Frailty and prognosis of biomarker-confirmed Alzheimer's disease: a Swedish, register-based, retrospective cohort study

Xin Xia, Maria Eriksdotter, Henrik Zetterberg, Silke Kern, Tobias Skillbäck, Marco Toccaceli Blasi, Bengt Winblad, Jonathan K L Mak, Alice Margherita Ornago, Elena Pinardi, Román Romero Ortuño, Linus Jönsson**

Summary

Background This study aimed to examine the value of frailty status (defined by the frailty index) in informing the prognosis of people living with Alzheimer's disease.

Methods In this retrospective cohort study, we used the Swedish Registry for Cognitive/Dementia Disorders linked to other Swedish health-care registers to collect data from May 1, 2007, to Dec 31, 2020. We included people with mild cognitive impairment or Alzheimer's disease dementia, both with cerebrospinal fluid (CSF) biomarkers supporting Alzheimer's pathology. We excluded people living in an institution or those who did not have at least one Mini-Mental State Examination (MMSE). We constructed a 41-item frailty index, incorporating diseases, symptoms, polypharmacy, nutritional status, and care dependency. Individuals with frailty index scores of 0·25 or above were considered frail. The associations between frailty and MMSE trajectories, subsequent institutionalisation, and mortality were evaluated by jointly modelling longitudinal and survival data. We also examined whether frailty could modify the associations between CSF amyloid β_{42}, phosphorylated tau_{181}, and total tau and cognitive decline.

Findings The study included 7251 individuals (mean age 72·7 years, 4271 [58·9%] females, 2980 [41·1%] males). Frailty was associated with a 0·723-point (95% CI 0·250–1·196) lower baseline MMSE but not with the rate of MMSE decline. Frailty was associated with a hazard ratio of 1·91 (1·43–2·54) for institutionalisation and 2·41 (1·73–3·33) for mortality. Individuals living with frailty had a 1·3-year (0·9–1·7) shorter lifespan and a 1·0-year (0·8–1·3) shorter non-institutionalised lifespan. Associations between CSF biomarkers and MMSE trajectories did not differ by frailty status.

Interpretation Frailty, measured by the frailty index, predicted institutionalisation and mortality in people with Alzheimer's disease, but its absence of association with cognitive decline suggests neurodegeneration as the primary driver.

Funding Innovative Health Initiative Joint Undertaking and Vinnova.

Introduction

Dementia is one of the leading contributors to morbidity and mortality in older adults, and Alzheimer's disease is the most common cause of dementia, accounting for up to 80% of cases.[1] Alzheimer's disease primarily affects older adults, with the majority of people with Alzheimer's dementia having an onset after age 65 years.[1]

Frailty is a geriatric syndrome characterised by dysregulation across multiple physiological systems, decreased physiological reserve, and increased vulnerability to stressors.[2] It has been associated with a higher risk of adverse events, including falls, institutionalisation, and mortality.[2] Frailty is common among individuals living with dementia and has important implications in Alzheimer's disease.[3] Previous studies have shown that frailty can predict cognitive deterioration in people with mild cognitive impairment and modify the associations between Alzheimer's neuropathology and clinical manifestations of dementia.[4–7] Furthermore, frailty also has potential implications in selecting the right patients for high-risk pharmacological treatments that are more frequently associated with adverse events in older adults with multimorbidity and disabilities, which is relevant to consider in the context of new disease-modifying treatments for Alzheimer's disease.[8,9]

There are various approaches in the literature to identify frailty, with the two most commonly used being the frailty index and the physical frailty phenotype.[2] Although these two approaches can be complementary, the frailty phenotype has disadvantages when applied to studies focusing on people living with dementia.[10] These include difficulties in understanding and completing the performance-based measures (eg, walking speed) and recall challenges for the other items (eg, unexplained weight loss). Conversely, the frailty index has the potential to overcome these limitations and is both feasible and quick to implement, particularly when derived from electronic health records or population-based registries.[11]

In this context, our study aimed to investigate the role of frailty, as measured by the frailty index, in the prognosis of individuals with Alzheimer's disease confirmed by

Lancet Healthy Longev 2025

Published Online
https://doi.org/10.1016/j.lanhl.2025.100797

*Joint senior authors

Division for Neurogeriatrics (X Xia PhD, Prof B Winblad MD, Prof L Jönsson MD) **and Division of Clinical Geriatrics** (Prof M Eriksdotter MD), **Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Solna, Sweden; Theme Inflammation and Aging, Karolinska University Hospital, Huddinge, Sweden** (Prof B Winblad MD, Prof M Eriksdotter MD); **Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (Prof H Zetterberg MD); **Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden** (Prof H Zetterberg MD); **Department of Neurodegenerative Disease, Queen Square Institute of Neurology, University College London, London, UK** (Prof H Zetterberg MD); **UK Dementia Research Institute at UCL, University College London, London, UK** (Prof H Zetterberg MD); **Hong Kong Center for Neurodegenerative Diseases, Hong Kong Special Administrative Region, China** (Prof H Zetterberg MD); **Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin–Madison, Madison, WI, USA** (Prof H Zetterberg MD); **Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (Prof S Kern MD, T Skillbäck PhD);

Clinical Dementia Research, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Prof S Kern MD, T Skillbäck PhD); **Department of Neuropsychiatry, Sahlgrenska University Hospital, Gothenburg, Sweden** (Prof S Kern MD); **Department of Human Neuroscience, Sapienza University, Rome, Italy** (M Toccaceli Blasi MD); **Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain** (M Toccaceli Blasi MD); **Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong Special Administrative Region, China** (J K L Mak PhD); **Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden** (J K L Mak PhD); **School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy** (E Pinardi MD); **Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden** (A M Ornago MD, E Pinardi MD); **Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland** (Prof R Romero Ortuño PhD); **Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland** (Prof R Romero Ortuño PhD); **Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA** (Prof H Zetterberg MD); **Centre for Brain Research, Indian Institute of Science, Bangalore, India** (Prof H Zetterberg MD)

Correspondence to:
Dr Xin Xia, Division for Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, 171 64 Solna, Sweden
xin.xia@ki.se

Research in context

Evidence before this study

We searched for relevant studies in PubMed with the search term "frailty" AND "Alzheimer's disease" AND ("prognosis" OR "cognitive decline" OR "cognitive deterioration" OR "institutionalization" OR "nursing home" OR "mortality" OR "survival") until Sept 8, 2025, without specifying an inception date. We identified two relevant cohort studies on the associations between frailty and the prognosis of Alzheimer's disease. Alzheimer's disease in these studies was not confirmed with biomarker testing. These studies suggest that frailty was associated with a higher mortality rate and faster cognitive decline.

