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# Association between frailty and cognitive performance across healthcare settings

**Myriam Oviedo Briones**
myriamr.oviedo@salud.madrid.org

Fundación para la Investigación e Innovación Biomédica del Hospital Universitario Infanta Sofía y Hospital Universitario del Henares, Madrid, Spain

**Alejandro Alvarez Bustos**
Universidad Villanueva

**Ángel Rodriguez-Laso**
Unidad Docente Multiprofesional de Atención Familiar y Comunitaria Centro. Comunidad de Madrid. Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12) ES

**Leocadio Rodriguez Mañas**
Fundación para la Investigación Biomédica del Hospital Universitario de Getafe

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## Abstract

**Objective:**
To examine the association between frailty and longitudinal cognitive decline in older adults across different healthcare settings.

**Methods:**

This is a multicenter longitudinal cohort study. A total of 1,440 individuals aged ≥75 years from five European countries were recruited from four clinical settings: geriatric inpatient wards, geriatric outpatient clinics, primary care, and nursing homes.
Cognitive outcomes were assessed using the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) at baseline and after 1-year follow-up. Frailty was evaluated using eight instruments: the Frailty Phenotype, FRAIL scale, SHARE-FI, 3-item Frailty Trait Scale (FTS-3), 5-item Frailty Trait Scale (FTS-5), 35-item Frailty Index (FI-35), Gérontopôle Frailty Screening Tool (GFST), and the Clinical Frailty Scale (CFS). To explore the association between frailty and cognitive decline, we used linear regression (MMSE), and logistic regression models (CDR). All models were adjusted for age, sex, and Charlson Comorbidity Index and stratified by clinical setting.

**Results:**
Among the 1,440 participants included from five European countries, most frailty scales were significantly associated with cognitive decline and clinically significant cognitive impairment. Particularly the FI-35 [△MMSE $\beta$ (95%CI) -2.00 (-2.32, -1.69); CDR OR (95%CI) 4.81 (3.78, 6.13)] and FTS-5 △MMSE $\beta$ (95%CI) -2.02 (-2.37, -1.66); CDR OR (95%CI) 4.49 (3.40, 5.93) scale, showed the most consistent associations with both cognitive outcomes. Although the magnitude of associations varied across healthcare settings, frailty measures remained significant predictors in several environments, particularly in hospital-based and institutional settings.

**Conclusions:** Frailty is strongly associated with cognitive decline in older adults across different care settings. Incorporating frailty assessment into routine clinical practice may facilitate earlier identification of individuals at risk of cognitive decline and support the development of targeted preventive strategies.


## BACKGROUND

The aging population represents a major global demographic shift, posing important challenges for healthcare systems worldwide [1]. As life expectancy increases, a growing proportion of older adults live with multiple chronic conditions, leading to a higher prevalence of frailty [2]. Frailty is a clinical syndrome characterized by diminished physiological reserve and increased vulnerability to stressors, resulting in adverse outcomes such as falls, disability, hospitalization, and mortality [3]. Closely associated with frailty is cognitive impairment, which critically affects an individual's ability to perform daily activities and significantly reduces quality of life [4].

Cognitive decline is not an inevitable consequence of aging but becomes increasingly prevalent among older adults, particularly among those who are frail [5]. Early identification of cognitive impairment is essential to facilitate timely interventions that may slow progression, enhance cognitive function, and support independence [5]. Traditional cognitive assessment tools, such as the Mini-Mental State Examination (MMSE) [6] and the Clinical Dementia Rating (CDR) [7], are widely used to detect cognitive impairment, although their performance may vary across populations and clinical contexts [5].

In recent years, frailty scales have gained increasing attention not only for assessing physical vulnerability but also as potential indicators of cognitive health. Systematic reviews and meta-analyses have consistently demonstrated a significant association between frailty and poorer cognitive performance, with frail older adults showing worse outcomes on both global and domain-specific cognitive tests [8]. Notably, specific components of frailty, such as slow gait speed and weak grip strength, have been linked to declines in executive function and processing speed [9]. Despite the proliferation of frailty assessment tools—more than 60 have been described [10]—there is still no universally accepted gold standard, and their predictive value for cognitive outcomes remains heterogeneous across studies [11].

Emerging constructs such as "cognitive frailty," which combines physical frailty with cognitive impairment in the absence of dementia, further highlight the close relationship between these syndromes and the need for integrated assessment approaches [12]. However, inconsistencies in operational definitions, measurement tools, and reported psychometric properties continue to limit comparability between studies and hinder their translation into routine clinical practice [13].

