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Frailty in prodromal Parkinson's disease in Medicare beneficiaries

George K. Karway [a], Jordan A. Killion [a], Irene M. Faust [a], Kassu M. Beyene [a], Brad A. Racette [a,b,c], Alejandra Camacho-Soto [d,*]

[a] Department of Neurology, Barrow Neurological Institute, 240 W. Thomas Road, Phoenix, AZ, 85013, USA
[b] Department of Neurology, Washington University in St. Louis, St. Louis, 660 S. Euclid Avenue, Campus Box 8111, St. Louis, MO, 63110, USA
[c] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, 27 St Andrews Road, Parktown, 2193, South Africa
[d] Department of Physical Medicine and Rehabilitation, University of Kansas Medical Center, 4000 Cambridge Street, Kansas City, KS, 66160, USA

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ABSTRACT

Introduction: Frailty, a common syndrome of aging associated with a decline in physiological reserve, places individuals with Parkinson's disease (PD) at a greater risk of poor health outcomes. We hypothesized that frailty would also be greater in prodromal PD patients compared to the general population and, thus, could be part of the prodromal phase of PD.

Methods: We conducted a population-based case-control study of incident PD cases (N = 82,560) and controls (N = 96,482) ages 70–90 identified in 2009. Using 2004–2009 Medicare data, we examined frailty in five individual 12-month time windows during the prodromal period using the claims-based frailty index (CFI), categorized as nonfrail, mildly frail, and moderately-to-severely frail. For each time window, we calculated the odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between frailty and PD, while adjusting for age, sex, race/ethnicity, and use of care. We examined variables in CFI that were associated with PD in the 12 months prior to diagnosis.

Results: Mildly frail (OR = 1.70, 95 % CI 1.62–1.78) and moderately-to-severely frail (OR = 1.29, 95 % CI 1.16–1.43) were associated with PD five years prior to diagnosis. This association strengthened in the final year prior to diagnosis: mildly frail (OR = 7.75, 95 % CI 7.51–7.99); moderately-to-severely frail (OR = 10.22, 95 % CI 9.63–10.86). In the 12 months prior to PD diagnosis, the CFI variable encompassing psychiatric/cognitive disorders had the most marked association with PD (OR = 4.63, 95 % CI 4.50–4.77).

Conclusions: Medicare beneficiaries with PD are frailer than controls in the prodromal period. Frailty was highest in the 12 months prior to PD diagnosis.

1. Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease, and among neurological disorders, it has the fastest increase in prevalence, death, and disability-adjusted life-years [1,2]. Although the clinical diagnosis of PD requires the presence of motor symptoms (e.g., bradykinesia, tremor, rigidity, and/or postural instability) [3], several non-motor symptoms often precede the motor symptoms by years or even decades [4]. The pre-diagnosis phase, also known as prodromal PD, may start as early as two decades before PD diagnosis and is characterized by various subclinical motor and non-motor manifestations [5]. These symptoms of PD often interact with other age-related syndromes, such as frailty, leading to acceleration of functional decline and other clinical complications.

Frailty is a syndrome of aging characterized by a weakened ability of the human body to respond to external stressors across multiple physiologic systems, resulting in poor health outcomes [6]. Frailty affects over 17 % of community-dwelling adults aged 50 and older, with prevalence varying by setting, population, approach to frailty measurement, and age [7]. In persons with PD (PwP), frailty may be even higher due to shared characteristics, underlying mechanisms, and potentially similar pathological processes [8–10]. One of the most common measurements used in frailty, the Fried Frailty Phenotype [11], includes variables such as fatigue, reduced gait speed, diminished grip strength, and weight loss, which are all common symptoms of PD [8–10]. As a result, previous studies in PD have reported a wide range of

* Corresponding author. University of Kansas Medical Center, 4000 Cambridge Street, Kansas City, KS 66160, USA.
E-mail addresses: George.Karway@barrowneuro.org (G.K. Karway), Jordan.Killion@barrowneuro.org (J.A. Killion), Irene.Faust@barrowneuro.org (I.M. Faust), Kassu.Beyene@barrowneuro.org (K.M. Beyene), Brad.Racette@Barrowneuro.org (B.A. Racette), acamacho-soto@kumc.edu (A. Camacho-Soto).

