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Frailty and Health Outcomes in People 65 Years or Older Living With Dementia: A Systematic Review of the Literature

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Keywords: Alzheimer's disease | cognitive impairment | dementia | frailty | geriatric care

ABSTRACT

Introduction: Although frailty is considered a potentially modifiable risk factor for dementia, its influence on health outcomes in individuals with established dementia remains unclear. This study aims to systematize the current evidence to understand the impact of frailty on the development of adverse outcomes in older adults with dementia.

Methodology: We conducted a systematic review to investigate which adverse outcomes in 65 years or older adults with dementia are influenced by frailty. A comprehensive search was conducted across three databases—MEDLINE, EMBASE, and Cochrane—to identify relevant studies addressing this research question as of November 2024. Studies were considered for inclusion if they were observational studies or clinical trials involving individuals with dementia, assessed frailty within this population, and documented adverse health outcomes. Two independent and blinded researchers performed screening, data extraction, and risk of bias assessment. PROSPERO register CRD42024543327.

Results: Our search identified 5891 articles, from which 12 were included after screening and eligibility assessment ($n = 172{,}025$ participants). Alzheimer's disease was the most studied type of dementia, and the prevalence of frailty ranged from 8% to 65.9%.

Miguel German Borda and Luis Carlos Venegas-Sanabria have contributed equally to the manuscript.

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The reported adverse outcomes associated with frailty in patients suffering from dementia were mortality, institutionalization, functional and cognitive decline, neuropsychiatric symptoms, reduced quality of life, caregiver burden, and hospitalization.
Discussion: Understanding frailty in older adults with dementia may inform improved care strategies. Our findings suggest that higher levels of frailty are associated with an increased risk of adverse health outcomes.

1 | Introduction

Population aging is increasing the incidence of age-related conditions such as dementia and frailty [1]. Dementia, characterized by cognitive and functional decline, impacts individuals, families, and society, and is linked to higher healthcare use, disability, institutionalization, reduced quality of life, and caregiver burden [2–4]. The global prevalence of dementia is projected to reach 150 million by 2050 [5], yet effective disease-modifying treatments remain lacking, with management largely focused on symptom relief, often through nonpharmacological interventions [5].

A similar scenario occurs in older adults living with frailty—a condition marked by gradual deterioration in multiple physiological systems, rendering individuals vulnerable to adverse health outcomes [1, 2]. Here too, pharmacological treatment is lacking, and the best strategies to mitigate frailty involve lifestyle interventions such as exercise, nutrition, and social engagement [6]. The overlap between dementia and frailty offers an opportunity to address both conditions through shared preventive and therapeutic strategies, starting with the detection of frailty in people with dementia and vice versa [7].

Frailty is a pathological feature of aging linked with a higher risk for age-related diseases, including dementia. Several studies have examined its relationship with cognition [8–10], increasingly recognizing it as a modifiable risk factor for dementia of various etiologies [1, 9–11]. Moreover, it influences the clinical manifestation of cognitive disorders and the phenotypic expression of underlying neuropathological changes [12]. Some studies show that frailty is associated with faster cognitive decline and deterioration of higher-level executive functions in healthy older adults [13–16]. This could be in line with the so-called hallmarks of aging, a number of molecular pathways that interact, giving rise to many of the changes that result in loss of function and in higher rates of chronic diseases with age [17]. Both conditions share molecular pathways still to be described and might share therapeutic targets that could even improve aging [18], including inflammation [19], impaired nutrient sensing and protein misfolding [20, 21].

Against this background, this systematic review aimed to synthesize current evidence on the association between frailty and adverse health outcomes in older adults with dementia.

2 | Methodology

2.1 | Information Sources

We conducted this systematic review following the Joanna Briggs Institute (JBI) methodology and reported findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) [22, 23]. PRISMA checklists are provided as (Tables S1 and S2). A comprehensive search was performed in MEDLINE, Embase, and the Cochrane Database, covering all studies published up to November 2024.

2.2 | Search Strategy and Selection of Studies

The strategy was developed using the main health-related thesaurus—MeSH (Medical Subject Headings), DeCS (Descriptors in Health Sciences), and Emtree (Embase Subject Headings)—plus free-text terms, so relevant variations were included. Reference lists of all eligible studies were also screened manually for additional publications. The full search strategy is detailed in Table S3.

2.3 | Eligibility Criteria

Studies were eligible if they: (i) included adults ≥ 65 years with dementia of any cause; (ii) assessed frailty using a validated tool; (iii) reported at least one adverse outcome related to dementia progression (mortality, institutionalization, malnutrition, functional/cognitive decline, neuropsychiatric or behavioral symptoms, quality of life, caregiver burden); and (iv) used an observational or clinical trial design. No language or year restrictions were applied.