Although several studies have explored the association between frailty and cognitive impairment, most have evaluated this relationship using a single frailty instrument and within a single clinical setting. Direct comparisons between different frailty scales remain limited, and few studies have examined their predictive performance across diverse healthcare environments [14]. Given that frailty prevalence, functional status, and clinical complexity vary substantially across settings such as hospitals, outpatient clinics, nursing homes, and primary care, understanding how different frailty instruments perform in these contexts is particularly relevant for clinical decision-making.

Thus, the present study aims to examine the association between eight frailty scales and cognitive outcomes among individuals aged 75 years and older recruited from different healthcare settings, including acute geriatric wards, outpatient clinics, primary care facilities, and nursing homes [15]. Specifically, we aimed to compare the predictive performance of these frailty instruments for two cognitive outcomes: longitudinal cognitive decline measured by the MMSE and incident clinically significant cognitive impairment assessed using the CDR. By evaluating the consistency and strength of these associations across clinical contexts, this study seeks to identify which frailty instruments provide the most reliable prediction of cognitive deterioration in older adults and to inform the selection of frailty assessment tools in clinical practice.

## MATERIAL AND METHODS

The FRAILTOOLS Project was an observational, longitudinal, and prospective study that recruited 1,440 participants aged 75 years and older from a variety of clinical and social settings. These included acute geriatric wards, geriatric outpatient clinics, primary care centers, and nursing homes across Spain, Italy, France, the United Kingdom, and Poland. The general exclusion criteria included an MMSE score of ≤20 points, terminal illness with a life expectancy of ≤6 months, a Barthel Index score of < 90, except for nursing home residents, from whom the cutoff was set at less than 40. Detailed methods have been published elsewhere [15].

Data collection was performed by experienced healthcare professionals of each setting. The Frailtools project was approved by the Ethics committee of each participating center and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent before participating. Participants were followed up for 12 months.

**Variables**

*Cognitive assessment*

*Cognitive performance was evaluated at baseline and at follow-up.*

**Mini Mental State Examination (MMSE):** This is a commonly employed assessment tool for screening cognitive impairment in older adults and monitoring changes in cognitive function over time [16]. The MMSE evaluates seven cognitive domains, including orientation to time and place, repetition, verbal recall, attention and calculation, language skills, and visual construction.

Changes in MMSE scores were calculated by subtracting the baseline scores from the final scores.

**The Clinical Dementia Rating (CDR)** is a crucial tool for assessing the severity of dementia, utilized in clinical settings and research [17]. This tool evaluates cognitive impairment across six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Using a scale from 0 (no dementia) to 3 (severe dementia), the CDR is administered through interviews with the patient and an informant.

Incident cognitive impairment was defined as an increase of ≥0.5 points in the CDR.

*Frailty assessment*

**The Frailty Phenotype (FP)** classifies an individual as frail if they meet three or more of the following five criteria: involuntary weight loss of 4.5 kg or more, self-reported exhaustion, low physical activity levels, reduced handgrip strength, and slow gait speed [18]. According to this tool, individuals are classified as robust (0 criteria), prefrail (1–2 criteria), or frail (≥3 criteria).

**The Survey of Health, Ageing and Retirement in Europe Frailty Index (SHARE-FI**) is an adaptation of the FP that incorporates handgrip strength along with four self-reported items: physical exhaustion, appetite loss, difficulties in walking, and low physical activity levels [19]. To determine if a participant is frail, the data is input into a web-based calculator. A score of less than 6 for females or less than 7 for males indicates frailty.

**The 5-item Frailty Trait Scale (FTS-5)** evaluates nutritional status via the Body Mass Index (BMI), balance through the Romberg test, activity levels with the Physical Activity Scale for the Elderly (PASE), along with poor handgrip strength and slow gait speed [20]. Each item is scored from 0 (optimal performance) to 10 (poor performance), and the total score ranges from 0 (robust) to 50 (maximum frailty), with a cutoff of greater than 25 to identify frailty.

**The 3-item FTS (FTS-3)** evaluates the BMI, balance, and physical activity components of the FTS-5 [21]. Each item is scored from 0 (best) to 10 (worst). A score greater than 15 is used as the threshold for identifying frailty.

**The FRAIL scale** assesses five self-reported components: Fatigue, Resistance, Ambulation, Illness, and Weight Loss [22]. Scores range from 0 to 5 (0 representing the best condition and 5 the worst), with frailty determined by the presence of three or more components.

**The 35-item Frailty Index (FI-35**) is based on the premise that aging is linked to the accumulation of health deficits, which can include signs, symptoms, chronic diseases, disabilities, and laboratory abnormalities [23]. This quantitative model for the current project utilized 35 items derived from medical records and/or self-reports from participants. The index is calculated as the ratio of the number of deficits present to the total number of considered deficits (n=35), with a cutoff of ≤0.25 indicating frailty.