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frailty, between 22.2 and 69.4 % due to the potential overlap between frailty and PD [12–15]. Frailty in PwP has been linked to worse motor severity [15], greater co-morbidities [14], greater non-motor symptom burden [12], worse overall disease severity, and poorer cognitive function [15]. Until recently [16], frailty research in PwP was primarily based on small samples [12–15,17]. This limitation is even more pronounced in the prodromal phase of PD, where data on frailty are limited to two European studies [18,19]. Given the strong association between frailty and adverse health outcomes [16], identification and consideration of frailty in early PD management is critical. While there is no cure for PD, frailty is modifiable and there are potential opportunities for intervention to prevent or reverse frailty progression, which could enhance the effectiveness of current treatments for PD symptoms [20,21].

Administrative data provides an opportunity to examine frailty and its associated outcomes using a frailty measure with a wide range of variables in a larger population [22,23]. Therefore, we conducted a case-control study identified from a geographically diverse United States (US) Medicare population to investigate the association between frailty and PD in five separate 12-month time windows within the prodromal period, as compared to controls. Additionally, we examined whether specific frailty variables were positively associated with PD in the 12 months prior to diagnosis. We hypothesized that frailty would be positively associated with PD in all five separate time windows prior to diagnosis and that the association would strengthen with proximity to diagnosis date.

2. Study materials and method

2.1. Standard protocol approvals, registrations, and patient consents

The Human Research Protections Office at Washington University in St. Louis, the St. Joseph's Hospital and Medical Center Institutional Review Board, and the Centers for Medicare & Medicaid Services (CMS) approved this study, which was deemed exempt, as it does not meet the definition for human subject research.

2.2. Study design and cohort

This study was constructed from a previous case-control data set using 2009 Medicare data that has previously been described [24]. Briefly, all eligible incident PD cases were obtained from 2009 along with a random sample of eligible controls. Beneficiaries had to have all available claims data including carrier (physician/supplier part B), outpatient, inpatient, skilled nursing facility, durable medical equipment, and home health claims from 2004 to 2009 along with demographic data obtained from the 2009 beneficiary annual summary file. The original study included all beneficiaries who met the following eligibility criteria: 1) born by February 1, 1942, 2) had Medicare parts A or B coverage without Medicare Advantage Plan coverage to exclude plans that do not report detailed claims to CMS, 3) US residence, 4) age $\leq$90 years or died by the end of 2009, and 5) age $\geq$66 years, 11 months to ensure incident cases who had a minimum of 2 years of claims data before PD diagnosis/control reference date in 2009 [24]. For the current study, we further required all beneficiaries to be at least 70 years of age at the time of PD diagnosis or control reference date in 2009 to have the full claims data for the five years preceding their date of PD diagnosis or control reference date.

2.3. Assessment of PD cases and controls in the prodromal period

We identified incident PD cases with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 332.0 or 332 in 2009, with no past occurrence of these codes in 2004–2008 [24]. We excluded beneficiaries with ICD-9-CM codes suggestive of secondary PD or Lewy body dementia (ICD-9-CM codes 333.0 and 331.82). Controls were randomly selected using random number generation from all remaining beneficiaries who met the same study eligibility criteria but with no ICD-9-CM code for PD, atypical Parkinsonism, or Lewy body dementia in 2004–2009, and were alive in 2009 prior to their randomly assigned reference date in 2009. The prodromal period was defined as the five years prior to PD diagnosis date or control reference date in 2009. We did not match controls to PD patients on demographic factors but instead adjusted for them in analyses to maintain sample size.

2.4. Assessment of frailty in the prodromal period

We used a previously validated claims-based frailty index (CFI), which was developed to measure frailty from administrative claims data [22,23]. The CFI is a measure of frailty status, using the cumulative deficit approach to quantify the proportion of symptoms, diseases, and disabilities present in each individual, reflecting the individual's risk of poor health outcomes and mortality [22,23]. The CFI model includes 93 variables using ICD-9-CM diagnosis codes, current procedural terminology (CPT) codes, and the healthcare common procedure coding system (HCPCS) from Medicare over a 12-month look back period [22,23]. The final codes for the CFI model were grouped based on previously defined chapters, subheadings, or categories of the ICD-9-CM coding system, CPT-4 services, and HCPCS level II supplies [22]. The total CFI score represents the proportion of total health deficits (out of the 93 variables) present in an individual, with higher scores indicating poorer health [22,23]. The complete list of the 93 variables included in the CFI can be found in Kim DH et al. [22]. In this study, we estimated frailty in five separate 12-month time windows during the prodromal period using the CFI as a continuous measure (ranging from 0 to 1) and then categorized using standard cut points: nonfrail ($<$0.25), mildly frail (0.25–0.34), moderately-to-severely frail ($\geq$0.35) [22,23].