Frailty was conceptualized as a clinical syndrome distinct from dementia, even when overlap exists in multidimensional models. We included studies using validated tools from various frameworks, including physical frailty (e.g., Fried criteria), deficit accumulation (e.g., Frailty Index and Clinical Frailty Scale), and multidimensional assessments (e.g., Edmonton Frailty Scale, Tilburg Frailty Indicator). We only included studies where frailty was measured independently from dementia, excluding constructs like cognitive frailty, as this concept overlaps conceptually with dementia and does not allow an independent assessment of frailty as a separate influencing factor on health outcomes after a dementia diagnosis.

Studies with mixed cognitive populations were eligible only if dementia-specific data were clearly defined or analyzed separately. Co-exposures, such as medication use, were not exclusion criteria if frailty remained the primary variable examined in relation to adverse outcomes.

The listed adverse outcomes were prespecified in PROSPERO as indicators of dementia progression and care burden. Other events (e.g., falls, incontinence, polypharmacy) were excluded unless linked to broader functional or clinical decline.

2.4 | Data Extraction and Data Items

Data extraction was conducted by two authors (M.G.B., S.P.G.), blind to each other's results; disagreements were resolved by a third researcher (L.C.V.). Baseline data included: author(s), year,

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Summary

- Key points
  - Frailty in people with dementia is consistently associated with worse health outcomes, including higher mortality and institutionalization.
  - As frailty exacerbates dementia's clinical course, it leads to accelerated cognitive decline and more frequent neuropsychiatric or behavioral symptoms.
  - Early detection and management of frailty may help improve prognosis and guide more effective dementia care.
- Why does this paper matter?
  - By showing that frailty predicts mortality, institutionalization, and functional decline in dementia, this review underscores the need to integrate frailty assessment into dementia management strategies.

country, sample size, mean age, sex distribution, dementia diagnostic criteria, type of dementia, frailty tool, and reported outcomes.

Given the substantial variability in how frailty was measured, we also extracted information on the specific instruments used and their conceptual frameworks. This allowed consideration of how differences in frailty operationalization—whether based on physical phenotype, deficit accumulation, or multidimensional assessments—might influence associations with adverse health outcomes.

Adverse outcomes included mortality, institutionalization, hospitalization, functional decline, accelerated cognitive decline, neuropsychiatric symptoms, caregiver burden, quality of life, and disability. Strength of association measures (e.g., odds ratio [OR], hazard ratio [HR]) and confidence intervals (95% CI) were also extracted.

2.5 | Risk of Bias and Quality Assessment

The risk of bias was assessed using the JBI Critical Appraisal Checklists for Observational Studies via the JBI SUMARI platform [23], according to the design of the respective study. Each item in the checklist was scored as "Yes" (low risk), "No" (high risk), or "Unclear" (insufficient information) by two independent reviewers (M.G.B., S.P.G.), with discrepancies resolved by consensus or by consulting a third reviewer (L.C.V.).

