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ASSOCIATIONS BETWEEN FRAILTY, NEURODEGENERATIVE BIOMARKERS, AND NEUROIMAGING MEASURES IN YOUNG-ONSET MILD COGNITIVE IMPAIRMENT

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Abbreviations

Aβ – Amyloid β
AD – Alzheimer's disease
ADL – Activities of Daily Living
ApoE – Apolipoprotein E
APP – Amyloid Precursor Protein
BET – brain-extracted
BMI – Body Mass Index
CBD – Corticobasal degeneration
CBS – Corticobasal syndrome
CDR – Clinical Dementia Rating
CSF – Cerebrospinal fluid
DTI – Diffusion tensor imaging
DLB – Dementia with Lewy-body
FA – Fractional anisotropy
FI – Frailty Index
FDA-NIH – Food and Drug Administration – National Institute of Health
FDG – ^{18}F-fluordeoxyglucose
FOV – Field of View
FSL – FMRIB Software Library
FTD – Frontotemporal dementia
FTLD – Frontotemporal lobar degeneration
FWE – Family-wise error
GDS – Global Deterioration Scale
GLM – General Linear Model
HD – Huntington's Disease
IADL – Instrumental Activities of Daily Living
IQR – Interquartile range
LBD – Lewy-body disease
MCI – Mild cognitive impairment
MD – Mean diffusivity
MIBG – Metaiodobenzylguanidine
MNI 152 – Montreal Neurological Institute's 152
MRI – Magnetic resonance imaging
NIA-AA – National Institute on Aging-Alzheimer's Association
NfL – Neurofilament light chain
NPI – Neuropsychiatric Inventory
PD – Parkinson's Disease
PET – Positron emission tomography
PPA – Primary progressive aphasia
PSEN1 – Presenilin 1 gene
PSEN2 – Presenilin 2 gene

p-tau – Phosphorylated tau
PSP – Progressive supranuclear palsy
RD – Radial diffusivity
SPECT – Single-photon emission computed tomography
TBSS – Tract-Based Spatial Statistics
TE – Echo Time
TFCE – Threshold-Free Cluster Enhancement
TIA – Transient Ischemic Attack
TR – Repetition Time
t-tau – Total tau
VaD – Vascular dementia
VBM – Voxel-based morphometry
VCI – Vascular cognitive impairment
WMHs – White matter hyperintensities

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1. Introduction

1.1. Background

The ageing population and the treatment of patients with cognitive disorders represent one of the major health challenges of the 21st century. Demographic projections indicate a significant increase in the elderly population in the coming decades. Considering that old age is one of the main risk factors for the development of dementia, it is reasonable to expect a significant increase also in the absolute number of people with this condition. The most recent forecasts estimate that 152 million people will suffer from dementia worldwide by 2050[1]. This phenomenon raises significant public health issues, since functional decline associated with cognitive impairments profoundly impact the quality of life of patients and available healthcare resources[2].

To anticipate the complications that this condition implies, it is necessary to identify at an early stage those individuals with a high risk of developing dementia[3]. In this context, individuals with mild cognitive impairment (MCI) constitute a heterogeneous population in which cognitive decline does not affect the patient's functional autonomy in performing the activities of daily living[4,5] and whose condition is often considered as an intermediate stage in the progression from normal cognitive functioning to dementia[6]. Recent evidence suggests, however, that not only can the condition of MCI remain stable over time, but it may even revert to normal cognition[3,7,8].

Therefore, it is meaningful to identify biomarkers that allow to stratify the risk of conversion from MCI to dementia. The most widely used biomarkers are measured in cerebrospinal fluid (CSF) and neuroimaging techniques[9], although plasma biomarkers have also been studied more recently for clinical use[10].

From a clinical point of view, biomarkers provide objective support for diagnosis and represent an important aid in the prognosis of MCI, allowing the identification of those subjects at greater risk of evolution to dementia[9].

In parallel, frailty has emerged as an important predictor of cognitive decline[11]. Frailty is a multidimensional clinical construct consisting of a condition of increased vulnerability of the organism to external stressors that leads to reduced functional reserve and progressive decline of physiological systems[12]. The main approaches to frailty include Fried's frailty phenotype - which identifies frailty based on the presence of at least three among unintentional weight loss, fatigue,

muscle weakness, slowed walking speed and reduced physical activity[13] - and the deficit accumulation model proposed by Rockwood, which quantifies frailty through the ratio of the number of accumulated deficits to the total number of assessable deficit[14].

Proper measurement of frailty is of primary importance, since frail patients often live with multiple pathologies that usually precede complications leading to loss of autonomy even after minor stress[15]. It should be considered that frailty correlates with polypharmacy and a higher risk of drug interactions, resulting in prolonged hospitalization, increased morbidity, and mortality[15]. It has been pointed out that not only could be there an additive interaction, but also synergy between comorbidities and polypharmacy, underlining how a correct framing of the frail patient is fundamental to understanding their health needs[16,17].

Recent studies showed that frailty assessment may have predictive, preventive and clinical value in individuals with MCI, where a multidisciplinary approach, review of drug therapy, prevention of falls, and personalised programmes are key elements in patient's management[18]. Furthermore, longitudinal studies[19,20] seem to indicate that frailty precedes and increases the risk of dementia even years before diagnosis. However, a reverse causality remains possible, i.e. diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) may themselves occur early with frailty[18].