Given that motor and non-motor symptoms of PD may contribute to the frailty phenotype and could potentially increase the frailty score in PD cases compared to controls, we conducted a sensitivity analysis by excluding codes suggestive of symptoms of PD. In this analysis, two physicians, including a movement disorder specialist, reviewed the frailty-related codes that were positively associated with PD. The second physician independently reviewed the code list, and any discrepancies were resolved through consensus. Codes suggestive of motor and non-motor symptoms of PD were excluded from the CFI and the model was re-estimated to assess the impact of their removal.

2.5. Assessment of covariates

Covariates included beneficiary demographic information (age, sex, and race/ethnicity) and use of medical care [25] in each individual time window. We classified race/ethnicity into six categories (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, Native American, and Other). We calculated age from beneficiaries' birth date and treated it as a continuous variable in the model. We also classified age into four categories for demographic summary (70–74, 75–79, 80–84, and 85–90). We treated sex as binary (female, male). We quantified use of medical care using beneficiaries' records from inpatient, outpatient, skilled nursing facility, and physician office, and calculated the total number of unique ICD-9-CM diagnosis and procedure codes observed within each 12-month window in the five-year prodromal period [25].

2.6. Statistical analysis

All statistical analyses were performed using Stata software (MP 14.2; StataCorp LLC, College Station, TX) or R version 3.6.3 (The R Project for Statistical Computing). We used logistic regression models to estimate the odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between frailty and PD in five individual 12-month time

Table 1
Characteristics of incident Parkinson's disease cases and randomly sampled population-based controls, United States, Medicare, 2009.

Characteristics	PD Cases N = 82,560	Controls N = 96,482	OR[a] (95 % CI)
Sex, n (%[b])			
Male	40,832 (49.46)	40,463 (41.94)	1.000 (reference)
Female	41,728 (50.54)	56,019 (58.06)	0.659 (0.646–0.672)
Race/Ethnicity, n (%)			
White	73,417 (88.93)	83,754 (86.81)	1.00 (reference)
Black	4833 (5.85)	7013 (7.27)	0.792 (0.760–0.826)
Hispanic	1768 (2.14)	1803 (1.87)	1.000 (0.930–1.075)
Asian/Pacific Islander	1434 (1.74)	2083 (2.16)	0.862 (0.801–0.927)
Other	851 (1.03)	1440 (1.49)	0.849 (0.775–0.930)
Native American	257 (0.31)	389 (0.40)	0.866 (0.732–1.025)
Age			
Mean (SD)	79.7 (5.42)	77.74 (5.54)	1.057 (1.055–1.059)
Category, n (%)			
70–74	17,522 (21.22)	34,180 (35.43)	1.000 (reference)
75–79	22,304 (27.02)	26,511 (27.48)	1.541 (1.500–1.583)
80–84	24,150 (29.25)	21,494 (22.28)	1.974 (1.920–2.029)
85–90	18,584 (22.51)	14,297 (14.82)	2.254 (2.187–2.323)
CFI Score[c]			
Mean (SD)	0.266 (0.08)	0.166 (0.06)	–
Category[d], n (%)			
Nonfrail	39,221 (47.51)	86,852 (90.02)	1.000 (reference)
Mildly Frail	31,515 (38.17)	7795 (8.08)	7.645 (7.410–7.888)
Moderately-to-Severely Frail	11,824 (14.32)	1835 (1.90)	10.194 (9.602–10.823)

Abbreviations: CFI, claims-based frailty index; CI, confidence interval; n, frequency; OR, odds ratio; PD, Parkinson's disease; SD, standard deviation.
[a] OR is adjusted for age, sex, race/ethnicity, and use of medical care.
[b] Percents may not sum to 100 due to rounding.
[c] CFI score is a continuous measure ranging from 0 to 1.
[d] CFI category is measured using standardized thresholds: Nonfrail (CFI <0.25), mildly frail (CFI = 0.25–0.34), moderately-to-severely frail (CFI ≥0.35).

intervals prior to PD diagnosis/control reference date in 2009. Our exposure variable was frailty [nonfrail (<0.25), mildly frail (0.25–0.34), moderately-to-severely frail (≥0.35)] and PD our outcome variable. We generated separate models for each time window: 0–1 year, 1–2 years, 2–3 years, 3–4 years, and 4–5 years prior to PD diagnosis/control reference date in 2009. In addition, we used a continuous CFI variable to compute the mean and standard deviation (SD) of CFI scores in each 12-month time window and used a two-sample *t*-test with unequal variances to compare the average CFI scores between PD cases and controls across the years. Next, we assessed the presence of a monotonic upward or downward trend in the mean CFI values over time using the Mann-Kendall test, which helped determine whether the mean CFI scores consistently increased or decreased over the five-year period. Finally, to determine which of the 93 frailty variables in the CFI were positively associated with PD in the final 12-months prior to diagnosis, we dichotomized each CFI variable [22] and included it as our exposure variable and PD as our outcome variable using a logistic model. All models were adjusted for age, sex, race/ethnicity, and use of medical care and statistical significance was set at $p<0.05$. When multiple comparisons were performed, the p values were adjusted using the Bonferroni post-hoc correction.