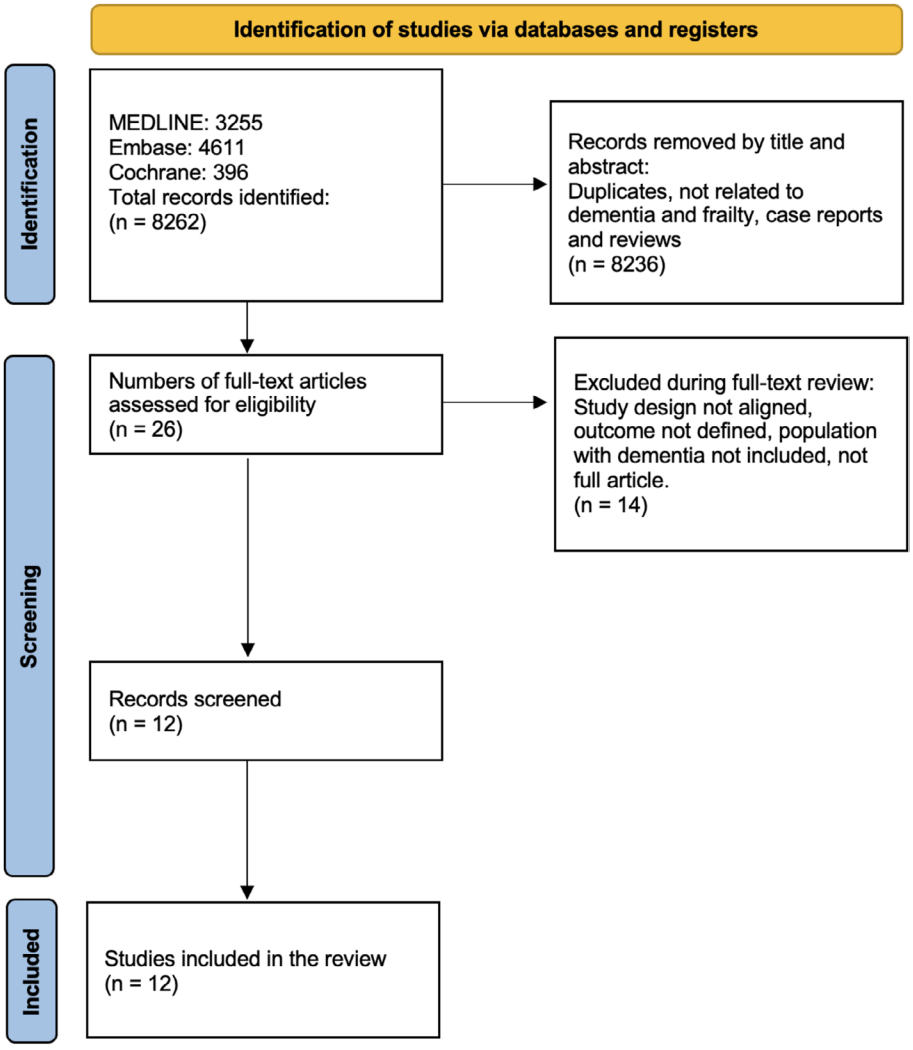


FIGURE 1 | PRISMA flow chart for the study selection process. Flowchart of the search according to PRISMA criteria.

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An overall risk of bias judgment (low, moderate, or high) was then assigned to each study based on the reviewers' qualitative assessment of the number, nature, and impact of unmet criteria, rather than by applying a fixed threshold or score. The item-level responses and overall risk ratings are reported in Tables S4 and S5.

2.6 | Assessment of the Results

Data were organized in Microsoft Excel (v.16.52 for iOS). Given methodological and clinical heterogeneity, we performed a narrative synthesis. Results were grouped thematically by outcome type and summarized in structured tables to allow comparison of effect direction and consistency across studies.

3 | Results

The initial search yielded 8262 records; after removing duplicates, 5891 articles remained for screening. Of these, 26 were reviewed in full text and 12 met inclusion criteria [24–35] (Figure 1), with a total of 172,025 participants between all included studies. Exclusions at the full-text stage were due to the inclusion of younger participants without dementia ($n=1$), lack of relevant health outcomes ($n=3$), or no cognitive assessment ($n=1$). Table 1 outlines the study characteristics, Table 2 provides a detailed overview of the outcome measurements reported in each study, and Figure 2 illustrates the impact of dementia and frailty on adverse outcomes.

3.1 | Diagnosis of Dementia

Dementia diagnoses were established using a variety of methods, including Clinical Dementia Rating (CDR) [24], DSM-IV-TR criteria [25–27], NINCDS-ADRDA guidelines [27–30], MMSE or physician diagnosis [31], a combination of CDR and MMSE [31], the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup criteria [33], and clinical diagnosis only [34, 35].

3.2 | Prevalence of Frailty

Frailty prevalence ranged from 8% to 65.9%, reflecting measurement and classification differences. The prevalences found in the different studies are presented in table 1 [24–35].

3.3 | Adverse Outcomes

Adverse outcomes included mortality, institutionalization, accelerated cognitive decline, functional decline, and other dementia manifestations, plus neuropsychiatric symptoms, caregiver burden, and quality of life. The results for each outcome are described in detail in the sections below and summarized in Table 2.

3.3.1 | Mortality

Bilotta et al. found that frailty significantly predicted one-year mortality (OR 11.2 [7]; 95% CI 1.64–77.72) [25]. Likewise, Haaksma et al. reported an association between frailty and mortality at 1 year (HR 1.79; 95% CI 1.24–2.59) and 3 years (HR 1.24; 95% CI 1.06–1.47), though not at 6 years. In one study, Kelaiditi et al. linked continuous FI to 2-year mortality (HR 1.019; 95% CI 1.002–1.037), though not with frailty defined categorically using a cut-off of FI >0.25 [29]. Maxwell et al. demonstrated that dementia combined with frailty was linked to higher mortality at 1 year (HR 2.15) in a large Ontario cohort [35], and in a separate cohort of the Ontario sample, risk was higher at 1 month but not at 3 or 6 months [34]. Finally, Solfrizzi et al. found frailty predicted 3-year (HR 3.33; 95% CI 1.29–8.29) and 7-year (HR 1.89; 95% CI 1.10–3.44) all-cause mortality in patients with dementia [32].

3.3.2 | Institutionalization

Kelaiditi et al. found frailty (FI ≥ 0.25) increased institutionalization risk (HR = 2.121, 95% CI: 1.352–3.325, $p=0.001$), though not when analyzed continuously (HR = 1.011, 95% CI: 0.997–1.025, $p=0.116$) [29]. Maxwell et al. reported higher long-term care admission among frail older adults with dementia (HR = 2.60, 95% CI: 2.53–2.67) [35], while Haaksma et al. found no significant predictive value at 1, 3 and 6 years of follow-up (HRs 1.04–1.16) [26].

3.3.3 | Accelerated Cognitive Decline

Kelaiditi et al. reported that frail participants (FI ≥ 0.25) had greater 1-year cognitive decline, with MMSE decreasing −1.57 ($p=0.001$) and ADAS-Cog increasing +4.86 ($p<0.001$) [28]. Oosterveld et al. found that higher frailty scores correlated with lower composite cognitive performance ($\beta=-0.14$, $p=0.04$), but the association lost significance after adjusting for comorbidity ($\beta=-0.08$, $p=0.31$) [27].