Although growing evidence supports a link between frailty and neurocognitive disorders[19,21], few studies have examined this relationship by integrating neuroimaging and fluid biomarkers in individuals with MCI, specifically in those with young onset MCI[19].

This thesis aims to investigate cross-sectional associations between frailty, fluid biomarkers, and brain imaging characteristics in young-onset MCI, with the objective of improving risk stratification and informing early intervention approaches.

1.2. Mild Cognitive Impairment (MCI)

1.2.1. Definition and criteria

MCI is an intermediate clinical condition between preserved cognition and dementia[4]. This definition has had a strong impact on the scientific community, by outlining clear diagnostic criteria:

- Presence of a subjective memory disorder, preferably confirmed by a reliable informant
- Objective memory decline by age and educational level
- General preservation of cognitive functions
- Independence in activities of daily living (ADL)
- Absence of dementia

This first model focused specifically on memory impairments.
These criteria were later expanded[5] to include subtypes of MCI, in particular:

- Amnestic MCI (a-MCI), if neuropsychological tests show a deficit predominantly at the level of episodic memory
- Non-amnestic MCI (na-MCI), if neuropsychological tests show deficits in other cognitive domains, such as executive functions, language, or visual-spatial abilities

The presence of isolated or multiple alterations was further added as feature to characterise MCI, thus defining the construct of single-domain MCI and multi-domain MCI[5,22].

Table 1 – Classification of clinical subtypes of mild cognitive impairment, inspired by Petersen RC, Mild cognitive impairment as a diagnostic entity, Journal of Internal Medicine. 2004;256(3): 183-194

	Single domain impairment	**Multiple domain impairment**
Memory impairment	Amnestic MCI Single Domain Impairment	Amnestic MCI Multiple Domain Impairment
Cognitive domain other than memory impaired	Non-Amnestic MCI Single Domain Impairment	Non-Amnestic MCI Multiple Domain Impairment

Single domain a-MCI is frequently a precursor to Alzheimer Dementia[23], while a higher heterogeneity is observed within the single and multiple domain na-MCI subtype, with patients progressing to diverse conditions such as vascular cognitive impairment (VCI), primary progressive aphasia (PPA), frontotemporal dementia, dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), or corticobasal degeneration (CBD)[24–26]. However, atypical phenotypes as well as mixed pathologies further complicates the evaluation of these patients.

1.2.2. Epidemiology

MCI is a highly prevalent clinical syndrome among older adults. According to the most recent studies, the prevalence of MCI is between 15-20% in population aged 50 years and older, with an increase with age[27–29]: according to the 2018 American Academy of Neurology guideline on MCI[30], MCI ranges from 6.7% for ages 60-64 to 25.2% for ages 80-84. In a community-based study[31], overall prevalence was 7,7%, and it ranged from 6,7% for age 65-74, to 9,8% for over 85.

From a geographical point of view, there could be potential regional differences in the progression from MCI to dementia. However, it must be considered that the differences could be due to study-specific characteristics and the difference in the prevalence of risk factors for MCI in individual regions of the world[8,32].

1.2.3. Clinical relevance

MCI is a heterogeneous condition, not only in terms of cognitive profiles, but also in terms of clinical trajectories: systematic reviews indicate that a significant proportion of individuals with MCI convert to dementia annually, although a substantial proportion remains stable or even reverts to normal cognitive function over time[3,7,8,27,28,33].

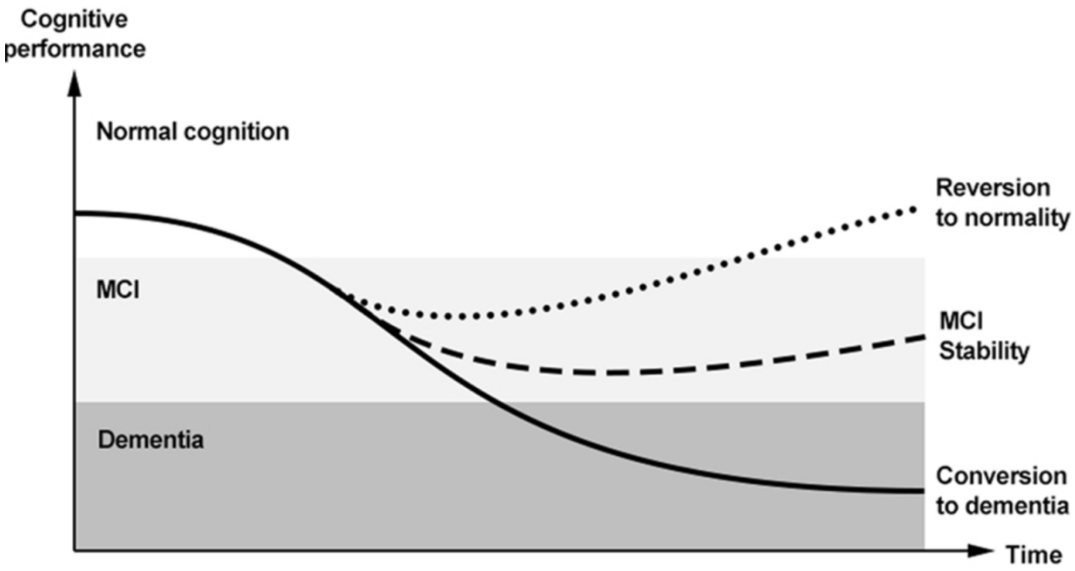

Figure 1 – Trajectories of cognitive functioning and possible outcomes of MCI in the so-called "dementia continuum"(Canevelli et al., 2017). Licenced under CC BY 4.0.