Added value of this study

This Swedish register-based cohort study found that frailty, measured by the frailty index, was associated with a higher hazard of future institutionalisation and mortality. Frailty was associated with 1·3-year shorter overall survival and 1·0 years fewer non-institutionalised life-years. However, frailty was not associated with cognitive decline rate, whereas cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease were significantly associated with cognitive decline rate. In addition, frailty did not modify the associations between Alzheimer's disease CSF biomarkers and cognitive decline rate.

Implications of all the available evidence

Frailty can inform the prognosis of Alzheimer's disease, especially institutionalisation and survival. Measuring frailty can help identify individuals with decreased physical and mental capacities in those with CSF biomarker-confirmed Alzheimer's disease. In addition, the frailty index can be a useful instrument for using real-world data to conduct post-authorisation safety and effectiveness evaluations of medicines in individuals with Alzheimer's disease who were frail, including emerging disease-modifying treatments.

cerebrospinal fluid (CSF) biomarkers. Specifically, we sought to: (1) evaluate the associations of the frailty index with cognitive trajectories, institutionalisation, and mortality; (2) assess whether these associations can be mediated by the use of cholinesterase inhibitors and memantine; and (3) examine whether frailty modifies the relationship between CSF biomarkers and cognitive decline.

Methods

Study design and population

In this retrospective cohort study, we used the Swedish Registry for Cognitive/Dementia Disorders (SveDem) linked to other Swedish health-care registers. SveDem covered 93% of specialist units and 60% of primary care centres in Sweden in 2012, and since then the coverage has continued to increase.[12] The study received approval from the Swedish Ethical Review Authority (DNR 2024-07272-02; on Nov 25, 2024). Each patient was informed about the registration of their data in SveDem and had a right to decline participation.[12] Written consent is not required for register-based studies in Sweden.

The observational period was between May 1, 2007, and Dec 31, 2020, and was decided according to the data availability. The study population consisted of people not living in an institution who were diagnosed with early-onset Alzheimer's disease dementia (onset age <65 years), late-onset Alzheimer's disease dementia (onset age ≥65 years), unspecified dementia (no specific dementia diagnosis reached), or mild cognitive impairment, all of whom had CSF biomarkers supporting the presence of Alzheimer's pathology and at least one Mini-Mental State Examination (MMSE) measurement. The presence of Alzheimer's pathology was defined as having a CSF amyloid β $(Aβ)_{42}$ to phosphorylated tau $(P\text{-tau})_{181}$ ratio of less than 14·887 or a CSF $Aβ_{42}/Aβ_{40}$ ratio of less than 0·072.[13] CSF biomarkers, including but not limited to $Aβ_{42}$, $P\text{-tau}_{181}$, and total tau (T-tau), were measured by an accredited university laboratory (Sahlgrenska University Hospital, Gothenburg, Sweden), following a standard procedure, as reported previously.[13]

Procedures

We collected data on age at diagnosis and type of cognitive diagnosis and sex, and items for the frailty index. Race and ethnicity data were not collected. Data on sex were collected from the Swedish personal number which is a 12-digit number assigned to everyone registered in Sweden's population register. The Swedish personal number only allows two categories, male and female, which is based on sex at birth. However, transgender or non-binary individuals can apply to change their legal sex and will then obtain a new personal number.

The frailty index was constructed using several Swedish registers and comprised 41 deficits, namely 36 chronic diseases and symptoms, polypharmacy, underweight, obesity, and two items for care dependency (panel). These items were guided by a previous frailty index developed for the Swedish older population and further refined through discussions with clinicians experienced in frailty research and care (RRO and MTB).[14] The presence or absence of each deficit at the time of Alzheimer's disease diagnosis was used to define the frailty index. We focus on this timepoint as it is the most relevant in terms of decision making—eg, informing the likely prognosis of the patients when disclosing diagnosis of Alzheimer's disease and deciding whether the risk will outweigh benefits of initiating treatments.

Details of operationalisation of the frailty index and coverage of the Swedish registers used for constructing the

Panel: **Deficits in the frailty index**

Diseases and symptoms

- Anaemia
- Anxiety
- Arthritis
- Asthma and chronic obstructive pulmonary disease
- Atrial fibrillation
- Cancer
- Cataract and other lens diseases
- Chronic kidney disease
- Chronic liver disease
- Chronic pain
- Depression
- Diabetes
- Dizziness or vertigo
- Fracture
- Glaucoma
- Hearing loss
- Heart failure
- Hyperlipidaemia
- Hypertension
- Hypotension
- Ischaemic heart disease
- Osteoporosis
- Other heart diseases
- Parkinson's disease
- Peptic ulcer
- Peripheral neuropathy
- Peripheral vascular disease
- Pulmonary disease
- Skin ulcer
- Sleeping disorders
- Syncope
- Transient ischaemic attack or cerebral infarction
- Thyroid disease
- Urinary disease
- Valvular disease
- Visual impairment

Polypharmacy

- Polypharmacy

Nutritional status

- Underweight (BMI <18·5 kg/m^2)
- Obesity (BMI ≥30 kg/m^2)

Care dependency

- Using home care (proxy for deficit in basic activities of daily living)
- Using housing support (proxy for deficit in instrumental activities of daily living)

frailty index are reported in the appendix (pp 2, 7–8). Frailty was defined as a frailty index of 0·25 or above, which is one of the two most commonly used cutoffs, with the other being 0·21.[15]

Outcomes

The prognosis of Alzheimer's disease encompasses multiple facets. For this study, we focused on the associations between frailty and cognitive decline, institutionalisation, and mortality, as key elements of Alzheimer's disease prognosis, chosen for their clinical relevance and data availability. Cognitive function was measured by the MMSE, which is commonly used for dementia assessment and follow-up examinations in Sweden.[16] Institutionalisation was ascertained through the National Register of Care and Social Services for the Elderly and Persons with Impairments. Mortality was ascertained from the Swedish National Cause of Death Register.