3.3.4 | Functional Decline and Other Clinical Manifestations of Dementia

Oosterveld et al. conducted a cross-sectional study assessing frailty's independent association with AD clinical manifestations, defined by cognitive performance, activities of daily living (ADL), and neuropsychiatric symptoms (Neuropsychiatric Inventory) [27]. Adjusted analyses showed that frailty ($\beta=-0.34$, $p<0.001$) correlated with worse overall manifestations, as well as poorer ADL performance specifically ($\beta=-0.37$, $p<0.001$) [27]. Solfrizzi et al. found that frailty did not significantly increase disability risk (≥ 1 ADL decline) in dementia patients [32].

3.3.5 | Other Outcomes

Abreu et al. found that frailty correlated with higher caregiver distress ($r=0.20$; $p=0.04$). Chi et al. and Sugimoto et al. observed that frailty was associated with more severe behavioral disturbances and, in Sugimoto et al.'s study, also with higher caregiver burden ($\beta=0.13$, $p<0.001$) [24].

Related to quality of life, among the included studies, only Mhaoláin et al. explicitly assessed health-related quality of life (HRQoL) in individuals with dementia. Using the frailty

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TABLE 1 | Characteristics of included studies.

Author	Country	Study design	Total sample and sample of patients with dementia	Mean or median of age (years)	Female (%)	Dementia definition/ type of dementia	Frailty definition	Prevalence of frailty (%)	Outcome
Solfrizzi	Italy	Cohort	$n = 2581$ (75 patients with dementia)	73.1 (not specified for sample with dementia)	45.2 (not specified for sample with dementia)	MMSE <23, or previous diagnosis reported by proxy. AD, vascular dementia and other	Cardiovascular Health Study modified criteria—presence of ≥3 criteria	52	Disability; Mortality
Bilotta	Italy	Cohort	$n = 109$ (all with dementia)	82.8	77	DSM-IV-TR AD	Study of Osteoporotic Fractures (SOF) Criteria	50	Mortality
Mhaoláin	Ireland	Cross-sectional	$n = 115$ (95 patients with dementia, the rest with MCI)	74.1 (not specified for sample with dementia)	62 (not specified for sample with dementia)	NINCDS-ADRDA AD	Frailty phenotype criteria	19.1	Quality of life.
Oosterveld	Netherlands	Cross-sectional	$n = 213$ (all with dementia)	75	58	DSM-IV-TR and NINCDS-ADRDA AD	Frailty phenotype criteria described by Fried	11	Clinical manifestation of AD: cognitive performance, disability, and NPS
Haaksma	Netherlands	Cohort	$n = 331$ (all with dementia)	76.2	54.7	DSM-IV-TR AD, vascular, mixed type	FI ≥0.25	65.9	Mortality; Institutionalization
Abreu	Portugal	Cross-sectional	$n = 102$ (all with dementia)	80.8	65.7	CDR criteria AD, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, mixed dementia, other types of dementia and etiology under study.	Edmonton Frailty Scale	8.8 mild 35.3 moderate 45.1 severe	Psychological distress and caregiver burden

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TABLE 1 | (Continued)

Author	Country	Study design	Total sample and sample of patients with dementia	Mean or median of age (years)	Female (%)	Dementia definition/ type of dementia	Frailty definition	Prevalence of frailty (%)	Outcome
Sugimoto	Japan	Cross-sectional	$n = 1193$ (all with dementia)	78.8	68.6	NIA-AA AD	FI ≥ 0.25	16.6	NPS; Caregiver burden
Chi	China	Cross-sectional and cohort	$n = 2155$ (387 patients with dementia)	73.3 (not specified for sample with dementia)	46.6 (not specified for sample with dementia)	NINCDS-ADRDA AD	Modified FI (score ≥ 3 points)	8	NPS
Kelaiditi	Multicenter among 12 European countries[a]	Cohort	$n = 1191$ (all with dementia)	76.2	63.8	NINCDS-ADRDA AD	FI ≥ 0.25	34.3	Hospitalization; Institutionalization; Mortality
Kelaiditi	Multicenter among 12 European countries[a]	Cohort	$n = 973$ (all with dementia)	76.2	64.3	NINCDS-ADRDA AD	FI ≥ 0.25	33.2	Cognitive decline
Maxwell	Canada	Cohort	$n = 153,125$ (40,956 patients with dementia)	80.1 (not specified for sample with dementia)	64.7 (not specified for sample with dementia)	Presence of a dementia-related hospitalization code (DAD), or three physician claims for dementia within a 2-year period each separated by 30 days (OHIP) or a prescription filled for a cholinesterase inhibitor. Not specified	FI ≥ 0.3	30.3	Urgent hospitalization; Institutionalization; Mortality

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TABLE 1 | (Continued)