**The Gerontopole Frailty Screening Tool (GFST)** begins with an introductory questionnaire assessing signs and symptoms that may indicate frailty [24]. In the second section, the clinician provides their assessment of the individual's frailty status, which informs the final determination of frailty.

**The Clinical Frailty Scale (CFS)** utilizes clinical descriptors and pictographs to categorize older adults based on their level of vulnerability, scoring from 1 (very fit) to 9 (terminally ill) [25]. This assessment relies on the clinician's guided judgment, with a final score of 4 or higher indicating frailty.

**Statistical Analysis**

Baseline characteristics were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Descriptive analyses were conducted for the overall sample and stratified by clinical setting (geriatric wards, nursing homes, outpatient clinics, and primary care). Additionally, we compared baseline characteristics between included and non-included participants at follow-up.

To examine the association between frailty and cognitive decline, separate regression models were performed for each frailty scale. Linear regression models were used to evaluate the relationship between frailty categories and changes in cognitive performance measured by changes in Mini-Mental State

Examination (△MMSE) scores over the follow-up period. Results are presented as beta coefficients ($\beta$) with 95% confidence intervals (CI). Logistic regression models were used to assess the association between frailty and cognitive impairment defined by the Clinical Dementia Rating (CDR). Results are reported as odds ratios (OR) with 95% confidence intervals.

Analyses were conducted for the overall cohort and stratified by clinical setting (geriatric wards, outpatient clinics, primary care, and nursing homes) to explore potential differences in the association between frailty and cognitive outcomes across healthcare environments.

All models were adjusted for age, sex, and the Charlson Comorbidity Index. Additional covariates were not included in the main models to avoid overadjustment and potential collinearity, as several health and functional domains are already incorporated into the frailty scales.

## RESULTS

## Participant characteristics (Table 1)

Table 1
Baseline Characteristics of Participants and 12-Month Follow-up Outcomes Across Healthcare Settings

| Variable | Geriatric wards | | | Nursing homes | | | Outpatient clinics | | |
|---|---|---|---|---|---|---|---|---|---|
| | Participants at baseline (n = 361) | Participants followed-up (n = 199) | Participants lost to follow up (n = 162; 44.9%) | Participants at baseline (n = 358) | Participants followed-up (n = 269) | Participants lost to follow up (n = 89; 24.9%) | Participants at baseline (n = 381) | Participants followed-up (n = 296) | Participants lost to follow up (n = 85; 22.3%) |