In particular, it has been observed that the proportion of people living with MCI who do not progress to dementia is around 50%, considering both clinical and community settings. Conversely, the likelihood of conversion to dementia is substantially higher in the clinical than in the community setting (41.5% vs 27.0%), while reversion rates show the opposite trend, being more frequent in the community-based setting (28.2% vs 8.7%)[8]. The most frequently encountered conversion is to AD, then VaD, FTD, and DLB follow[8,30].

The recognition of MCI represents an important opportunity to programme effective interventions since it marks a phase in which cognitive decline is objectively measurable, without impairing functional independence yet, and enabling the implementation of preventive, monitoring, and therapeutic strategies, particularly concerning modifiable risk factors such as hypertension, diabetes, social isolation, and cognitive inactivity[34,35].

Proper assessment of MCI is crucial to exclude reversible causes of cognitive impairment, to help patients and family members understand the origin of cognitive impairments, to consciously address the prognostic significance of diagnosis, and to facilitate future planning[24,30]. For this reason, the clinical interview is a key aspect for the identification of amnesic disorders or impairments in other domains, in the presence of a reliable informant.

Furthermore, it is fundamental to conduct a comprehensive physical examination including a neurological assessment to exclude non-degenerative causes of cognitive changes, to collect a complete medication history to identify possible drugs with adverse effects on cognitive function, to assess the patient's sleep to identify dementias associated with sleep-related disorders as well as proper sleep hygiene, which can significantly affect cognitive performance, to exclude underlying psychiatric conditions, particularly depression[36,37].

Neuropsychological tests provide an objective measure of cognitive functions and can help to exclude confounders such an underlying depressive disorder[24]. Some assessment scales, such as the Clinical Dementia Rating (CDR) and the Global Deterioration Scale (GDS), contribute to the characterisation of the degree of impairment, but are not sufficient on their own to make a diagnosis of MCI[30].

Some studies have pointed out that the conversion rate of MCI to dementia decreases progressively during follow-up[8,38,39]. Two hypotheses have recently been proposed for this observation: the first suggests that the likelihood that a neurodegenerative disease is the cause of MCI decreases over time;

the second proposes that in some subjects, although a neurodegenerative disease is underlying, due to clinical and functional characteristics, the condition of MCI stabilises or decelerate in its evolution[8].

1.3.Frailty

1.3.1. Definition

Frailty is a clinical condition characterised by a reduced capacity to respond to physiological stressors, resulting from an age-related multisystemic decline. This state of vulnerability increases the risk of adverse events, such as disability, hospitalisation, and death[40] .

The concept of frailty was initially developed on physical criteria, proposed by Linda Fried[13], as follows:

- Involuntary weight loss
- Weakness
- Slowness in gait
- Low physical activity
- Exhaustion

Simultaneously, Arnold Mitniski formalised a version of frailty interpreted as accumulation of deficits or clinical frailty, which includes:

- Comorbidities
- Disabilities
- Symptoms
- Clinical signs
- Polypharmacy
- Alterations in laboratory measurements
- Sensory deficits
- Low social support
- Functional impairments

These features ultimately lead to higher incidence of hospitalization and death[14,40].

Following this model, Mitnitski and Kenneth Rockwood successively operationalized frailty as accumulation of deficits through a detailed scale which considers the ratio of the number of deficits to the total number of assessable items, defined as Frailty Index (FI)[14].

According to Canevelli et al.[18], frailty is a cross-sectional indicator of elderly health, influencing the prognosis of many neurological conditions, including dementia and cognitive decline[41]. The multidimensional approach allows frailty to be viewed as an interaction between biological, psychological, and environmental factors, suggesting that its assessment may provide relevant clinical indications for the treatment of elderly patients[11].

Of relevance, MCI is not considered in the definition of physical frailty, although there may be pathophysiological associations between cognitive deficits and frailty[19,42,43]. Furthermore, not only is frailty associated with an increased risk of cognitive decline, but it has also been observed that the presence of cognitive decline could expose individuals to increased frailty[20,44]. Hence, it is important to consider frailty as a possible determinant of the evolution of cognitive decline[2,44], both because of the possible biological and aetiological implications that exist between these two conditions[20,44], and because of the impact on the subjects' global functionality and the incidence of adverse negative outcomes[18].

1.3.2. Prevalence

Epidemiological estimates of frailty in the literature have shown a variable prevalence in the elderly population[45]. The results obtained from some systematic reviews have found a variable prevalence, influenced by the care context and the criteria used to define it[46–48].

In people living in the community, the prevalence is between 10-15% based on the physical model, and 20-30% in studies which adopted the FI[49]. Not surprisingly, in hospital settings, these percentages increase significantly, even exceeding 40-50% as reported by other studies[48]. Therefore, the estimation of prevalence not only is the result of the different characteristics of the populations, but it is made ulteriorly complicated by the different scales adopted in the scientific field, which reflect various approaches to the definition of this construct[47].