Table 2
Association between claims-based frailty index[a] and PD in five separate 12-month time windows[b] prior to PD diagnosis/control reference date in 2009[c].

Characteristics	PD Cases N = 82,560	Controls N = 96,482	OR[d] (95 % CI)
0–1 year, n (%)			
Nonfrail	39,221 (47.51)	86,852 (90.02)	1.00 (reference)
Mildly Frail	31,515 (38.17)	7795 (8.08)	7.75 (7.51–7.99)
Moderately-to-Severely Frail	11,824 (14.32)	1835 (1.90)	10.22 (9.63–10.86)
1–2 years, n (%)			
Nonfrail	63,342 (76.72)	88,943 (92.19)	1.00 (reference)
Mildly Frail	15,374 (18.62)	6326 (6.56)	2.38 (2.30–2.47)
Moderately-to-Severely Frail	3844 (4.66)	1213 (1.26)	2.31 (2.15–2.49)
2–3 years, n (%)			
Nonfrail	68,426 (82.88)	90,559 (93.86)	1.00 (reference)
Mildly Frail	11,623 (14.08)	5041 (5.22)	2.10 (2.02–2.19)
Moderately-to-Severely Frail	2511 (3.04)	882 (0.91)	1.90 (1.74–2.07)
3–4 years, n (%)			
Nonfrail	71,786 (86.95)	91594 (94.93)	1.00 (reference)
Mildly Frail	8943 (10.83)	4137 (4.29)	1.84 (1.76–1.92)
Moderately-to-Severely	1831 (2.22)	751 (0.78)	1.55 (1.41–1.71)
4–5 years, n (%)			
Nonfrail	74,015 (89.65)	92,388 (95.76)	1.00 (reference)
Mildly Frail	7257 (8.79)	3500 (3.63)	1.70 (1.62–1.78)
Moderately-to-Severely Frail	1288 (1.56)	594 (0.62)	1.29 (1.16–1.43)

Abbreviations: CFI, claims-based frailty index; CI, confidence interval; n, frequency; OR, odds ratio; PD, Parkinson's disease.
[a] Claims-based frailty index (CFI) category is measured using standardized thresholds: Nonfrail (CFI <0.25), mildly frail (CFI = 0.25–0.34), moderately-to-severely frail (CFI ≥0.35).
[b] The five 12-month time windows include: 0–1 year, 1–2 years, 2–3 years, 3–4 years, and 4–5 years prior to PD diagnosis/control reference date.
[c] PD diagnosis date is the date PD was first diagnosed in 2009, and control reference date is a randomly selected date in 2009 for eligible controls.
[d] OR was adjusted for age, sex, race/ethnicity, and use of medical care.

3. Results

3.1. Beneficiaries' characteristics

Compared to controls (N = 96,482), PD cases (N = 82,560) were more likely to be male, non-Hispanic White, and older (Table 1). The mean (SD) CFI score for PD cases in the final 12 months leading up to PD diagnosis was 0.27 (0.08), with 47.5 % nonfrail, 38.2 % mildly frail, and 14.3 % moderately-to-severely frail. For controls, the mean (SD) of CFI scores was 0.17 (0.06), with 90.0 % nonfrail, 8.1 % mildly frail, and 1.9 % moderately-to-severely frail (Table 1). The mean frailty scores in this final year leading up to PD diagnosis or control reference date were higher in PD cases compared to controls ($p < 0.001$).

3.2. Frailty assessment

In all five time-windows, the mean CFI scores were higher in cases than controls ($p < 0.001$). The mean (SD) CFI score for PD cases was 0.17 (0.06) in the 4–5 year time window, and increased to 0.27 (0.08) in the 0–1 year time window (Supplementary Table 1). While the mean CFI scores for both cases and controls increased with proximity to PD diagnosis or control reference date, the trend was statistically significant only for PD cases ($p < 0.05$). When examining the OR between frailty

and PD, we similarly observed that the OR increased with proximity to PD diagnosis or control reference date (Table 2). We observed that mildly frail (OR = 1.70, 95 % CI 1.62–1.78) and moderately-to-severely frail (OR = 1.29, 95 % CI 1.16–1.43) were positively associated with PD in the 4–5 year time window prior to diagnosis (Table 2) and the association strengthened in the final year leading up to diagnosis: mildly frail (OR = 7.75, 95 % CI 7.51–7.99); moderately-to-severely frail (OR = 10.22, 95 % CI 9.63–10.86).

