 3A, 3B.
MP: 1A, 1B, 2A, 2C, 3A, 3B.

All authors worked collectively to develop the protocols and methods described in this paper. MP had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis.

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Disclosures

Ethical Compliance Statement: Ethical approval for the 10/66 study was granted by the local ethics committees and the King's College London Research Ethics Committee. All study participants gave written informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data supporting the findings of this study are derived from the 10/66 Dementia Research Group's population-based study. Data are available upon reasonable request to the 10/66 Dementia Research Group and subject to the approval of the respective data governance committees. Data requests can be submitted via the Alzheimer's Disease Data Initiative (ADDI) platform. ■

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Supporting Information

Supporting information may be found in the online version of this article.

TABLE S1. The STROBE Checklist.

TABLE S2. The UK Parkinson's Disease Society Brain Bank diagnostic criteria.

TABLE S3. Definition of frailty in the 10/66 survey.

TABLE S4. Missingness in key demographic, parkinsonism, PD, and frailty-related variables in the 10/66 baseline survey.

TABLE S5. Cohort characteristics at baseline, overall and by individual country.

TABLE S6. Baseline characteristics by follow-up status of the 10/66 Latin American cohort.

TABLE S7. Prevalence of parkinsonism and Parkinson's disease by frailty status at baseline by imputed dataset.

TABLE S8. Cause-specific hazard ratios (95% CIs) of the prospective association between parkinsonism and Parkinson's disease and incident frailty.

Figure S1. Venn diagram of frail participants at baseline.

Figure S2. Flow diagram of study participants.

Figure S3. Odds ratios (95% CIs) of the cross-sectional association between parkinsonism and frailty according to the frailty phenotype (A), multidimensional frailty (B), and frailty index (C) using complete cases.

Figure S4. Odds ratios (95% CIs) of the cross-sectional association between PD and frailty according to the frailty phenotype (A), multidimensional frailty (B), and frailty index (C) using complete cases.