In addition, frailty condition is more prevalent among women than men[50,51], while pre-frailty is estimated about 30-50% of people aged over 65 years old[46,51,52].

1.3.3. Frailty measurement

It is crucial to assess frailty properly because if identified and treated, the incidence of adverse events such as falls, disability, and hospitalisation could be reduced[13,53]. In clinical and research settings, measuring frailty requires standardised and reproducible instruments [54,55]. Currently, most of the tools used to establish frailty are based on the physical frailty model[13] and the deficit accumulation model or Frailty Index (FI)[14].

Whereas phenotypic frailty is considered to be the result of a multisystem biological decline that manifests itself through the core symptoms[13], the deficit accumulation model measures frailty providing an overall measure of clinical risk independent of a specific biological mechanism[14].
The frailty phenotype proposed by Fried is the most cited tool to assess frailty[56]. This model has considerable clinical relevance because it has identified three different phenotypes, based on the number of criteria presented: the frail phenotype requires at least three out of five criteria, pre-frailty corresponds to the presence of one or two criteria, while robustness to their complete absence. This is essential since it has made it possible to stratify individuals at higher risk of death, disability, disease complications, through criteria that are easy to apply in the clinical setting[13,50]. The measures for physical frailty are[13]:

- 5% body weight loss in the last year
- decreased grip strength for weakness
- increased time to walk 15 feet for slowness,
- <383 Kcals spent per week for males and <270 Kcals for females for reduced physical activity
- self-reported exhaustion

Although this is the best-known model for measuring frailty, it has some limitations: it does not consider psychosocial components for frailty assessment, while it includes grip strength as criterion, which is not commonly measured in clinical practice[55].

In contrast, the accumulation of deficit model quantifies frailty through the sum of a certain number of items who express an impairment or the presence of a pathology in a particular domain[14,40]. The

assessment is generally based on the compilation of at least 20 items, with the final score reflecting the proportion of the detected deficits in relation to the total items considered[14]. One of the main strengths of this method lies in the fact that it can be constructed from data already available in clinical documentation, making it particularly suitable for retrospective use[45].

In addition, the FI has demonstrated high sensitivity in detecting adverse clinical events in both hospital and community settings, although its operational complexity limits its use in routine clinical practice[55].

An electronic FI (eFI) has been developed and validated in the UK using available primary care electronic health record data from more than 900,000 patients[57,58]. Recently, an updated version of the eFI – the eFI2 – has been developed, showing even higher overall performance than the original eFI in predicting adverse frailty-related outcomes[59]. Furthermore, the eFI2, rather than the eFI, has the advantage of weighting deficit variables, including time constraints and frailty category cut-points mapped from a reference standard. The major advantage of these scales is their external validation and, in the future, they will play a role in the management of people living with frailty to implement prevention strategies for negative outcomes[57,59].

1.4. Biomarkers and MCI

1.4.1. General definition and role of biomarkers in cognitive disorders

In clinical and research settings, the use of biomarkers has become essential to objectively measure biological changes related to disease and health states. According to the FDA-NIH Biomarker Working Group, a biomarker is 'A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics'[60].

Biomarkers are a key factor in the early detection of diseases that lead to the development of dementia. In particular, they find application in early diagnosis[61,62], in monitoring disease progression over time[63,64], and in risk stratification of conversion from MCI to dementia[65]. Furthermore, they are used as endpoints in clinical trials investigating disease-modifying drugs[66,67].

Currently, several updated documents and guidelines from scientific societies are available to define how to use biomarkers effectively and appropriately in patients with MCI or dementia[9,68–71].

1.4.2. Biomarkers in MCI

As mentioned above, biomarkers are widely used in the characterisation of patients with MCI mainly for the following reasons:

- Making an early diagnosis of neurodegenerative diseases
- Monitoring the course of any underlying disease process
- Identifying patients that could access clinical trials

The biomarkers studied are mainly obtained from CSF or by neuroimaging techniques[72]. Recently, serum biomarkers such as neurofilament light chain (NfL) have also been considered[10,73].

European recommendations for a biomarker-based diagnosis of neurocognitive disorders were published in 2024[9]. This consensus was not limited to the diagnostic workflow for AD, but it also investigated the best diagnostic practices for other disorders responsible for cognitive deterioration, such as frontotemporal lobar degeneration (FTLD), Lewy body disease (LBD), atypical Parkinsonisms such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), vascular cognitive impairment (VCI), and other neurological or psychiatric disorders[9,74–76].

In particular, starting from a clinical suspicion of MCI or mild dementia, the diagnostic work-up includes a complete clinical examination, comprehensive of blood tests to exclude vitamin deficits, neuropsychological tests, and a neuroimaging examination possibly with structural MRI with dedicated sequences[9].

Based on the diagnostic suspicion following the results obtained, first-line biomarkers are determined. Specifically, CSF biomarkers of β-amyloid plaques (Aβ) and fibrillar tau protein should be measured in suspected AD, while FDG-PET should be performed in suspected FTLD or movement tauopathy (e.g. PSP or CBS)[9]. Likewise, a DAT-SPECT is indicated when LBD is suspected[77].