When examining the CFI variables in the final year leading up to PD diagnosis or control reference date, we observed that 34 out of the 93 CFI variables were positively associated with PD (Fig. 1). Supplementary Table 2 includes all individual ORs, 95 % CIs, and frequency of cases and controls for individual CMS-established ICD-9-CM codes included in the top three CFI variables most positively associated with PD: "organic psychotic conditions," "symptoms," and "other psychoses." In the 12 months prior to PD diagnosis, the CFI variable "organic psychotic conditions" [individual CMS-established ICD-9-CM codes Supplementary Table 2a] had the most marked association with PD (OR = 4.63, 95 % CI 4.50–4.77) (Fig. 1). The next two CFI variables that were most strongly positively associated with PD included: "symptoms," [individual CMS-established ICD-9-CM codes including signs and symptoms suggestive of PD in addition to signs and symptoms of other diseases/medical conditions; Supplementary Table 2b] (OR = 3.87, 95 % CI 3.73–4.00) (Fig. 1), and "other psychoses" [individual CMS established ICD-9-CM codes suggestive of various mood disorders; Supplementary Table 2c] (OR = 3.46, 95 % CI 3.34–3.58) (Fig. 1).

Twenty-two out of the 93 variables were inversely associated with PD in the 12 months prior to diagnosis (Fig. 2). The top three CFI variables most strongly inversely associated with PD included: "allergy and clinical immunology" (OR = 0.43, 95 % CI 0.32–0.56), "oxygen delivery systems and related supplies" (OR = 0.58, 95 % CI 0.54–0.63), and "therapeutic drug assays" (OR = 0.58, 95 % CI 0.48–0.70) (Fig. 2).

3.3. Sensitivity analysis

The mean (SD) CFI scores did not change after excluding signs and symptoms most clinically associated with PD in our sensitivity analysis. The frequency and percentage of beneficiaries categorized as nonfrail, mildly frail, and moderately-to-severely frail in each 12-month period across the five years were similar as well (Supplementary Table 3; Sensitivity Analysis). The top three CFI variables and associated ORs most positively associated with PD slightly changed in our sensitivity analysis to "organic psychotic conditions (OR = 4.20, 95 % CI 4.06–4.35),""other psychoses (OR = 3.92, 95 % CI 3.75–4.09)," and "other disorders of the central nervous system (OR = 2.78, 95 % CI 2.68–2.89)." While "symptoms" was still positively associated with PD, the OR decreased after excluding codes suggestive of motor and non-motor symptoms of PD (OR = 2.04, 95 % CI 1.98–2.09).

4. Discussion

In this large population-based case-control study, we demonstrated that frailty is positively associated with PD in all five individual time-windows prior to PD diagnosis/control reference date and that the association was strongest in the 12 months prior to PD diagnosis date. We also observed that psychiatric and cognitive disorders within the CFI were more strongly associated with PD as compared to other CFI variables in the 12 months prior to PD diagnosis. Our study has several important strengths. We used CFI, a well-established and validated method for measuring frailty when using claims data, which has been shown to outperform other claims-based frailty models [23]. The CFI accounts for the total number of diseases, symptoms, and disabilities