| | Mean (SD) | | | | | | | | |
| **Age (years)** | 83.2 (5.4) | **82.7 (5.0)*** | **83.9 (5.8)*** | 85.8 (5.9) | **86.2 (5.6)*** | **84.5 (6.3)*** | 79.9 (4.2) | 79.9 (4.3) | 80.0 (4.1) |
| **Barthel Index** | 96.0 (4.5) | 96.2 (4.5) | 95.7 (4.5) | 76.8 (19.2) | **79.8 (17.8)***** | **67.9 (20.6)***** | 97.5 (3.4) | 97.2 (3.7) | 98.1 (2.8) |
| **Lawton and Brody Index** | | | | | | | | | |
| **Men (5 items)** | 3.5 (1.5) | **3.7 (1.4)*** | **3.2 (1.5)*** | 2.1 (1.1) | 2.2 (1.2) | 1.9 (0.8) | 4.7 (0.8) | 4.7 (0.7) | 4.7 (0.8) |
| **Women (8 items)** | 5.5 (2.5) | 5.8 (2.4) | 5.2 (2.5) | 2.0 (1.8) | **2.2 (1.9)**** | **1.5 (1.3)**** | 7.4 (1.3) | 7.3 (1.5) | 7.6 (0.8) |
| **Age Adjusted Charlson Index** | 6.2 (2.4) | 6.2 (2.6) | 6.3 (2.1) | 6.1 (1.9) | **6.3 (1.9)*** | **5.8 (1.9)*** | 4.8 (2.2) | 4.9 (2.4) | 4.5 (1.4) |
| **PASE** | 52.6 (53.1) | **59.1 (55.3)*** | **44.7 (49.2)*** | 17.6 (26.5) | **20.9 (28.2)***** | **7.6 (17.7)***** | 98.7 (68.5) | 103.0 (72.0) | 89.6 (59.3) |
| **BMI** | 26.1 (4.5) | 25.8 (4.4) | 26.5 (4.5) | 26.0 (5.4) | 26.3 (5.4) | 25.0 (5.4) | 27.2 (4.3) | **27.6 (4.4)*** | **26.4 (4.0)*** |
| | Number (%) | | | | | | | | |
| **Gender (Female)** | 197 (54.7) | 108 (54.3) | 89 (55.3) | 250 (69.8) | 191 (71.0) | 59 (66.3) | 208 (61.4) | 143 (61.6) | 65 (60.7) |
| **Partner status** | | | | | | | | | |
| **Married** | 143 (39.7) | 85 (42.7) | 58 (36.0) | 49 (13.8) | 39 (14.6) | 10 (11.2) | 177 (52.2) | **117 (50.4)***** | **60 (56.1)***** |
| **Divorced** | 11 (3.1) | 4 (2.0) | 7 (4.3) | 17 (4.8) | 14 (5.2) | 3 (3.4) | 21 (6.2) | **11 (4.7)***** | **10 (9.3)***** |
| **Widowed** | 181 (50.3) | 99 (49.7) | 82 (50.9) | 239 (67.1) | 175 (65.5) | 64 (71.9) | 125 (36.9) | **90 (38.8)***** | **35 (32.7)***** |
| **Single** | 25 (6.9) | 11 (5.5) | 14 (8.7) | 51 (14.3) | 39 (14.6) | 12 (13.5) | 16 (4.7) | **14 (6.0)***** | **2 (1.9)***** |
| **Cohabitation** | | | | | | | | | |
| **Alone** | 141 (39.2) | **66 (33.2)***** | **75 (46.6)***** | 12 (3.4) | **9 (3.3)***** | **3 (3.4)***** | 131 (38.6) | **89 (38.4)***** | **42 (39.3)***** |
| **Spouse** | 142 (39.4) | **84 (42.2)***** | **58 (36.0)***** | 13 (3.6) | **10 (3.7)***** | **3 (3.4)***** | 174 (51.3) | **115 (49.6)***** | **59 (55.1)***** |
| **Family member** | 59 (16.4) | **34 (17.1)***** | **25 (15.5)***** | 5 (1.4) | **2 (0.7)***** | **3 (3.4)***** | 27 (8.0) | **23 (9.9)***** | **4 (3.7)***** |
| **Professional caregiver** | 7 (1.9) | **6 (3.0)***** | **1 (0.6)***** | 249 (69.6) | **178 (66.2)***** | **71 (79.8)***** | 1 (0.3) | **1 (0.4)***** | **0 (0.0)***** |
| **Others** | 11 (3.1) | **9 (4.5)***** | **2 (1.2)***** | 79 (22.1) | **70 (26.0)***** | **9 (10.1)***** | 6 (1.8) | **4 (1.7)***** | **2 (1.9)***** |
| **Missing** | 1 | | 1 | | | | 1 | | 1 |