Based on the results obtained from first-line biomarkers, the workup then provides whether an aetiological diagnosis can be determined or whether it is excluded and alternative diagnoses should be considered. In case of diagnostic uncertainty, second-line biomarkers should be measured.

According to this consensus, there is moderate agreement on searching for biomarkers routinely in patients under 70 years of age who present with cognitive complaints[9].

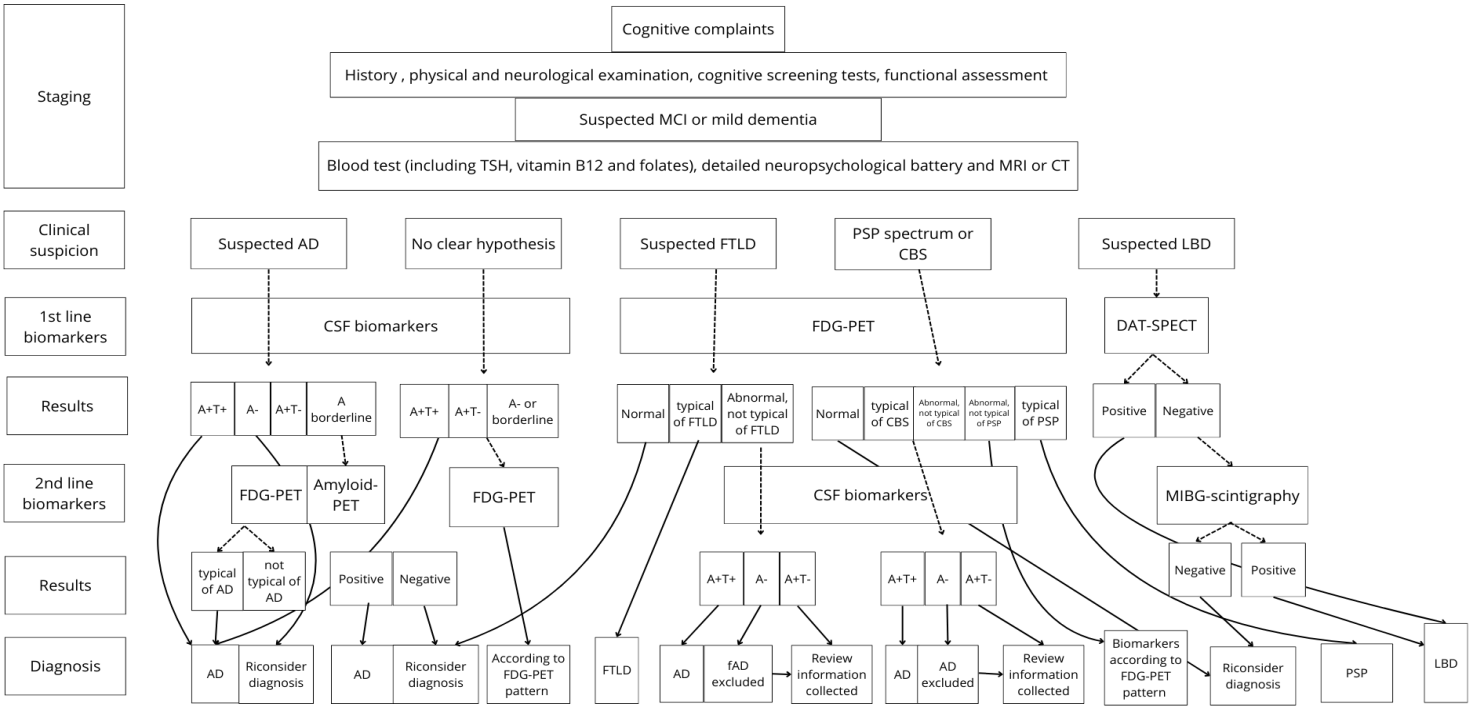

Figure 2 – Diagnostic workflow based on biomarkers proposed by the European consensus. Adapted from Frisoni G et al., European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders. The Lancet Neurology. 2024;23(3):302-312

Regarding the biological diagnosis of AD, the NIA-AA Research Framework in 2018 proposed the ATN classification for the diagnosis of AD[72], where:

- 'A' stands for biomarkers of β-amyloid plaques (Aβ)
- 'T' stands for biomarkers of fibrillar tau protein
- 'N' represents the biomarkers of neurodegeneration

As reported by this model, the biomarkers of Aβ are cortical amyloid-PET ligand binding or low CSF $A\beta_{42}$[78], the proposed biomarkers for fibrillar tau protein are increased phosphorylated tau protein (p-tau) in CSF[78], and cortical tau-PET ligand binding. Finally, biomarkers of neurodegeneration are CSF t-tau, FDG-PET hypometabolism, and atrophy on MRI.

Referring to the latter, it is relevant to underline that these biomarkers are not specific for the diagnosis of AD, but are indicative of neuronal damage due to various causes and provide important information about the prognosis of the cognitive decline[72], being neurodegeneration the aspect that correlates the most with decline in cognitive functions[79].

Finally, another noteworthy biomarker of neuronal degeneration which is not included in the NIA-AA Research Framework is CSF NfL, which is associated with hippocampal and grey matter atrophy[80].

As can be seen, a complete characterisation according to the ATN model is only possible by performing a lumbar puncture and imaging examination[72], and only pathological Aβ au protein should be considered as specific hallmarks of AD[72].