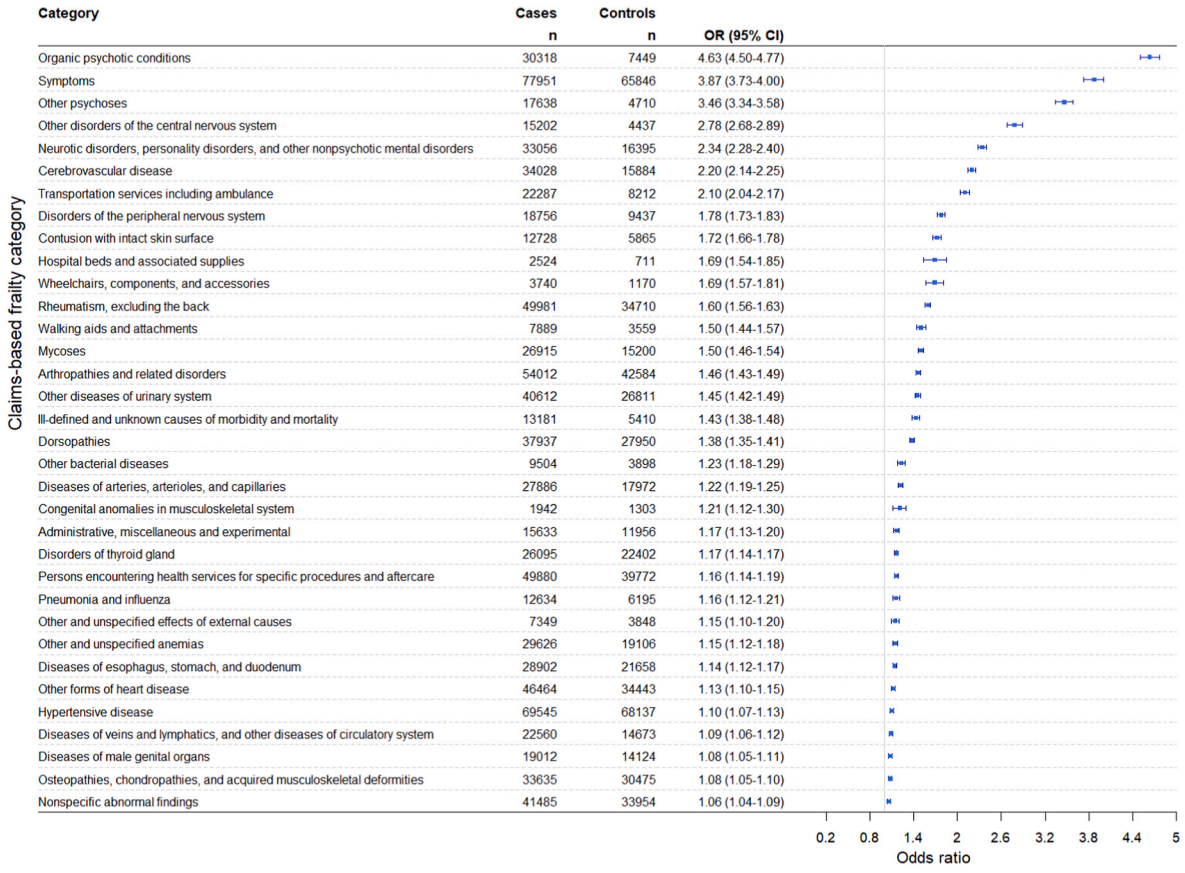


Fig. 1. Odds ratios (ORs) and the 95 % confidence intervals (CIs) for variables in the claims-based frailty index (CFI) that were positively associated with PD in the final 12 months prior to PD diagnosis or control reference date. Note: OR was adjusted for age, sex, race/ethnicity, and use of medical care.