*Notes.* SD: Standard deviation, PASE: Physical Activity Scale for the Elderly, BMI: Body mass index.

*p < 0.05. **p < 0.01. ***p < 0.001

A total of 1,440 participants were included at baseline across four healthcare settings (geriatric wards, nursing homes, outpatient clinics, and primary care). Baseline characteristics and follow-up status at 12 months are presented in Table 1.

Of the initial cohort, 361 participants were recruited from geriatric wards, 358 from nursing homes, 381 from outpatient clinics, and 340 from primary care. After 12 months, 996 participants (69.2%) completed follow-up, while 444 (30.8%) were lost to follow-up, with the highest proportion observed in geriatric wards (44.9%), followed by nursing homes (24.9%), outpatient clinics (22.3%), and primary care (22.3%).

## Association Between Frailty Scales and Cognitive Decline

# Overall Association with MMSE Change

Most frailty scales showed significant associations with cognitive decline measured by MMSE in the overall sample, although the magnitude of the associations varied across instruments and clinical settings (Table 2).

Table 2
Association Between Frailty Scales and Cognitive Decline Measured by MMSE Across Healthcare Settings

| | All | Geriatric Wards | Nursing homes | Geriatric Clinic | Primary Care |
|---|---|---|---|---|---|
| | β (95%CI) | β (95%CI) | β (95%CI) | β (95%CI) | β (95%CI) |
| **FP Prefrail** | -0.33 (-0.86, 0.20) | 1.24 (-1.07, 3.54) | -2.14 (-4.34, 0.06) | -0.22 (-0.84, 0.39) | -0.07 (-0.98, 0.84) |
| **FP Frail** | **-1.40 (-1.96, -0.83)** | 0.78 (-1.50, 3.06) | -3.60 (-5.76, -1.43) | -0.36 (-1.20, 0.47) | -0.60 (-1.65, 0.44) |
| **FRAIL Prefrail** | **-0.90 (-1.25, -0.55)** | 0.12 (-0.92, 1.15) | **-1.49 (-2.55, -0.43)** | -0.10 (-0.60, 0.40) | -0.14 (-0.68, 0.41) |
| **FRAIL Frail** | **-1.32 (-1.72, -0.91)** | -0.03 (-1.07, 1.00) | **-1.24 (-2.33, -0.16)** | -0.42 (-1.29, 0.44) | -0.51 (-1.41, 0.38) |
| **FI35 Frail** | **-2.00 (-2.32, -1.69)** | **-1.62 (-2.26, -0.98)** | **-2.93 (-4.20, -1.66)** | **-1.22 (-1.87, -0.57)** | **-0.75 (-1.42, -0.07)** |
| **CFS Frail** | **-1.69 (-2.00, -1.38)** | **-1.22 (-1.87, -0.57)** | **-1.99 (-2.74, -1.24)** | **-0.81 (-1.44, -0.17)** | -0.27 (-0.93, 0.38) |
| **SHARE. FI Prefrail** | -0.10 (-0.66, 0.47) | 0.36 (-1.07, 1.79) | -0.48 (-2.42, 1.46) | -0.13 (-0.88, 0.62) | 0.39 (-0.49, 1.26) |
| **SHARE. FI Frail** | **-1.28 (-1.86, -0.70)** | -0.25 (-1.60, 1.11) | **-2.07 (-3.91, -0.22)** | 0.03 (-0.86, 0.92) | -0.11 (-1.08, 0.86) |
| **GFST Frail** | **-1.73 (-2.03, -1.43)** | **-1.53 (-2.23, -0.83)** | **-1.15 (-2.05, -0.25)** | **-0.92 (-1.40, -0.44)** | **-1.37 (-1.89, -0.86)** |
| **FTS-3 Frail** | **-2.05 (-2.37, -1.74)** | **-1.82 (-2.44, -1.20)** | **-1.70 (-2.41, -0.99)** | -0.56 (-1.46, 0.33) | -0.53 (-1.38, 0.31) |
| **FTS-5Frail** | **-2.02 (-2.37, -1.66)** | **-1.01 (-1.92, -0.10)** | **-2.15 (-2.95, -1.35)** | **-1.22 (-2.09, -0.34)** | **-0.78 (-1.52, -0.03)** |

*Notes.* FP: Frailty Phenotype. SHARE-FI: Survey of Health. Ageing and Retirement in Europe Frailty Index. FTS-3: 3-item Frailty Trait Scale. FTS-5: 5-item Frailty Trait Scale. FI-35: 35-item Frailty Index. GFST: Gérontopôle Frailty Screening Tool. CFS: Clinical Frailty Scale.

[a]Cut-off scores: FP: ≥ 3. FRAIL: ≥ 3. FI-35: ≥0.25. CFS: ≥4. SHARE-FI: <6 females < 7 men. GFST: yes. FTS-3: ≥15. FTS-5: ≥25

In the overall sample, frailty defined by the FI-35 (β = −2.00; 95% CI: −2.32 to − 1.69), FTS-3 (β = −2.05; 95% CI: −2.37 to − 1.74), FTS-5 (β = −2.02; 95% CI: −2.37 to − 1.66), GFST (β = −1.73; 95% CI: −2.03 to − 1.43), and CFS (β = −1.69; 95% CI: −2.00 to − 1.38) showed the strongest associations with MMSE decline. Prefrailty categories generally showed weaker associations, with significant effects observed only for the FRAIL scale (β = −0.90; 95% CI: −1.25 to − 0.55).

Across settings, the strength of associations differed. In geriatric wards, significant associations were observed for FI-35, CFS, GFST, FTS-3, and FTS-5, while the FP and FRAIL scales were not significantly associated with cognitive decline. In nursing homes, FI-35 and FTS-5 showed the strongest associations, followed by SHARE-FI (only frail), CFS, GFST, FTS-3 and FRAIL. In contrast, FP demonstrated non-significant relationships.

In geriatric outpatient clinics, significant associations were identified for FI-35, CFS, GFST, and FTS-5, whereas FP, FRAIL, SHARE-FI, and FTS-3 were not significantly associated with MMSE decline. In primary care, fewer scales remained significantly associated, with GFST, FI-35, and FTS-5 showing significant although smaller effect sizes.

Overall, multidimensional frailty indices (FI-35, FTS-3, and FTS-5) and the GFST showed the most consistent associations with cognitive decline across settings, whereas phenotype-based or simpler screening tools such as FP and SHARE-FI demonstrated weaker and less consistent predictive performance.

# Association between frailty scales and cognitive impairment using CDR

Table 3 presents the association between frailty assessed using different scales and clinically significant cognitive impairment measured by the CDR across care settings.