In sensitivity analyses, we tested the alternative frailty cutoff of 0·21, identified comorbidities differently, excluded home care and housing support from the frailty definition, and restricted the frailty status and Alzheimer's disease prognosis analysis to people with at least three MMSE measurements.

Statistical analysis

The characteristics of the study population at baseline (ie, at the time of receiving a diagnosis of mild cognitive impairment or dementia in SveDem) were described by means and SDs for continuous variables and numbers and proportions for binary and categorical variables.

We conducted age-adjusted and sex-adjusted joint modelling of MMSE decline, institutionalisation, and mortality to investigate the associations between frailty status and MMSE decline in the follow-up period (ie, time since baseline). Rationales behind choosing joint modelling and prototype equations are reported in the appendix (pp 3–4). In addition to frailty status, we evaluated frailty index on a continuous scale in relation to the prognosis of Alzheimer's disease. Age, frailty index, and CSF biomarkers were Z-standardised in the analyses to facilitate comparisons.

We explored whether the use of cholinesterase inhibitors and memantine could mediate the associations between frailty status and Alzheimer's disease prognosis by including these factors in the joint models. Additionally, we examined whether the association between frailty and Alzheimer's disease prognosis differed between early-onset and late-onset dementia by including an interaction term between the frailty index and age at dementia diagnosis in the joint model, excluding individuals with mild cognitive impairment. This analysis was not done for frailty status because of few events among individuals with frailty and early-onset dementia. Furthermore, we estimated standardised cumulative incidences of institutionalisation by frailty status and took competing risk of death into account as well as restricted survival time for institutionalisation with flexible parametric survival models adjusted for age, sex, and MMSE. We also estimated mortality risks and overall restricted survival times by frailty status with the same approach. Lastly, we tested if frailty could modify the associations between CSF biomarkers and cognitive

See Online for appendix

decline by including interaction terms between these CSF biomarkers and frailty in the joint models.

We did several sensitivity analyses to assess the robustness of our results. First, we repeated the analyses with the alternative frailty cutoff of 0·21. Second, we repeated the analyses with an alternative approach to identify comorbidity deficits that prioritised specificity over sensitivity. Third, we excluded home care and housing support from the frailty definition and reanalysed the data to determine whether the associations between frailty and Alzheimer's disease prognosis were primarily driven by these proxies for functional ability. Lastly, we restricted our analysis of frailty status in association with Alzheimer's disease prognosis to individuals with at least three MMSE measurements to evaluate the robustness of our results.

In the presence of missing covariates (ie, CSF P-tau$_{181}$ and T-tau, cholinesterase inhibitor use, and memantine use), we did complete-case analyses. This approach was chosen over more advanced methods for handling missingness, such as multiple imputation, because joint models are already computationally intensive.

The statistical analyses were done in R (version. 4.3.3) and Stata Statistical Software (version 18.0). Joint models were done with R package JMbayes2. Flexible parametric survival models were done with Stata packages stpm2 and standsurv.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The study included 7251 individuals (mean age 72·7 years, 4271 [58·9%] females, 2980 [41·1%] males) with a mean MMSE of 22·3, and 7215 (99·5%) individuals were clinically diagnosed with dementia as opposed to mild cognitive impairment (figure 1; table 1). Compared with individuals who were excluded from the study, those included were younger, had higher MMSE scores, and were less likely to be frail (appendix pp 9–10).

Among the study population, 385 (5·3%) individuals had frailty at baseline (table 1). People with frailty were older, had lower MMSE scores, had lower levels of CSF P-tau$_{181}$, and were less likely to use cholinesterase inhibitors (table 1). The prevalences of individual deficits are reported in the appendix (pp 11–12). Hypertension, polypharmacy, and depression were the most prevalent deficits (appendix pp 11–12).

Individuals included in the study had a mean of two (SD 1·3) MMSE measurements, and the mean follow-up time was 4·5 (2·6) years. Frailty was associated with a 0·723-point (95% CI 0·250–1·196) lower MMSE intercept but not with the MMSE decline rate (table 2; appendix p 13). The associations were attenuated but remained after adjusting for the use of cholinesterase inhibitors and memantine. Frailty index on a continuous scale was not associated with the MMSE intercept but was associated with a slower

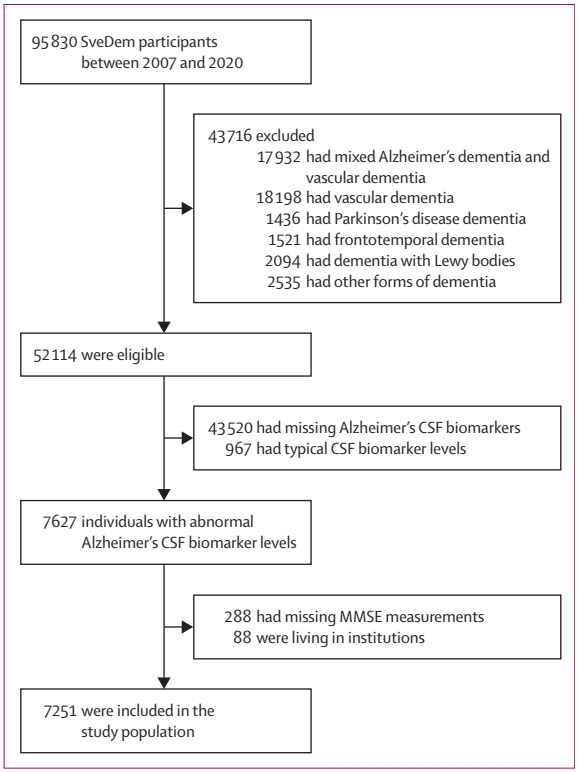

Figure 1: **Flowchart of study participants**
CSF=cerebrospinal fluid. MMSE=Mini-Mental State Examination. SveDem=the Swedish Register of Cognitive/Dementia Disorders.