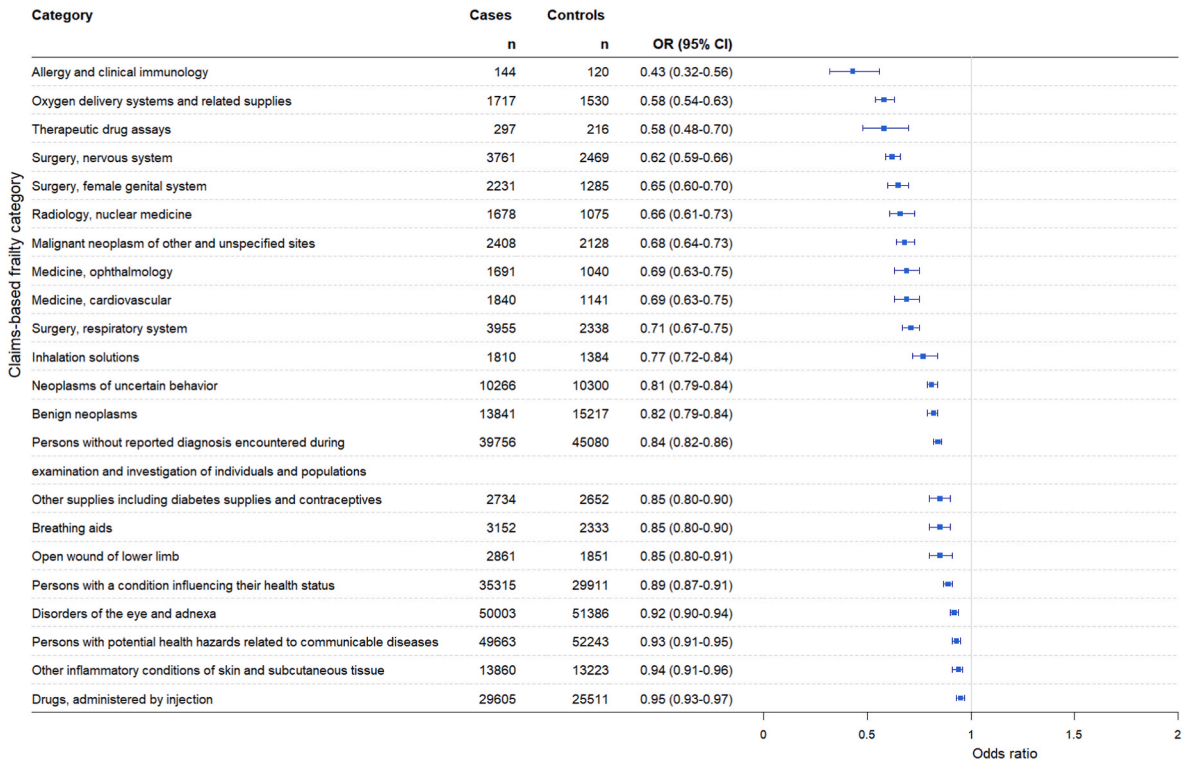


Fig. 2. Odds ratios (ORs) and the 95 % confidence intervals (CIs) for variables in the claims-based frailty index (CFI) that were inversely associated with PD in the final 12 months prior to PD diagnosis or control reference date.
Note: OR was adjusted for age, sex, race/ethnicity, and use of medical care.

using claims data. Predictors in the CFI model use a variety of data including ICD-9-CM, CPT, and HCPCS codes to avoid omission of key predictors that may not be used in clinical frailty models. Our study offers unique insights into the temporal association of frailty and PD diagnosis, supporting the notion that frailty may serve as an important risk factor for PD and should be considered at the time of PD diagnosis particularly as it relates to the management and treatment of PD symptoms.

The clinical importance of frailty is gaining increasing recognition in neurology [26] and in PD [12–17,27–32]. The largest and most comprehensive study to date used a national sample of older Medicare beneficiaries diagnosed with PD [16]. In this study, researchers applied the CFI model to assess frailty levels and examined associations with clinical outcomes in 62,786 beneficiaries with PD diagnosed in 2013. Our study findings, demonstrating a higher prevalence of frailty in PD during the prodromal phase, were consistent with that Medicare claims-based study examining prevalent PD [16]. Specifically, they found that frail individuals with established PD were older, exhibited a greater burden of comorbidities, and experienced poorer health outcomes compared to their non-frail counterparts [16]. These findings, in conjunction with ours, support using the CFI across the spectrum of PD, from the prodromal phase to established disease. Studying frailty in the prodromal phase may minimize the potential confounding effect of PD disease severity on frailty scores, given the potential overlap of PD symptomatology and frailty variables, a limitation often acknowledged in studies of frailty in prevalent PD [16,32]. Studies of frailty during the prodromal phase of PD are limited to only two studies to date – with one employing the frailty phenotype model [19] and another using a frailty index with limited variables [18]. Both were conducted in European populations. The frailty phenotype model, while it is simple to use, is known to have substantial overlap with PD symptomatology and other clinical features [10], which may lead to an overestimation of frailty in PD cases compared to controls. The frailty index consists of only 38 variables may omit some key aspects of frailty, particularly in PD [33]. In contrast, the CFI model used in this study contained 93 variables comprised of the combination of diseases, symptoms, and disabilities using multiple data sources from CMS (e.g., hospital vs. outpatient, and diagnosis vs. procedure codes) [22,23,33].

Using Medicare, a population-based dataset that covers over 98 % of Americans aged 65 and older, allowed us to focus on the elderly US population that is at higher risk for both PD and frailty. While one of the prior studies has provided valuable insights on how frailty differentially impacts PD cases and controls in the years leading up to PD diagnosis or control reference date [19], the focus on a mixture of middle-aged and older individuals may limit its generalizability in the US. The majority of adults aged 65 and older in the US are eligible for Medicare coverage for health-related expenses, however, this is not the case for individuals <65 years of age. Frailty may be underestimated when combining middle-aged and older individuals due to key differences in how frailty affects diverse age groups. Additionally, adults of various age demographics may access health care settings differently due to age-related comorbidities more common with age, such as cancer or stroke [34]. Similarly, the other prodromal PD frailty study from Greece used a small sample size from a homogenous group of Greek community-dwelling adults [18]. Using Medicare data to study frailty in prodromal PD in demographically and geographically diverse US populations aged 65 and older makes our results more generalizable to the US population of older adults and may inform future studies assessing frailty in neurodegenerative diseases.