Table 3
Association Between Frailty Scales and Clinical Dementia Rating (CDR) Across Healthcare Settings

| | | All | Geriatric Wards | Nursing homes | Geriatric Clinic | Primary Care |
|---|---|---|---|---|---|---|
| | | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| **FP** | **Prefrail** | **1.66 (1.02, 2.70)** | 2.39 (0.45, 12.69) | 8.53 (0.99, 73.45) | 1.91 (0.92, 3.99) | 0.60 (0.26, 1.39) |
| | **Frail** | **4.58 (2.77, 7.57)** | 2.73 (0.52, 14.31) | **22.56 (2.63, 193.51)** | **5.05 (2.08, 12.27)** | 1.32 (0.52, 3.37) |
| **Frail** | **Prefrail** | **2.20 (1.70, 2.85)** | 1.33 (0.71, 2.48) | **2.31 (1.17, 4.56)** | 1.62 (0.98, 2.68) | 1.35 (0.81, 2.23) |
| | **Frail** | **2.98 (2.23, 4.00)** | 1.49 (0.80, 2.78) | 1.85 (0.92, 3.72) | **4.32 (2.04, 9.16)** | 2.09 (0.99, 4.42) |
| **FI35** | **Frail** | **4.81 (3.78, 6.13)** | **4.86 (3.13, 7.56)** | **6.99 (2.70, 18.11)** | **3.25 (1.79, 5.89)** | **2.22 (1.23, 4.01)** |
| **CFS** | **Frail** | **4.32 (3.42, 5.45)** | **3.92 (2.51, 6.11)** | **2.68 (1.64, 4.37)** | **4.49 (2.51, 8.05)** | **2.48 (1.41, 4.38)** |
| **Share-FI** | **Prefrail** | 1.02 (0.67, 1.53) | 0.53 (0.22, 1.30) | 0.84 (0.24, 2.93) | 0.98 (0.47, 2.04) | 1.76 (0.79, 3.95) |
| | **Frail** | **2.54 (1.67, 3.88)** | 0.75 (0.32, 1.76) | 2.63 (0.81, 8.59) | 1.49 (0.63, 3.49) | **2.75 (1.11, 6.81)** |
| **GFST** | **Frail** | **3.54 (2.81, 4.46)** | **2.95 (1.85, 4.72)** | **1.97 (1.12, 3.47)** | **2.64 (1.65, 4.23)** | **3.57 (2.17, 5.86)** |
| **FTS3** | **Frail** | **3.87 (3.05, 4.92)** | **2.73 (1.78, 4.19)** | **2.15 (1.37, 3.38)** | **4.80 (2.10, 11.0)** | 1.58 (0.75, 3.36) |
| **FTS5** | **Frail** | **4.49 (3.40, 5.93)** | **2.49 (1.34, 4.64)** | **2.83 (1.70, 4.72)** | **5.27 (2.33, 11.9)** | **2.59 (1.37, 4.90)** |

*Notes.* FP: Frailty Phenotype. SHARE-FI: Survey of Health. Ageing and Retirement in Europe Frailty Index. FTS-3: 3-item Frailty Trait Scale. FTS-5: 5-item Frailty Trait Scale. FI-35: 35-item Frailty Index. GFST: Gérontopôle Frailty Screening Tool. CFS: Clinical Frailty Scale.

[a]Cut-off scores: FP: ≥ 3. FRAIL: ≥ 3. FI-35: ≥0.25. CFS: ≥4. SHARE-FI: <6 females < 7 men. GFST: yes. FTS-3: ≥15. FTS-5: ≥25

In the overall sample, frailty was consistently associated with higher odds of cognitive impairment across most instruments. The strongest associations were observed for the FI-35 (OR = 4.81; 95% CI: 3.78–6.13), Fried Frailty Phenotype (OR for the frail category = 4.58; 95% CI: 2.77–7.57), FTS-5 (OR = 4.49; 95% CI: 3.40–5.93), and the Clinical Frailty Scale (OR = 4.32; 95% CI: 3.42–5.45). Similarly, the Gérontopôle Frailty Screening Tool (OR = 3.54; 95% CI: 2.81–4.46) and FTS-3 (OR = 3.87; 95% CI: 3.05–4.92) showed significant associations with cognitive impairment. Prefrailty categories generally showed weaker associations, although significant effects were observed for the Fried phenotype and FRAIL scale.