Author	Country	Study design	Total sample and sample of patients with dementia	Mean or median of age (years)	Female (%)	Dementia definition/ type of dementia	Frailty definition	Prevalence of frailty (%)	Outcome
Maxwell	Canada	Cohort	$n = 9910$ (87.8% of patients had dementia, exact number not mentioned but approximately 8700)	82.79 (not specified for sample with dementia)	60.1 (not specified for sample with dementia)	Presence of a dementia-related hospitalization code (DAD), or three physician claims for dementia within a 2-year period each separated by 30 days (OHIP) or a prescription filled for a cholinesterase inhibitor. Not specified	FI ≥ 0.3	29.6	Mortality

Abbreviations: AD, Alzheimer's Dementia; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADL, Activities of daily living; BSI, Brief Symptom Inventory; CDR, Clinical Dementia Rating; DBD, Dementia Behavior Disturbance Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; FI, Frailty Index; GSI, Global Severity Index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NIA-AA, National Institute on Aging and Alzheimer's Association workgroups criteria; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI, neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; NR, no reported; ZBI, Zarit Burden Interview.
[a]Sweden, Denmark, England, Germany, Netherlands, France, Spain, Italy, Switzerland, Belgium, Greece, Romania.

phenotype criteria, the authors found that frailty was associated with poorer HRQoL ($\beta = -0.192$, $p = 0.047$) after adjusting for neuropsychiatric symptoms, functional limitations, and illness severity [26]. In a subgroup analysis stratified by stage of cognitive decline, this association was no longer significant in those with more severe cognitive impairment (MMSE ≤ 20), suggesting that the impact of frailty on HRQoL may be more evident in earlier stages of dementia [26].

3.4 | Risk of Bias and Critical Appraisal

Cross-sectional studies met 81.2% of criteria; only 25% controlled for confounding, giving low to moderate risk (see Tables S2 and S3). Limited control for confounding may have influenced effect estimates and warrants caution in interpreting associations.

Cohort studies achieved a 71.5% compliance rate, characterized by strong exposure, outcome, and follow-up reporting. None adequately addressed confounding or attrition, resulting in moderate risk ratings, although no study was rated as high risk.

4 | Discussion

This systematic review examines frailty's role in increasing adverse outcomes or worsening dementia-related trajectories in older adults. According to our results, frailty was associated with increased mortality, institutionalization, functional decline, more severe neuropsychiatric symptoms, poorer quality of life, and higher caregiver burden.

As noted in the introduction, no treatments currently modify the course of dementia; however, identifying and managing frailty may help improve cognition, physical function, and other symptoms, and ultimately enhance prognosis. Indeed, frailty moderates the risk associated with biomarkers [36], including neuropathology [9], genetic factors [1], and poor neuropsychological test performance [37]. Furthermore, among individuals with mild cognitive impairment (MCI), frailty was associated with a lower likelihood of AD biomarker positivity, potentially indicating alternative pathophysiological mechanisms contributing to cognitive impairment [38]. Therefore, addressing frailty may alter the trajectory of functional decline and reduce negative consequences associated with the combination of these two conditions. Ultimately, this approach will benefit both individuals and caregivers, as greater awareness of frailty may enhance the individual's adherence to interventions [39].

While our findings indicate an association between frailty and adverse outcomes in dementia, the relationship is likely bidirectional. Dementia may accelerate frailty via reduced mobility, malnutrition, neuropsychiatric symptoms, and medication effects. These associations may reflect shared pathophysiological mechanisms—such as inflammation, vascular dysfunction, or neurodegeneration—rather than direct causality. This complexity has implications for intervention design, highlighting the need to address both cognitive and physical decline jointly. Additionally, some outcomes may reflect terminal decline rather than frailty per se, given the short average time from dementia diagnosis to death. Most included studies did not adjust for

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TABLE 2 | Adverse outcome measurements in patients with dementia and concomitant frailty across included studies.

Study	Instrument/outcome	Follow-up/setting	Effect measure	Estimate (95% CI)
Mortality				
Solfrizzi	—	3 years	HR	3.33 (1.28–8.29)
		7 years		1.89 (1.10–3.44)
Bilotta	—	1 year	OR	11.27 (1.64–77.72)
Haaksma	—	1 year	HR	1.79 (1.24–2.59)
		3 years		1.24 (1.06–1.47)
		6 years		1.01 (0.90–1.13)
Kelaiditi	Continuous FI	—	HR	1.19 (1.002–1.037)
	FI > 0.25			1.409 (0.997–1.992)
Maxwell	Continuous FI	—	HR	0.87 (0.84–0.89)
Maxwell	—	1 month	HR	1.74 (1.40–2.17)
		3 months		1.25 (1.00–1.56)
		6 months		1.02 (0.75–1.38)
Institutionalization/hospitalization				
Haaksma	—	1 year Institutionalization	HR	1.16 (0.85–1.60)
		3 years Institutionalization		1.06 (0.89–1.27)
		6y Institutionalization		1.04 (0.89–1.21)
Kelaiditi	Continuous FI	Institutionalization	HR	1.011 (0.997–1.025)
	FI > 0.25			2.121 (1.352–3.325)
	Continuous FI	Hospitalization	HR	1.017 (1.005–1.030)
Maxwell	Continuous FI	Hospitalization	HR	0.84 (0.83–0.86)
	Continuous FI	Institutionalization	HR	2.60 (2.53–2.67)