MMSE decline (coefficient for slope 0·172 [95% CI 0·093–0·251]; appendix p 14). This association was slightly attenuated after adjusting for the use of cholinesterase inhibitors and memantine. When evaluating whether age at dementia diagnosis modified the association between frailty index and the rate of MMSE decline, the results indicated that the association between higher frailty index and a slower MMSE decline was weaker among individuals with late-onset dementia (appendix p 15).

Frailty was associated with a hazard ratio (HR) of 1·91 (95% CI 1·43–2·54) for institutionalisation, even after accounting for cognitive decline rate (table 2). The mortality rate in individuals with frailty was significantly higher than in individuals without frailty (HR 2·41 [95 CI 1·73–3·33]; table 2). Similarly, a higher frailty index was also associated with higher likelihood of institutionalisation (appendix p 14).

The incidence of institutionalisation within 7 years of an Alzheimer's disease diagnosis was slightly higher in individuals with frailty than in those without frailty, peaking at year 4 with a maximum difference of 8·2% (95% CI 3·8–12·5; figure 2A). Non-institutionalised life-years were 1·0-years (0·8–1·3) shorter in people with frailty compared with people without frailty (figure 2B). The average survival probability was lower in individuals with frailty than those without frailty. The difference in survival probability peaked at 15·1% (95% CI 10·7–19·6) approximately 7 years

after an Alzheimer's disease diagnosis (figure 2C). Overall, individuals with frailty had a 1·3-year (95% CI 0·9–1·7) shorter lifespan than those without frailty (figure 2D).

Each CSF biomarker was individually associated with MMSE trajectories. A higher concentration of CSF $A\beta_{42}$ was associated with better cognitive function at baseline and a slower cognitive decline rate, whereas higher concentrations of CSF P-tau_{181} and CSF T-tau were associated with faster cognitive decline (table 3). There were no significant interactions between frailty status and these CSF biomarkers. Similarly, when modelled as a continuous variable, frailty index did not modify the associations between CSF biomarkers and MMSE trajectories, except for the association between $A\beta_{42}$ and the MMSE intercept (appendix p 16).

When choosing the alternative 0·21 cutoff in the frailty index to define frailty, the association between frailty and MMSE intercept was attenuated, and frailty was still significantly associated with institutionalisation and mortality (appendix p 17). In the sensitivity analysis in which the frailty index was constructed to prioritise specificity over sensitivity, the association between frailty and MMSE intercept was no longer significant, whereas the associations of frailty with institutionalisation and mortality remained significant (appendix p 18). Excluding home care or housing support use when defining frailty also attenuated the association between frailty and the MMSE intercept, but frailty remained significantly associated with institutionalisation and mortality (appendix p 19). When restricting the analysis of the association between frailty and Alzheimer's disease prognosis to individuals with three or more MMSE measurements, the magnitude of the association between frailty and the MMSE intercept was larger, and frailty was still significantly associated with a higher hazard of institutionalisation in the future (appendix p 20). However, the association between frailty and mortality was no longer significant, likely due to too few events.

	Non-frail (n=6866)	Frail (n=385)	Overall (n=7251)
Age, years	72·4 (7·7)	77·6 (6·8)*	72·7 (7·7)
Sex			
Female	4032 (58·7%)	239 (62·1%)	4271 (58·9%)
Male	2834 (41·3%)	146 (37·9%)	2980 (41·1%)
MMSE score	22·3 (4·7)	21·7 (4·6)†	22·3 (4·7)
Clinical diagnosis			
Late-onset Alzheimer's dementia	4389 (63·9%)	251 (65·2%)	4640 (64·0%)
Early-onset Alzheimer's dementia	1440 (21·0%)	26 (6·8%)	1466 (20·2%)
Unspecified dementia	1002 (14·6%)	107 (27·8%)	1109 (15·3%)
Mild cognitive impairment	35 (0·5%)	1 (0·3%)	36 (0·5%)
CSF $A\beta_{42}$, ng/L	444 (173)	454 (166)	445 (173)
CSF P-tau_{181}, ng/L	79·6 (35·4)	74·8 (34·1)†	79·3 (35·4)
CSF T-tau, ng/L	713 (390)	665 (340)	710 (388)
Cholinesterase inhibitor use	5085 (74·1%)	224 (58·2%)*	5309 (73·2%)
Memantine use	821 (12·0%)	55 (14·3%)	876 (12·1%)

Data are mean (SD) or n (%). Four people were missing data for P-tau_{181}, four were missing T-tau, 80 were missing cholinesterase inhibitor use, and 133 were missing memantine use. Aβ=amyloid β. CSF=cerebrospinal fluid. MMSE=Mini-Mental State Examination. P-tau=phosphorylated tau. T-tau=total tau. *p value <0·01 for the association between the characteristic and frailty status in linear regression models adjusted for age and sex, except when age or sex was the characteristic of interest. †p value <0·05 for the association between the characteristic and frailty status in linear regression models adjusted for age and sex, except when age or sex was the characteristic of interest.

Table 1: **Baseline characteristics**

	Number of events	Model 1	Model 2
Coefficients (95% CI) for the associations between frailty and longitudinal MMSE*			
Intercept	..	–0·723 (–1·196 to –0·250)	–0·546 (–1·038 to –0·057)
Slope	..	0·125 (–0·257 to 0·499)	0·071 (–0·290 to 0·432)
Hazard ratio (95% CI) for the associations between frailty and institutionalisation†			
Without frailty	3514/6866	1 (ref)	1 (ref)
With frailty	228/385	1·91 (1·43 to 2·54)	1·87 (1·39 to 2·52)
Hazard ratio (95% CI) for the associations between frailty and mortality†			
Without frailty	619/6866	1 (ref)	1 (ref)
With frailty	64/385	2·41 (1·73 to 3·33)	2·38 (1·71 to 3·29)

Model 1 adjusted for Z-standardised age and sex. Model 2 additionally adjusted for the use of cholinesterase inhibitors and memantine. MMSE=Mini-Mental State Examination. *The results are coefficients from the mixed-effect submodel of the joint models. †The results are hazard ratios from the survival submodel of the joint models.