Table 2 – Biomarker profiles proposed by the 2018 NIAA-AA research framework to indagate the AD continuum classification[72]

AT(N) profiles	Biomarker category
A-T-(N)-	Normal AD biomarkers
A+T+(N)-	AD*
A+T+(N)+	AD*
A+T-(N)-	Alzheimer's pathogenesis*
A+T-(N)+	Alzheimer's pathogenesis*
A-T+(N)-	Non-AD pathogenesis
A-T-(N)+	Non-AD pathogenesis
A-T+(N)+	Non-AD pathogenesis

*Alzheimer's pathogenetic continuum: umbrella term that applies both to Alzheimer's pathogenesis, in an early phase, and AD in a later phase.

In addition to fluid biomarkers, imaging is widely employed in MCI for risk stratification and early diagnosis of diseases that may evolve towards dementia[9].

Neuroimaging biomarkers frequently evaluated in cognitive disorders are:

- Grey matter atrophy
- White matter hyperintensities (WMHs)
- Structural brain connectivity

Grey matter atrophy is an early indicator of neurodegenerative causes of MCI, and the reduction in hippocampal volume is considered a biomarker of Alzheimer's disease[81,82]. In addition to hippocampus degeneration, a volume reduction can be observed in the temporo-parietal associative cortices, particularly in regions involved in cognitive integration and spatial memory processes [83].

WMHs and cerebral microangiopathy are frequently observed in individuals with MCI[84,85]. WMHs are white matter lesions visible on MRI, often related to chronic vascular dysfunction. Their extent has been associated with more pronounced cognitive deficits and an increased risk of transition to dementia[86,87].

Changes in brain connectivity represent another recent relevant aspect in MCI[88]. Studies based on advanced neuroimaging techniques, such as Diffusion Tensor Imaging (DTI), have revealed reduced white matter integrity in the connections between the hippocampus and associative cortical regions, impairing the efficiency of communication between different brain areas[89].

2. Aim of the study

In recent years, there has been a growing interest in the study of the association between MCI and frailty.

A recent study by Canevelli et al. that considered a 40-items FI for the study of frailty and biomarkers of AD including CSF $A\beta_{1-42}$, 181p-tau e t-tau, hippocampal volume at MRI, study of FDG-PET, and F-AV-45-PET in a cohort including cognitively normal, MCI and dementia subjects, found that subjects with higher frailty had lower CSF and PET amyloid burden as well as lower hippocampal volume and FDG-PET metabolism. These authors also showed that increasing frailty levels were associated with a weakened relationship between these biomarkers and the severity of dementia, suggesting that frailty contributes to the discrepancies between AD pathology and its clinical manifestations [90]. Similarly, another very recent study found that, in patients with MCI, frailty was associated with a lower likelihood of AD biomarker positivity, suggesting that frailty may reflect additional mechanisms contributing to cognitive impairment different from those specifically associated with AD pathophysiology [20].

A study conducted in an Australian memory clinic found that frailty was associated with imaging markers indicating small vessel disease such as white matter hyperintensities (WMH) and cortical siderosis, but not with imaging markers of neurodegeneration such as hippocampal volume and FDG-PET metabolism[42]. With few exceptions[91–94], most of previous studies have explored the associates of frailty considering whole-brain or single measures of brain parameters (i.e., hippocampal volume, or global brain volume, or volume of WMH) without exploring them at the regional, voxel-based level.

To the best of our knowledge, no studies have investigated the correlates of frailty in people with young-onset cognitive impairment, i.e. those in whom cognitive symptoms started before the age of 65.

The present study aims to investigate the cross-sectional correlations between frailty and fluid and neuroimaging biomarkers in individuals with the onset of MCI before the age of 65.

Using the FI as a multidimensional measure of physiological physical vulnerability, the goal is to examine whether frailty is associated with biological changes characteristic of neurodegenerative processes, thus improving our ability to detect high-risk individuals at a prodromal stage. Using voxel-based measures of both grey matter volume (VBM) and white matter microstructural integrity (DTI) this study also aims to deepen the knowledge of the brain mechanisms that may be most associated with frailty scores in this population.

Through this integrative approach, the study intends to provide information that will pave the road to the future development of targeted strategies for prevention and early intervention.

3. Methods and materials

3.1. Participants

For the present study, the 40-item bespoke checklist was retrospectively applied to subjects with mild cognitive symptoms previously enrolled from two hospitals with neurological clinics specialised in the treatment of cognitive disorders located in Emilia-Romagna, Northern Italy (Ospedale Civile of Azienda Ospedaliero-Universitaria di Modena and Arcispedale Santa Maria Nuova of Azienda USL di Reggio Emilia), in the period January 2019- April 2021, part of a prospective study lasting 3 years. The study was conducted under ethical approval of the Local Ethics Committee (832/2018/SPER/AOUMO) and all subjects gave written informed consent. before recruitment.
The inclusion criteria were the following:

- Clinical diagnosis of MCI at baseline according to Petersen's criteria[22]
- Absence of dementia
- Age at recruitment younger than 70 years
- Reported symptoms' onset before age 65
- Ability to write and read Italian
- Presence of a reliable caregiver available to answer questionnaires.