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TABLE 2 | (Continued)

Study	Instrument/outcome	Follow-up/setting	Effect measure	Estimate (*p* value)
Clinical manifestations of dementia and cognitive decline				
Oosterveld	ADL	—	*β*	−0.37, $p < 0.001$
	Clinical manifestation of AD	—	*β*	−0.34, $p < 0.001$
Kelaiditi	MMSE	1 year	—	0.63–4.63 points on the MMSE, $p = 0.01$
	ADAS-Cog Cognitive decline			2.87–11.1 points on the ADAS-Cog, $p = 0.001$
Quality of life				
Mhaoláin	Moderate–severe or mild cognitive impairment	—	*β*	−0.192, $p = 0.047$
	Moderate–severe cognitive impairment (MMSE < 20)			−0.240, $p = 0.037$
	Moderate–severe cognitive impairment (MMSE ≥ 21)			−0.212, $p = 0.250$
Caregiver distress				
Abreu	GSI	—	A positive correlation	$r = 0.28$, $p = 0.003$
Sugimoto	DBD	—	*β*	0.30, $p < 0.001$
	J-ZBI			0.13, $p < 0.001$
Study	**Instrument/outcome**	**Follow-up/setting**	**Effect measure**	**Estimate (*p* value/95% CI)**
Oosterveld	NPI total score	—	*β*	0.17, $p = 0.03$
	Apathy			0.27, $p = 0.01$
	Agitation			0.25, $p = 0.04$
Sugimoto	Aggression	—	*β*	0.14, $p < 0.001$
	Agitation			0.13, $p < 0.001$
	Aberrant motor behavior			0.09, $p = 0.005$

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TABLE 2 | (Continued)

Study	Instrument/outcome	Follow-up/setting	Effect measure	Estimate (*p* value/95% CI)
Chi	Depression	—	OR	2.33 (1.03–5.50)
	Anxiety			2.85 (1.10–8.44)
	Agitation			2.52 (1.04–6.62)
	Aberrant motor behavior			14.45 (2.72–267.91)
	Appetite changes			3.62 (1.24–13.26)
Study	**Instrument/outcome**	**Follow-up/setting**	**Effect measure**	**Estimate (95% CI)**
Disability				
Solfrizzi	—	3 years	HR	1.84 (0.54–6.31)
		7 years		1.28 (0.41–3.43)

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL, activities of daily living; CI, confidence interval; DBD, Disruptive Behavior Disorders Scale; FI, Frailty Index; GSI, Global Severity Index; J-ZBI, Japanese Zarit Burden Interview; MMSE, Mini-Mental State Examination; NPI, neuropsychiatric inventory.

proximity to death, limiting the ability to distinguish stable frailty from late-life deterioration. Clinically, however, both processes likely contribute to poor outcomes and require integrated care. Recent longitudinal evidence also suggests that frailty often accelerates years before dementia onset, implying that elevated frailty may be part of the prodromal phase rather than a consequence [10]. This complicates causal interpretation and underscores the need for early frailty detection in dementia risk stratification and care planning.

The treatment of frailty relies on a multidimensional approach [7] that is supported by a comprehensive geriatric assessment. Studies have shown that exercise can improve health-related outcomes in individuals with dementia, and a randomized controlled trial found that increasing muscle strength significantly lowered the risk of falls in older adults with mild to moderate AD [40]. On the other hand, adequate caloric and protein intake is essential for maintaining muscle mass, recovery, and overall body function [41]. In fact, recent research from our group demonstrated that malnutrition negatively impacts functional decline trajectories in individuals newly diagnosed with dementia [42]. Additionally, reviewing and adjusting medications that may cause adverse effects such as interactions, falls, weakness, and dizziness is critical. Several studies have reported that antipsychotics and benzodiazepines, especially in combination, are linked to higher risks of falls, fractures, functional decline, and mortality [43–45]. However, the evidence supporting the effectiveness of these interventions specifically in individuals living with both dementia and frailty remains limited. Most studies address these components independently, and few evaluate their impact within this dual-risk population. More targeted trials are needed to guide comprehensive, condition-specific care.

On the other hand, cognitive and social engagement appear to be essential for maintaining mental well-being, as demonstrated by dementia prevention programs like the FINGER study, which have included this area as an important core of their intervention [46]. A recent study reported that loneliness increased the risk for Alzheimer's by 14%, vascular dementia by 17%, and cognitive impairment by 12% [7, 47]. Taken together, these factors (physical activity, nutrition, adequate sleep, appropriate medication management and chronic disease control, and cognitive and social engagement) can promote improvement or even reverse frailty, ultimately enhancing quality of life and overall health outcomes for older adults living with dementia.