Table 2: **The associations between frailty and cognitive function, institutionalisation, and mortality in people with Alzheimer's disease**

Discussion

In this Swedish register-based cohort study of more than 7000 individuals with Alzheimer's disease confirmed through CSF biomarkers, we found that frailty (as defined by the frailty index) was associated with higher risks of institutionalisation and mortality, shorter overall lifespan, and shorter non-institutionalised lifespan. However, the association between frailty and cognitive decline was not evident, whereas CSF $A\beta_{42}$, P-tau_{181}, and T-tau remained strong predictors for cognitive decline. In addition, frailty did not significantly modify the associations between these CSF biomarkers and cognitive decline.

There is little research on the prevalence of frailty in biomarker-confirmed or clinically diagnosed Alzheimer's disease. A meta-analysis of small studies on the prevalence of physical frailty in clinically diagnosed Alzheimer's disease dementia reported a pooled prevalence of 31·9% (95% CI 15·7–48·5).[17] The prevalence of frailty in our study is low, possibly due to two factors. First, our study population consisted of non-institutionalised Alzheimer's disease patients who had CSF testing and therefore might be less frail than the general clinically diagnosed Alzheimer's disease population. Second, our study might have underestimated the prevalence of frailty in people with biomarker-confirmed Alzheimer's disease due to the scarce primary data for constructing the frailty index. Therefore, further research is needed to better understand the prevalence of frailty in this population.

Studies investigating factors other than antidementia medications (eg, cholinesterase inhibitors) that can predict cognitive decline after the onset of Alzheimer's disease dementia reported inconsistent findings.[18–20] Frailty has been insufficiently investigated in relation to cognitive decline in individuals with Alzheimer's disease. Two

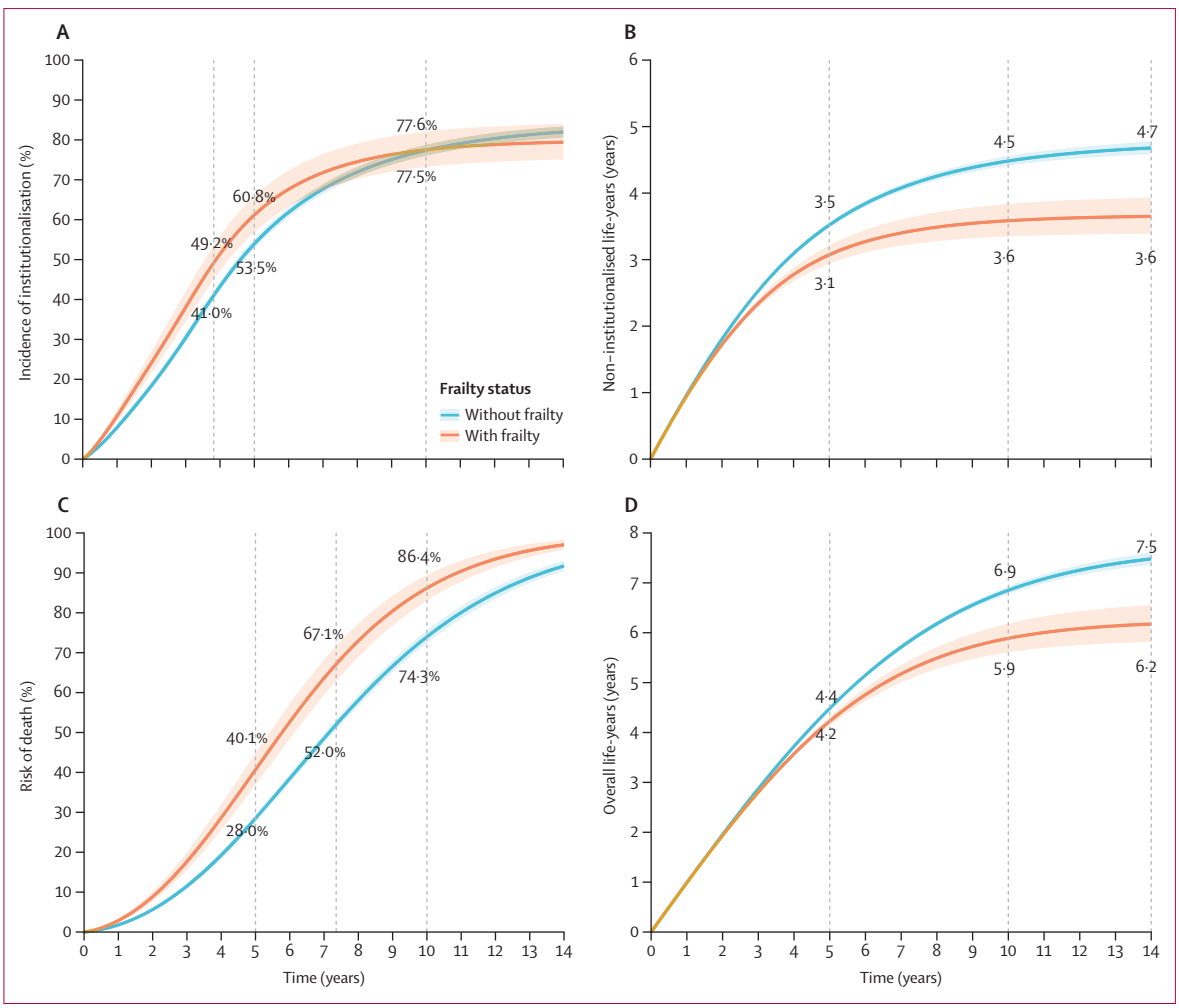

Figure 2: **Absolute risks and survival times by frailty status in people with Alzheimer's dementia**
(A) Incidence of institutionalisation over 14 years of follow-up. (B) Non-institutionalised life-years. (C) Risk of death. (D) Overall life-years.