The exclusion criteria were the following:

- Denial or withdrawal of informed consent
- Clinical diagnosis of dementia at baseline
- Diagnosis of other neurological conditions within the previous two years that could impact cognitive function, such as Parkinson's Disease (PD), Huntington's Disease (HD), possible vascular aetiology of the cognitive disorder confirmed during the diagnostic process, head trauma, or other focal brain injury
- Diagnosis of major psychiatric disorders (schizophrenia, bipolar disorder)
- Pregnancy status of female participants
- Lack of a reliable caregiver at follow-up
- Loss at follow-up

3.2. Data collected

The subjects underwent a complete neurological evaluation, including:

- Complete neurological examination at baseline and follow-up
- Search for biomarkers and routine blood tests at baseline
- Frailty assessment for study purposes (retrospectively applied to medical records)
- Evaluation of patient's neuropsychiatric symptoms with the Neuropsychiatric Inventory (NPI)[95], assessment of daily activities with the Activities of Daily Living (ADL)[96] and Instrumental Activities of Daily Living (IADL)[97] through the caregiver interview at baseline

3.2.1. Biomarkers measurement

The following tests were performed to complete the diagnostic procedure and detect biomarkers used in the present work:

- Routine blood tests (including lipid balance, electrolytes, liver function, kidney function, thyroid function, and vitamin B12) to exclude other conditions at baseline and follow-up
- Serum NfL concentrations at baseline
- CSF analysis at baseline to determine Aβ1-42, Aβ1-40, Aβ40/42 ratio, t-tau, p-tau and NfL concentration at baseline in subjects with a clinical indication
- Brain MRI, which included high-resolution T1-weighted and resting functional sequences
- Amyloid PET with 18F-Flutemetamol when Brain MRI was contraindicated (e.g. anticoagulant therapy) at baseline in subjects with a clinical indication
- Screening for ApoE polymorphism, PSEN1, PSEN2, APP mutations at baseline in subjects with a clinical indication
- Screening for progranulin, tau, C9orf72 mutations at baseline to investigate the presence of FTLD at baseline in subjects with a clinical indication

3.2.2. Frailty measurement

Frailty measurement was performed by adopting a Frailty Index (FI) according to the frailty model as accumulation of deficits[14,40,54].

Frailty was retrospectively estimated through medical records at baseline and follow-up for all included, referring to remote pathological history, pharmacological history, objectivity and blood tests.

In particular, we adopted a 40-item FI structured as follows:

- 26 items investigated the presence of chronic pathologies in different physiological apparatuses and systems.
- 5 items investigated what is defined as physical frailty[13]
- 4 items investigated the presence of alterations in the social-relational sphere
- 5 items investigated IADLs

The various items were operationalised in the following way:

Table 3 – Operationalisation criteria adopted for the creation of a 40-item FI

Item	Operationalisation
1.Hypertension	Remote pathological history and/or drug history
2.Dyslipidemia	Remote pathological history and/or drug history and/or latest exams
3.Neoplasms	Remote pathological history
4.Osteoporosis	Remote pathological history and/or drug history
5.Gastrointestinal disorders	Remote pathological history and/or drug history
6.Renal insufficiency	Remote pathological history and/or latest exams
7.Thyroid disorders	Remote pathological history and/or drug history and/or latest exams
8.Respiratory diseases	Remote pathological history and/or drug history
9.Arrhythmias	Remote pathological history and/or drug history
10.Osteoarthritis	Remote pathological history and/or drug history
11.TIA/Stroke	Remote pathological history
12.Diabetes	Remote pathological history and/or drug history
13.Heart failure	Remote pathological history and/or drug history
14.Genitourinary diseases	Remote pathological history and/or drug history
15.Sleep disorders	Remote pathological history and/or drug history
16.Peripheral neuropathy	Remote pathological history and/or drug history
17.Falls in the past 6 months	Remote pathological history
18.Unintentional weight loss (≥4.5 kg in the past 6 months)	Remote pathological history
19.Hearing loss	Remote pathological history and/or recent pathological history and/or objective examination

20.Visual disorders (excluding presbyopia)	Remote pathological history and/or recent pathological history and/or objective examination
21.Peripheral edema	Remote pathological history and/or recent pathological history and/or objective examination
22.BMI > 30 or < 18.5	Remote pathological history and/or objective examination
23.Dizziness	Remote pathological history and/or recent pathological history and/or objective examination
24.Head trauma	Remote and/or recent pathological history
25.Difficulty maintaining balance	Remote pathological history and/or recent pathological history and/or objective examination
26.Difficulty walking more than 400 meters	Remote and/or recent pathological history
27.Tremor	Remote pathological history and/or recent pathological history and/or objective examination
28.Irritability	Remote pathological history and/or recent pathological history and/or objective examination
29.Disinhibition	Remote pathological history and/or recent pathological history and/or objective examination
30.Depressed mood	Remote pathological history and/or next pathological history and/or pharmacological history and/or objective examination
31.Fatigue	Remote pathological history and/or recent pathological history and/or objective examination
32.Headache	Remote pathological history and/or next pathological history and/or pharmacological history and/or objective examination
33.Dyspnea on exertion	Remote pathological history and/or recent pathological history and/or objective examination
34.Sphincter incontinence	Remote pathological history and/or drug history
35.Urinary urgency	Remote pathological history and/or drug history
36.Difficulty using public transportation	Remote pathological history and/or recent pathological history and/or objective examination
37.Difficulty managing money	Remote pathological history and/or recent pathological history and/or objective examination
38.Difficulty managing the household	Remote pathological history and/or recent pathological history and/or objective examination
39.Difficulty taking medications properly	Remote pathological history and/or recent pathological history and/or objective examination
40.Difficulty using the telephone	Remote pathological history and/or recent pathological history and/or objective examination