A promising new direction in this field is suggested by the geroscience hypothesis [48]. which argues that addressing aging itself may be an effective way to prevent or treat age-related diseases [49]. While this idea may have seemed speculative when first proposed in 2014, by 2019 the first report of an FDA-approved Phase I clinical trial had already been published [50]. Preliminary data are now available on how a senolytics strategy might be used to treat people at risk of Alzheimer disease by virtue of the combination of older adults with slow walking speed and MCI [51]. That combination was noted to be a "precursor of frailty", and although walking speed and grip strength were measured (and a variety of other potential health deficits were evaluated) the study did not mention frailty. Currently, the geroscience approach may improve trial design by incorporating molecular pathways that contribute both to aging as a whole and

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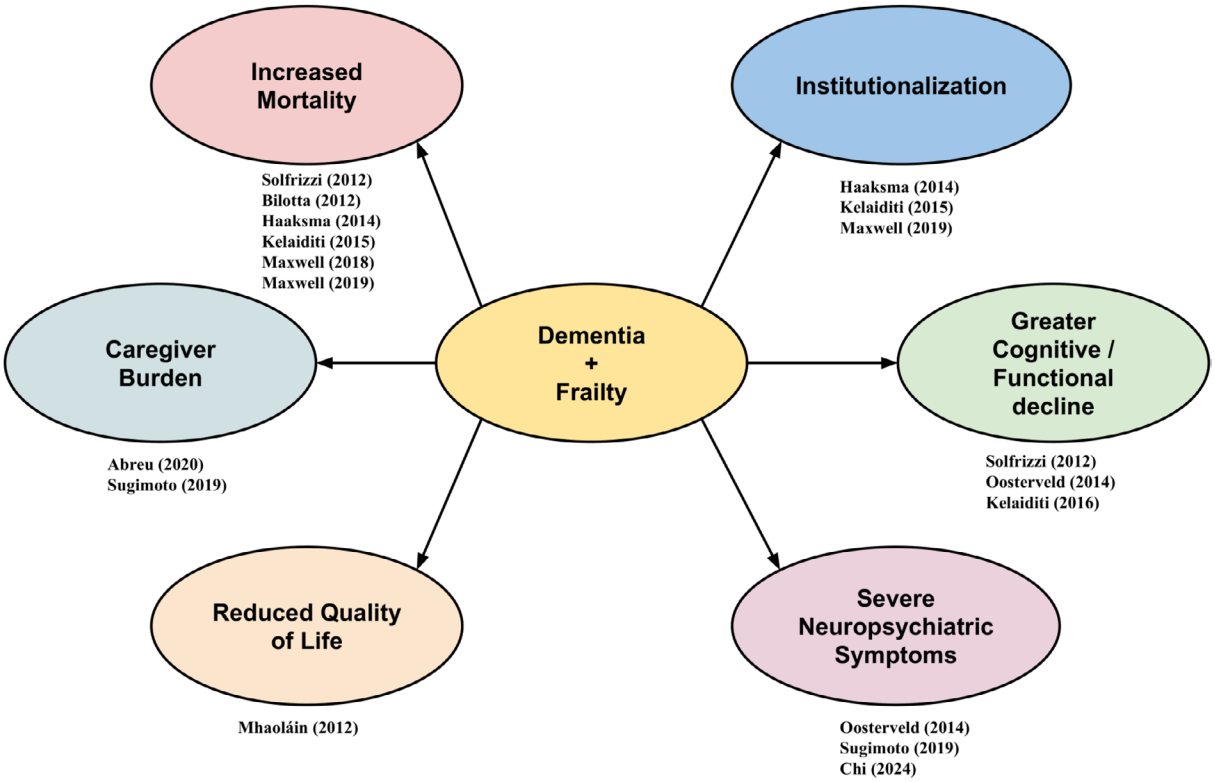


FIGURE 2 | Impact of dementia and frailty in terms of adverse outcomes. Frailty in individuals with dementia has been linked to multiple adverse outcomes, including increased mortality, higher risk of institutionalization, greater cognitive and functional decline, severe neuropsychiatric symptoms, reduced quality of life, and increased caregiver burden.

to conditions such as dementia and frailty, thereby opening the door to high-impact treatments with the potential to extend the health span of older adults [52].

Several methodological issues should be considered when interpreting these findings. One of the main limitations of the current study is the few studies available on this topic, which restricted the ability to perform a quantitative evidence synthesis, such as a meta-analysis. Therefore, to strengthen the analysis, we included cross-sectional studies, recognizing their potential to provide valuable insights into the relationship between frailty and adverse outcomes in individuals with dementia. Furthermore, neither the JBI Manual nor Cochrane guidelines restrict the inclusion of different study designs in systematic reviews, supporting our methodological approach. Another limitation is that not all the included studies were originally designed to assess the direct relationship between dementia and frailty. As a result, the findings reported in this review are often based on secondary analyses, which may introduce potential biases or limit causal inferences. Furthermore, the literature search was restricted to MEDLINE, Embase, and Cochrane databases. Although these are major databases in clinical and epidemiological research, the exclusion of other databases (e.g., PsycINFO, CINAHL, Scopus) may have resulted in the omission of potentially relevant studies.