studies found that patients with dementia and frailty had faster cognitive decline than those without frailty during a 1-year or shorter follow-up period.[6,21] Our study found that people with Alzheimer's disease with frailty had a lower baseline cognitive function but a similar cognitive decline rate than those without frailty, and the association between frailty and lower baseline cognitive function is likely to be clinically subtle. Meanwhile, Alzheimer's disease CSF biomarkers remained key predictors of cognitive decline rate. Notably, frailty in older adults has been linked to brain pathologies beyond Alzheimer's disease pathology, including vascular pathologies.[22] Our study population was more homogeneous than in other studies and consisted of individuals with pathology confirmed through CSF biomarkers, making it probable that Alzheimer's disease pathology was the primary driver of cognitive decline. An alternative explanation for the observed absence of association between frailty and cognitive decline is that the onset of Alzheimer's disease could already signify a substantially diminished physiological reserve, at which point the primary pathological processes driving the disease are likely to predominate in determining its progression. In a retrospective study that reviewed post-mortem brain tissue but not in-vivo CSF biomarkers, frailty index was shown to modify the association between Alzheimer's disease pathology and the clinical manifestation of dementia.[7] However, our study did not support that frailty could modify the associations of CSF biomarkers for Alzheimer's disease with cognitive function or cognitive decline. Nevertheless, considering a mean of two MMSE measurements per individual, a low frailty prevalence, and a relatively homogeneous study population, our findings need to be interpreted with caution and substantiated in future studies incorporating more frequent and comprehensive cognitive assessments.

Factors influencing the risk of institutionalisation in people with Alzheimer's disease have been less investigated.[23,24] Two studies from the Netherlands, one using data from memory clinics and the other using data from primary care registers, reported inconsistent associations

between frailty and institutionalisation.[23,24] Our study found that frailty was a significant predictor of institutionalisation in people with Alzheimer's disease. Frailty reflects decreased physical and mental capacities and can capture people at risk of functional decline, which can explain the association between frailty and institutionalisation.[25] It is noteworthy that excluding proxies for functional ability in the definition of frailty did not alter the significant association between frailty and institutionalisation, meaning that this association could not be explained by baseline functional ability.

Previous research has identified many factors that can influence mortality in Alzheimer's disease.[26] However, relatively few studies have explored the value of frailty in predicting mortality in people with Alzheimer's disease. These studies showed that patients with dementia and frailty had higher mortality rates than patients with dementia but without frailty.[23,24,27] The present study supported the value of frailty, as defined by the frailty index, in predicting mortality rates and life expectancy in individuals with CSF biomarker-confirmed Alzheimer's disease. At age 70 years, the median life expectancy of people with dementia is 4·8 years for men and 7·2 years for women.[28] Therefore, the 1·3-year shorter life-years observed in people with Alzheimer's disease and frailty compared with those without frailty in our study represents a more than 10% reduction in overall life expectancy. Additionally, frailty was associated with a 1·0 years fewer non-institutionalised life-years. Such a decrease can substantially affect the timing of advance care planning, legal and financial arrangements, and the pursuit of personal goals.

This study has important clinical implications. It substantiates the value of the frailty index in predicting major health outcomes, suggesting that the frailty index could serve as a useful tool to identify vulnerable individuals in those with CSF biomarker-confirmed Alzheimer's disease. Individuals with Alzheimer's disease pathology confirmed with CSF biomarkers represent a target group for emerging disease-modifying therapies targeting Aβ. It has been recommended that post-authorisation safety and effectiveness evaluations of medicines for older adults should consider potential differences in safety and effectiveness between individuals with and without frailty.[29] The frailty index could serve as a valuable instrument in such evaluations using real-world registry data. If future research establishes the effect of frailty on the effectiveness and safety of new disease-modifying therapies for Alzheimer's disease, frailty assessment could help identify patients who are more likely to benefit from these treatments and tailor safety monitoring protocols. Furthermore, the frailty index could be used for forecasting health-care resource use and life expectancy in people with Alzheimer's disease. Lastly, our study indicates that the frailty index might have little use in informing disease progression in CSF biomarker-confirmed Alzheimer's disease, whereas CSF biomarkers continue to serve as crucial predictors of cognitive decline.

	Coefficient for intercept (95% CI)	Coefficient for slope (95% CI)
CSF $A\beta_{42}$	0·300 (0·191 to 0·409)	0·144 (0·082 to 0·206)
Interaction between CSF $A\beta_{42}$ and frailty status	–0·345 (–0·836 to 0·147)	0·014 (–0·215 to 0·253)
CSF P-tau_{181}	–0·098 (–0·210 to 0·012)	–0·301 (–0·374 to –0·229)
Interaction between CSF P-tau_{181} and frailty status	–0·031 (–0·523 to 0·464)	–0·048 (–0·313 to 0·214)
CSF T-tau	–0·396 (–0·507 to –0·288)	–0·341 (–0·412 to –0·273)
Interaction between CSF T-tau and frailty status	0·071 (–0·481 to 0·618)	–0·125 (–0·408 to 0·154)

The results are coefficients from the mixed-effect submodel of the joint models with CSF biomarkers and their interactions with frailty included, adjusted for age and sex. CSF biomarkers and age were Z-standardised, and one joint model was applied for each CSF biomarker. Aβ=amyloid β. CSF=cerebrospinal fluid. MMSE=Mini-Mental State Examination. P-tau=phosphorylated tau. T-tau=total tau.