There has been a growing interest in understanding the relationship between frailty and PD given the effects of frailty on movement, cognition and overall health. Frailty in PwP is associated with greater disease severity as measured by higher unified Parkinson's disease rating scale scores, recurrent falls, loss of independence, decreased quality of life, institutionalization, and higher use of medical care [12,13]. While the exact underlying mechanisms of frailty in PD are still unfolding, an inability to recover from a stressful event due to age-related changes to multiple physiological systems that interact

cumulatively and detrimentally, often describes the frail older adult [35]. The proposed mechanisms involved in the onset of frailty syndrome include chronic inflammation and oxidative stress, which have also been described in neurodegeneration [36,37]. Frailty in prodromal PD likely represents a combination of direct organ pathology due to PD [38] and comorbid conditions contributing to worse overall health. Future studies are needed to understand whether frailty mechanisms differ in PD compared to other aging adults without neurodegeneration and whether these differences contribute to more adverse outcomes or acceleration of PD symptoms.

There are several potential limitations of this study. Medicare is limited to specific patient populations including adults 65 years of age and older, however, our analysis was limited further to beneficiaries aged 70 years and older to allow us to compute the CFI using the full five-year assessment windows prior to PD diagnosis/control reference date. As a result, our findings are generalizable to those elderly adults who were healthy enough to survive until age 70. Nevertheless, we applied the same inclusion criteria for both cases and controls. Future studies should examine frailty in prodromal PD in younger individuals given that Medicare is only population based for those $\geq$65 in the US. We were also unable to examine frailty in beneficiaries enrolled in a Medicare Advantage plan (Part C) given that their data are not always submitted to CMS. In addition, Medicare data are not collected for primary research purposes but rather from health care provider charges submitted to CMS for reimbursement, therefore our codes rely on accurate provider diagnoses and charge entries by billing staff. However, previous studies have shown that the accuracy of Medicare claims has improved over time [39]. Frailty measured from claims data is only a proxy for frailty, and the specific CFI used in this study is based on deficit accumulation using 12 months of retrospective claims data and may not capture symptom severity or management. Additionally, CFI variables include deficits that may be suggestive of PD motor and non-motor symptoms. Therefore, frailty scores in PD may be falsely inflated compared to controls. However, there are equally important medical conditions, such as certain types of cancer, which may contribute strongly to frailty and have been reported to be inversely associated with PD [40,41]. Furthermore, the CFI model has previously been applied successfully to prevalent PD cases, differentiating between frail and non-frail individuals, and revealing poorer outcomes in the frail PD group [16]. In our sensitivity analyses that excluded codes suggestive of motor and non-motor symptoms of PD, there was no material change to our results. Finally, the association between frailty and prodromal PD, identified in this study, may not be causally related, as PD has a long prodromal phase and we were limited to only 5 years prior to PD diagnosis date. Future studies should examine whether the frailty syndrome itself is part of the prodromal period of PD. Despite these limitations, this study provides unique insights into the changes in frailty as an individual approaches PD diagnosis. Our work highlights the potential value of incorporating frailty assessment into the diagnostic workup of patients undergoing evaluation for neurological conditions such as PD, prior to a formal diagnosis. This period represents a critical window of opportunity to identify individuals at higher risk and to guide early clinical decision-making.

5. Conclusion

This US population-based study offers important insights into the temporal relationship between frailty and PD diagnosis and provides evidence that PD cases are more frail than the general elderly population as early as five years before their diagnosis. Health care providers should be screening newly diagnosed PD patients for frailty given the adverse effects of frailty on both motor and non-motor symptoms, overall quality of life, morbidity, and life expectancy.

CRediT authorship contribution statement

George K. Karway: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jordan A. Killion:** Writing – review & editing, Resources, Methodology, Investigation. **Irene M. Faust:** Writing – review & editing, Methodology. **Kassu M. Beyene:** Writing – review & editing, Methodology. **Brad A. Racette:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization. **Alejandra Camacho-Soto:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization.

Data statement

The de-identified individual level research data and associated materials used in this study cannot be made publicly available due to data use agreements with the Centers for Medicare & Medicaid Services (CMS). We obtained the data through a formal Data Use Agreement with CMS via a secure, CMS-approved data access method. The data we used are a custom dataset as described in the methods. All summary data that we were able to share are contained in the manuscript and the supplementary materials.

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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.parkreldis.2025.107965.

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