In addition, differences in the methods used to diagnose dementia, ranging from simple cognitive tests to formal clinical criteria, may influence reported prevalence and complicate interpretation of findings, emphasizing the need for greater standardization in future research.

Another important source of variability is the heterogeneity in how frailty was measured. The included studies employed diverse instruments—ranging from physical phenotypes to deficit accumulation models and multidimensional tools—leading to inconsistent operationalization. This variability may have influenced both the prevalence estimates and the strength of associations with outcomes such as mortality, cognitive decline, or caregiver burden. This is still an ongoing debate in geriatric medicine and aging research, but it is important to acknowledge to have an appropriate interpretation of the results.

It is plausible that frailty instruments incorporating cognitive items could inflate associations with cognitive outcomes, although current evidence does not confirm this. Most studies avoid such overlap to prevent circularity, while strategies such as sensitivity analyses, time-lagged assessments, or excluding shared risk factors are recommended when overlap cannot be avoided [53]. Interaction analyses and reporting results by dementia stage (such as using the Clinical Dementia Rating) are also valuable strategies [54]. Notably, features like slow walking speed—associated with the Motoric Cognitive Risk syndrome—can serve as risks for dementia and are common in frail individuals, highlighting the overlap between frailty and cognitive decline [55]. Studies such as the Rush Memory and Aging Project have shown that increases in physical frailty are linked to higher risks of MCI and that changes in gait and strength may result from various brain pathologies, including both neurodegenerative and vascular changes [56]. These findings highlight the complex, bidirectional relationships between late-life frailty and dementia, where symptoms and mechanisms overlap.

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Frailty may reduce physical activity, thereby exacerbating neuropathology, leading both conditions to progress in parallel and underscoring the importance of integrated approaches to assessment and intervention [57–59].

While Alzheimer's disease is most frequently represented, other dementia subtypes (e.g., vascular, Lewy body, frontotemporal) remain underreported or inconsistently classified. These etiologies may interact with frailty through distinct mechanisms, contributing to variability in outcomes that cannot be explained solely by methodological differences. Heterogeneity in dementia diagnosis further complicates interpretation and may generate misleading associations. Additional research is warranted, and in recent work our group has provided recommendations on approaches most useful for assessing frailty and cognition in both clinical and research contexts.

Another consideration is that the variability in follow-up times across studies may have affected comparability between studies and contributed to the wide confidence intervals observed in some analyses (e.g., Billotta et al.). These differences in study duration and outcome measurement complicate comparisons and should be taken into account when interpreting associations, particularly for outcomes such as cognitive decline.

Finally, punctual events such as falls, incontinence, or polypharmacy were not included as primary outcomes, as our focus was on endpoints reflecting dementia progression. While these factors may provide relevant clinical insights, their exclusion may have narrowed the scope of outcomes considered in this review.

Despite these limitations, this review has notable strengths. To our knowledge, it is the first to focus specifically on frailty among individuals with a confirmed dementia diagnosis, exploring its role in shaping adverse outcomes. Unlike previous reviews that centered on cognitive decline or the transition from MCI to dementia [60, 61], we targeted those already living with dementia and examined a broad set of clinically relevant endpoints. By conceptualizing frailty as a modifiable condition, this review highlights its relevance for designing targeted interventions and integrated care strategies in dementia.

Furthermore, our broad inclusion criteria allowed us to capture a wide range of studies, providing a comprehensive overview of the available evidence. This review serves as a foundation for future research, emphasizing the need for high-quality longitudinal studies to clarify the complex interplay between frailty and dementia outcomes.

5 | Conclusion

Overall, the evidence from these 12 studies highlights the association between frailty and adverse health outcomes in older adults with dementia, including increased mortality, higher rates of hospitalization or institutionalization, more severe neuropsychiatric symptoms, and greater burden on caregivers in individuals suffering from dementia. Although the studies varied in their operational definitions of both dementia and frailty, their findings collectively address the importance of frailty in people living with dementia.

Author Contributions

Miguel German Borda: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing – original draft preparation, writing – review and editing. **Luis Carlos Venegas-Sanabria:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing – original draft preparation, writing – review and editing. **Marco Canevelli and Francesco Landi:** conceptualization, data curation, formal analysis, investigation, validation, visualization, writing – review and editing. **Salomón Páez-García:** conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization. **Kevin O'Hara-Veintimilla:** conceptualization, data curation, formal analysis, methodology, writing – original draft preparation, software. **Lindsay Wallace, Kenneth Rockwood, Tommy Cederholm, Gustavo Duque, Mario Ulises Pérez-Zepeda, and Dag Aarsland:** supervision, visualization, writing – review and editing.

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Disclosure

The funders had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** PRISMA 2020 abstract checklist **Table S2:** PRISMA 2020 checklist **Table S3:** MEDLINE search strategy **Table S4:** Critical appraisal results for analytical cross-sectional studies **Table S5:** Critical appraisal results for cohort studies.

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