Table 3: **Interactions between CSF biomarkers and frailty status in relation to MMSE trajectories**

This study has several strengths. It included a large cohort of patients with available core Alzheimer's disease CSF biomarkers, enabling the assessment of the value of the frailty index in patients with CSF biomarker-confirmed pathology and the index's interactions with these biomarkers in predicting cognitive decline. Additionally, the study had a long follow-up period, which allowed for the evaluation of long-term associations of frailty with institutionalisation and mortality. The study also provides insights into the relative importance of chronological age, frailty, and CSF biomarkers in predicting various health outcomes. Furthermore, the study employed joint modelling to help mitigate potential biases in assessing the association between frailty and cognitive decline, accounting for the impact of major events such as institutionalisation and mortality. However, several limitations of the study should be acknowledged. The absence of primary care data may result in undetected diseases and symptoms when calculating the frailty index. While we attempted to address this limitation by incorporating medication use, future studies should assess whether using primary care data to calculate frailty index enhances its prognostic value in individuals with Alzheimer's disease. Similarly, due to the lack of functional assessment data and malnutrition data, we relied on social care data as a proxy for functional ability and BMI for nutritional status. As operationalised, the frailty index in this study places greater weight on comorbidity deficits than functional deficits. However, frailty index is still a commonly used frailty operationalisation that quantifies biological vulnerability. Additionally, we used MMSE as the outcome measure for evaluating the association between frailty and cognitive decline, and the average number of MMSE assessments per person was low. Future research incorporating more comprehensive cognitive assessments is needed to confirm our findings. Moreover, due to lacking relevant data, our study did not examine other important health outcomes relevant to individuals with Alzheimer's disease, such as falls or quality of life. Another limitation of this study is that there were very few individuals with mild cognitive impairment, making it impossible to investigate whether the association between

frailty and Alzheimer's disease prognosis varies by Alzheimer's disease stage. Lastly, our study population was younger and less frail than other dementia patients in SveDem; thus, our findings may not be generalisable to all individuals with Alzheimer's disease in Sweden or other settings.

In conclusion, our study suggests that frailty is associated with a worse prognosis, and the frailty index is a feasible tool to identify frailty in people with Alzheimer's disease. Frailty index is particularly valuable for predicting future institutionalisation and mortality risk but may have limited value in predicting cognitive decline compared with Alzheimer's disease CSF biomarkers.

Contributors

XX conceived the idea, designed the study, analysed data, and drafted and revised the manuscript. LJ and RRO contributed to the conceptualisation of the study. LJ acquired funding for this study. LJ, ME, HZ, SK, and TS contributed to data acquisition and had access to the data. All authors reviewed the manuscript, provided critical feedback, and approved the submission of the manuscript for publication. XX is the guarantor of the study. XX and LJ accessed and verified the raw data.

Declaration of interests

HZ has served at scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, Wave, Merck Sharp & Dohme, and ScandiBio Therapeutics; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, Roche, WebMD, LabCorp, and OyMedix Biochemica; and is a cofounder of Brain Biomarker Solutions in Gothenburg, which is a part of the GU Ventures Incubator Program, and a shareholder of CERimmune Therapeutics (outside the submitted work). ME has served as a speaker and/or consultant on dementia on sporadic advisory board meetings for Biogen, Eisai, Bioarctic, Roche, Eli Lilly, NovoNordisk, and Gothia Kompetens; has received meeting fees from the Swedish Dementia Centre; has served as a board member of Queen Silvia Dementia Foundation, Foundation Borgerskapets Enkehus och Gubbhus, and Nasjonalforeningen for folkehelsen Oslo (unpaid). BW has served at scientific advisory boards for Artery Therapeutics, NSC Therapeutics, and Phanes Biotech; has served at the data safety monitoring board for PRImus-AD; and holds stocks in Artery Therapeutics and AlzeCure. LJ receives licence fees from RUD instrument and consulting fees from Lundbeck, Takeda, and TEVA Pharmaceuticals; has given lectures sponsored by Eli Lilly and Novo Nordisk; and has received support for travelling or conferences from Bioarctic. SK has served at scientific advisory boards, as a speaker, and/or as a consultant for Roche, Eli Lilly, Geras Solutions, Optoceutics, Biogen, Eisai, Merry Life, Triolab, Novo Nordisk, and Bioarctic, unrelated to present study content. All other authors declare no competing interests.

Data sharing

In accordance with Swedish regulations, we are unable to share the data used in this study. Researchers can access the Swedish Registry for Cognitive/Dementia Disorders (SveDem) and other Swedish registers after receiving ethical approvals from ethical review authorities and approvals from the register holders.

Acknowledgments

Data for this study were obtained from the (SveDem). SveDem is funded by the Swedish Association of Local Authorities and Regions. This project is supported by the Innovative Health Initiative Joint Undertaking under grant agreement 101112145. The Joint Undertaking receives support from the EU's Horizon Europe Research and Innovation Programme, Combinostics Oy, and Bioarctic. Views and opinions expressed are those of the authors and do not necessarily reflect those of the aforementioned parties. None of the aforementioned parties can be held responsible for them. This research was partly funded by Vinnova (grant number 2021–02680). HZ is a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council supported by grants from the Swedish Research Council (2023-00356, 2022-01018, and 2019-02397), the EU's Horizon Europe Research and Innovation Programme (101053962), Swedish State Support for Clinical Research (ALFGBG-71320), the Alzheimer Drug Discovery Foundation, USA (201809-2016862), the Alzheimer's Disease Strategic Fund and the Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, ADSF-21-831377-C, and ADSF-24-1284328-C), the European Partnership on Metrology, co-financed from the EU's Horizon Europe Research and Innovation Programme and by the Participating States (NEuroBioStand, 22HLT07), the Bluefield Project, Cure Alzheimer's Fund, the Olav Thon Foundation, the Erling-Persson Family Foundation, Familjen Rönströms Stiftelse, Familjen Beiglers Stiftelse, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2022-0270), the EU's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement (860197; MIRIADE), the EU Joint Programme—Neurodegenerative Disease Research (JPND2021-00694), the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, the UK Dementia Research Institute at UCL (UKDRI-1003), and an anonymous donor. SK was financed by grants from the Swedish State under the agreement between the Swedish Government and the county councils, the ALF agreement (ALFGBG-1005471, ALFGBG-965923, ALFGBG-81392, ALFGBG-771071), the Alzheimerfonden (AF-842471, AF-737641, AF-929959, AF-939825), the Swedish Research Council (2019–02075, 2019–02075_15), Stiftelsen Psykiatriska Forskningsfonden, and the Swedish Brain Foundation (FO2024–0097). RRO is funded by a grant from Research Ireland (18/FRL/6188). BW is supported by the foundation Margaretha af Ugglas, the Swedish Research Council (2024–03573), and the Swedish Brain Foundation (FO2024–0287). ME was funded by the Swedish Research Council (2024–03573), Swedish Brain Foundation (FO2024–0339), the ALF agreement (FoUI-975207), and the Paulsson foundation. LJ is funded by the Innovative Health Initiative Joint Undertaking (101112145), PREDEM (Vinnova grant 2021-02680), the Swedish Research Council for Health, Working Life and Welfare, and Novo Nordisk.