Across clinical settings, the magnitude of associations varied. In geriatric wards, FI-35 (OR = 4.86; 95% CI: 3.13–7.56) and the Clinical Frailty Scale (OR = 3.92; 95% CI: 2.51–6.11) showed the strongest associations with cognitive impairment. In nursing homes, the FI-35 demonstrated the most robust association (OR = 6.99; 95% CI: 2.70–18.11). Although the Fried Frailty Phenotype showed a high nominal OR of 22.56 in this setting, its extremely wide confidence interval (2.63–193.51) indicates statistical instability, likely due to the very low prevalence of non-frail individuals experiencing cognitive impairment in this specific environment. In geriatric outpatient clinics, although FTS-5 and FTS-3 showed high odds ratios, the Clinical Frailty Scale (OR = 4.49; 95% CI: 2.51–8.05) provided greater statistical precision. In primary care, associations were generally weaker, although significant relationships were observed for GFST (OR = 3.57; 95% CI: 2.17–5.86), FTS-5 (OR = 2.59; 95% CI: 1.37–4.90), FI-35 (OR = 2.22; 95% CI: 1.23–4.01), and CFS (OR = 2.48; 95% CI: 1.41–4.38).

## DISCUSSION

This multicenter longitudinal study demonstrates that frailty is consistently associated with longitudinal cognitive deterioration among older adults across different healthcare settings. In this large cohort including participants from geriatric wards, nursing homes, outpatient clinics, and primary care, most frailty instruments evaluated were significantly associated with both cognitive decline measured by MMSE and clinically significant cognitive impairment assessed with CDR. These findings reinforce the growing evidence that frailty and cognitive impairment represent closely interconnected manifestations of biological vulnerability in aging [26, 27].

When comparing the predictive performance of the different frailty instruments, two frailty measures stand out for their strong and consistent associations across cognitive measures and settings: FI-35 and FTS-5. These findings suggest that instruments integrating multiple domains such as functional status, comorbidity, and global clinical judgment (FI-35) or including alternative items to that of the frailty phenotype (FTS-5) may better capture the complex mechanisms linking frailty and cognitive deterioration [28, 29].

In relation to clinical care settings, their predictive performance was stronger in geriatric wards and nursing homes. These settings include older adults with higher levels of multimorbidity, disability, and physiological vulnerability, where multidomain frailty measures may better reflect the overall biological reserve underlying cognitive trajectories [30]. In outpatient settings, both remained very strongly associated with MMSE deterioration, although results were less clear for CDR deterioration, suggesting that physical frailty manifestations may remain relevant in ambulatory populations [31].

Among the screening instruments, the GFST showed relatively consistent associations across settings, particularly in relation to clinically significant cognitive impairment. Its simplicity and multidimensional orientation may make it a practical option for routine frailty screening in environments where time and resources for more detailed assessments are limited [32, 33].

An important finding of this study is that the pattern of associations varied depending on the cognitive outcome considered. While several frailty instruments were associated with longitudinal changes in MMSE scores, the statistical significance of these associations was less consistent across healthcare settings. In contrast, frailty scales such as FI-35, FTS-5, CFS, and GFST showed a more consistent pattern of significant associations with CDR-defined cognitive impairment across multiple care environments.

Given the different statistical approaches used for MMSE (linear regression) and CDR (logistic regression), comparisons in the magnitude of these associations should be interpreted with caution. Instead, these findings suggest that the CDR may provide a more stable outcome measure across settings. This pattern may reflect the fact that the CDR captures clinically meaningful functional consequences of cognitive decline, whereas small variations in MMSE scores may be more susceptible to measurement variability and differences in baseline cognitive reserve [34, 35]. A major strength of this study is the inclusion of two complementary cognitive outcomes: the MMSE, providing a quantitative screening of global cognition, and the CDR, capturing clinically significant functional decline. By using the CDR as a robust outcome measure—rather than a predictor—we were able to validate that the association between frailty and cognitive health translates into meaningful clinical changes across all healthcare settings.

The relationship between frailty and cognitive deterioration may be explained by several shared biological mechanisms. Chronic low-grade inflammation, oxidative stress, vascular dysfunction, and mitochondrial impairment have been implicated in both frailty and neurodegeneration [36, 37]. These systemic processes may simultaneously affect skeletal muscle and brain function, supporting the concept of a common biological substrate underlying physical and cognitive vulnerability [38]. In addition, frailty may indirectly accelerate cognitive decline through behavioral and social pathways, including reduced physical activity, nutritional deficits, and social isolation, all of which contribute to neurodegenerative and vascular cognitive changes [39].

From a clinical perspective, these findings highlight the potential value of frailty assessment as part of the routine evaluation of older adults. Identifying frailty may not only help predict traditional geriatric outcomes but also allow clinicians to detect individuals at higher risk of cognitive deterioration and implement early preventive strategies [40]. Multidimensional instruments such as FI-35, FTS-5, and CFS appear particularly informative in this regard. However, the heterogeneity observed across healthcare settings suggests that instrument selection should be context-specific, balancing predictive accuracy with feasibility [41]. Simpler tools such as GFST may be especially useful in primary care and outpatient environments where rapid screening is required [32, 33].