References

1 No authors listed. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement* 2024; **20:** 3708–821.
2 Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet* 2019; **394:** 1365–75.
3 Koria LG, Sawan MJ, Redston MR, Gnjidic D. The prevalence of frailty among older adults living with dementia: a systematic review. *J Am Med Dir Assoc* 2022; **23:** 1807–14.
4 Ward DD, Wallace LMK, Rockwood K. Frailty and risk of dementia in mild cognitive impairment subtypes. *Ann Neurol* 2021; **89:** 1221–25.
5 Trebbastoni A, Canevelli M, D'Antonio F, et al. The impact of frailty on the risk of conversion from mild cognitive impairment to Alzheimer's disease: evidences from a 5-year observational study. *Front Med* 2017; **4:** 178.
6 Benussi A, Mattioli I, Silvestri C, et al. Defining the role of frailty in the transition from mild cognitive impairment to dementia and in dementia progression. *Dement Geriatr Cogn Disord* 2024; **53:** 57–65.
7 Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol* 2019; **18:** 177–84.
8 Kim DH, Rockwood K. Frailty in older adults. *N Engl J Med* 2024; **391:** 538–48.
9 Dobson R, Patterson K, Malik R, et al. Eligibility for antiamyloid treatment: preparing for disease-modifying therapies for Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2024; **95:** 796–803.

10 Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 2014; **43:** 10–12.

11 Orkaby AR, Callahan KE, Driver JA, Hudson K, Clegg AJ, Pajewski NM. New horizons in frailty identification via electronic frailty indices: early implementation lessons from experiences in England and the United States. *Age Ageing* 2024; **53:** afae025.

12 Religa D, Fereshtehnejad SM, Cermakova P, et al. SveDem, the Swedish Dementia Registry—a tool for improving the quality of diagnostics, treatment and care of dementia patients in clinical practice. *PLoS One* 2015; **10:** e0116538.

13 Gobom J, Parnetti L, Rosa-Neto P, et al. Validation of the LUMIPULSE automated immunoassay for the measurement of core AD biomarkers in cerebrospinal fluid. *Clin Chem Lab Med* 2021; **60:** 207–19.

14 Mak JKL, Hägg S, Eriksdotter M, et al. Development of an electronic frailty index for hospitalized older adults in Sweden. *J Gerontol A Biol Sci Med Sci* 2022; **77:** 2311–19.

15 Gordon EH, Reid N, Khetani IS, Hubbard RE. How frail is frail? A systematic scoping review and synthesis of high impact studies. *BMC Geriatr* 2021; **21:** 719.

16 Socialstyrelsen. Nationella riktlinjer för vård och omsorg vid demenssjukdom. 2017. https://www.socialstyrelsen.se/contentassets/8315c1b65e064fcb92065392c74b942c/2017-12-2.pdf (accessed Sept 24, 2025).

17 Kojima G, Liljas A, Iliffe S, Walters K. Prevalence of frailty in mild to moderate Alzheimer's disease: a systematic review and meta-analysis. *Curr Alzheimer Res* 2017; **14:** 1256–63.

18 Zuliani G, Zuin M, Romagnoli T, Polastri M, Cervellati C, Brombo G. Acetyl-cholinesterase-inhibitors reconsidered. A narrative review of post-marketing studies on Alzheimer's disease. *Aging Clin Exp Res* 2024; **36:** 23.

19 Gottesman RT, Stern Y. Behavioral and psychiatric symptoms of dementia and rate of decline in Alzheimer's disease. *Front Pharmacol* 2019; **10:** 1062.

20 Loeffler DA. Modifiable, non-modifiable, and clinical factors associated with progression of Alzheimer's disease. *J Alzheimers Dis* 2021; **80:** 1–27.

21 Kelaiditi E, Canevelli M, Andrieu S, et al, and the Impact of Cholinergic Treatment Use Study/DSA Group. Frailty index and cognitive decline in Alzheimer's disease: data from the Impact of Cholinergic Treatment Use Study. *J Am Geriatr Soc* 2016; **64:** 1165–70.

22 Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. *Neurology* 2013; **80:** 2055–61.

23 Haaksma ML, Rizzuto D, Ramakers IHGB, et al. The impact of frailty and comorbidity on institutionalization and mortality in persons with dementia: a prospective cohort study. *J Am Med Dir Assoc* 2019; **20:** 165–70.e2.

24 Joling KJ, Janssen O, Francke AL, et al. Time from diagnosis to institutionalization and death in people with dementia. *Alzheimers Dement* 2020; **16:** 662–71.

25 Li X, Ma L. From biological aging to functional decline: insights into chronic inflammation and intrinsic capacity. *Ageing Res Rev* 2024; **93:** 102175.

26 Zheng X, Wang S, Huang J, Li C, Shang H. Predictors for survival in patients with Alzheimer's disease: a large comprehensive meta-analysis. *Transl Psychiatry* 2024; **14:** 184.

27 Kelaiditi E, Andrieu S, Cantet C, Vellas B, Cesari M, and the ICTUS/DSA Group. Frailty index and incident mortality, hospitalization, and institutionalization in Alzheimer's disease: data from the ICTUS study. *J Gerontol A Biol Sci Med Sci* 2016; **71:** 543–48.

28 Brück CC, Mooldijk SS, Kuiper LM, et al. Time to nursing home admission and death in people with dementia: systematic review and meta-analysis. *BMJ* 2025; **388:** e080636.

29 Denkinger M, Knol W, Cherubini A, et al. Inclusion of functional measures and frailty in the development and evaluation of medicines for older adults. *Lancet Healthy Longev* 2023; **4:** e724–29.