This study has several strengths. It is a longitudinal study involving older adults from four clinical settings across five European countries, employed eight validated frailty assessment scales, and utilized a dual-outcome approach (MMSE and CDR) to ensure both psychometric and clinical sensitivity in detecting cognitive decline.

Nevertheless, some limitations must be acknowledged. First, frailty and cognition were measured using several different scales that evaluate distinct domains, limiting direct comparability across instruments. Second, despite the large overall sample, the relatively small number of participants in certain sub-groups—such as non-frail individuals in specific settings like nursing homes—and of cognitive deterioration events (as defined by the CDR) may have limited statistical power. This resulted in lower precision and wider confidence intervals for some associations, which should therefore be interpreted with caution. Third, although the MMSE and CDR are effective and widely used, they are not without limitations, particularly their subjectivity and dependence on informant information. Nonetheless, both remain key elements of standard dementia evaluation. Finally, since associations were assessed over a one-year period, any generalization to other time frames should be interpreted cautiously.

## CONCLUSIONS

Frailty is strongly associated with cognitive decline among older adults across different healthcare settings, particularly when assessed using FI-35 and FTS-5. These findings suggest that frailty assessment may help identify older adults at increased risk of clinically relevant cognitive deterioration. Incorporating frailty screening into routine geriatric assessment may therefore provide an opportunity for earlier detection of cognitive vulnerability and facilitate the implementation of preventive and personalized interventions across healthcare settings.

## Abbreviations

o **MMSE**
Mini-Mental State Examination
o **CDR**
Clinical Dementia Rating
o **FP**
Frailty Phenotype
o **SHARE-FI**
Survey of Health, Ageing and Retirement in Europe Frailty Index
o **FTS-3**
3-item Frailty Trait Scale
o **FTS-5**
5-item Frailty Trait Scale
o **FI-35**
35-item Frailty Index
o **GFST**

Gérontopôle Frailty Screening Tool
o **CFS**
Clinical Frailty Scale
o **CI**
Confidence Interval (Intervalo de confianza)
o **OR**
Odds Ratio (Razón de momios / Razón de probabilidades)
o **BMI**
Body Mass Index (Índice de Masa Corporal)
o **PASE**
Physical Activity Scale for the Elderly

## Declarations

- **Ethics approval and consent to participate:**

All participants who decided to participate in the study signed an informed consent form prior to their inclusion in the study.

The following Ethics Review Boards approved the protocol: Ethics Committee of Getafe University Hospital (Spain) with reference number A17/15; Ethics Committee of Fondazione Policlinico Gemelli Protocollo Unico, Università Cattolica del Sacro Cuore, Italy, with reference number 0027036/16–04/07/2016; Committee for the Defence of Individuals (C.P.P.P.) Sud-Ouest et Outre-Mer II (Gérontopôle de Toulouse, France) with reference number 2016-A00819–42; Health Research Authority (HRA, United Kingdom) with reference number IRAS Project ID 213693; Bioethics Committee of the Jagiellonian University (Poland) with reference number 122.6120.227.2016.

- **Consent for publication:** Not aplicable.
- **Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- **Competing interests:** The authors declare that they have no competing interests.
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The Sponsor will be responsible for providing an insurance policy if required by the regulations in each country and will fulfill all local legal requirements.

- **Availability of data and materials**

The Sponsor, in this case the FIB-HUG, is responsible for the data management including: Data base: data will be registered in digital form. Data validation: data will be validated according to contingency and frequency tables verified.

Applicable regulations for storage, transmittal and disclosure of subject information will be followed at all times. Following formal admission to the study will be recorded in the FIB-HUG case record in the usual way. Additionally, data will be held in Query-Case Report Form (eCRF) from Clindox company. These files will be identified by a study code and date of entry.

Representatives from the Sponsor and from the regulatory authorities will be given access to the records that relate to the study. They will have full access to the anonymous eCRFs for the purposes of data validation. At no time will this be done in such a way that an individual subject may be identified.

The datasets generated and/or analysed during the current study are available to any scientist who wishing to use them for non-commercial purposes, respecting the participant confidentiality.

- **Authors' contributions:** LRM conceptualized the study. MOB and AAB managed data collection. ARL performed the statistical analysis. MOB wrote the first draft of the manuscript. All authors read and approved the final manuscript.
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**Contributor Information**

Myriam Oviedo-Briones, EMail: myriamr.oviedo@salud.madrid.org.

Alejandro Alvarez Bustos: Email: a.alvarezbu@gmail.com

Angel Rodriguez Laso: arodriguez.laso@salud.madrid.org

Leocadio Rodriguez-Mañas, Email: leocadio.rodriguez@salud.madrid.org.

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