Based on the presence or absence of a certain condition, a score was given 0 = absence of the condition or 1 = presence of the condition. When there were no data on a certain condition, the attributed score was 0. The score was calculated by adding the individual items, resulting in a score ranging from 0 to 40. Then to calculate the FI, the score obtained was divided by the total number of items, so the final FI is a number ranging from 0 to 1.

3.3.Acquisition and analysis of imaging

A 3T GE Signa Architect scanner at Ospedale Civile di Baggiovara, Modena, Italy, equipped with a 48-channel-array head coil was used to acquire MRI sequences. The multimodal MRI protocol included, among others, high-resolution T1- weighted 3D BRAVO structural images (Repetition Time (TR) 2.15 sec; Echo Time (TE) 3.1 msec; Field of View (FOV) 256 × 256 × 344 mm^3; voxel dimension 1 mm isotropic) and DTI (TR 7 sec; TE 108.7 msec; slice thickness 2.5 mm; voxel dimension 2.5 mm isotropic; 64 diffusion directions; b 1000 sec/mm2) images.

Structural T1-weighted data were analysed with FSL-Voxel Based Morphometry (VBM)[98], an optimized VBM protocol[99] carried out with FSL (FMRIB Software Library v6.0, https://fsl.fmrib.ox.ac.uk/fsl) tools[100]. Single-subject structural images were firstly brain-extracted (BET) and grey matter-segmented and then registered to the Montreal Neurological Institute's 152 (MNI 152) standard space using non-linear registration[101].

The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. All native grey matter images were then non-linearly registered to this study-specific template and 'modulated' to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. These modulated grey matter images were finally smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

DTI images were initially pre-processed with BET. Subsequently, the EDDY FSL algorithms allowed us to correct for eddy currents and patient motion. Then, the FSL DTIFIT tool (https://fsl.fmrib.ox.ac.uk/fsl) was used for DTI parameters computation, i.e., fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD). Finally, DTI maps from different subjects were registered to 1 × 1 × 1 mm FMRIB58_FA standard space, using Tract-Based Spatial Statistics (TBSS)[102]. The spatial analyses were conducted only on FA skeleton, obtained with a threshold of 0.2 on the map of mean FA across subjects.

Pre-processed imaging data were analysed with whole-brain correlational analyses (i.e., VBM and TBSS). Correlations between frailty score and grey matter and whole brain FA, MD, and RD were analysed voxelwise. Values obtained from pre-processed images were used in regression analyses (General Linear Models – GLM) using *randomise*[103], a permutation-based non-parametric testing (5000 permutations), also including sex, years of education, and age as covariates of no interest. Threshold-Free Cluster Enhancement (TFCE) method with Family-wise error (FWE) rate for correction for multiple comparison was used for the analyses, and the statistical threshold was set at $p < 0.05$.

3.4.Statistical analyses

Demographical and biomarker features statistical analyses were performed with JASP v0.19.3, and $p < 0.05$ was considered significant. The normal distribution was evaluated using Shapiro-Wilk test. Since a non-normal distribution was displayed by the continuous variables studied, median and

interquartile range (IQR) were reported for descriptive analyses. Categorical variables were described as absolute frequencies and percentages and were compared between groups through chi-square tests. Correlations between continuous variables were analysed using Spearman's coefficient (ρ) and were calculated on the total sample and the only-AD and only-non-AD subgroups, separately.

4. Results

4.1. Participants' features

A total of 146 patients with Young Onset MCI (e.g. with the onset of symptoms before the age of 65) were considered eligible for the present study. Table 4 shows the demographic and fluid biomarker characteristics of the examined population: 84 women and 62 men were recruited, the median age at diagnosis was 61 years, with a minimum of 40 and a maximum of 73, while the median value of years of education was 11, with a minimum of 3 and a maximum of 18.

FI had a median score of 0.075, with a minimum value of 0 and a maximum value of 0.250. 91 subjects underwent lumbar puncture for the CSF biomarker assay, while serum NfL was assayed in 145 patients.

Table 4 – Scio-demographic, frailty, and fluid biomarker features of the participants

Variable	N° eligible (%)	Median (IQR)	Min-Max
Age at diagnosis	146	61.0 (8.8)	40.0-73.0
Sex F:M (%F)	84:62 (58%)	-	-
Years of education	146	11.0 (5.0)	3.0-18.0
FI	146	0.075 (0.050)	0-0.250
AD P:N (%P)	37:84 (31%)	-	-
ApoE-ε4 P:N (%P)	30:60 (33%)	-	-
CSF $A\beta_{1-42}$ (pg/mL)	91	864 (615)	281-2335
CSF $A\beta_{1-40}$ (pg/mL)	91	10604 (5765)	4429-28116
Ratio $A\beta_{42-40}$	91	0.091 (0.042)	0.03-0.12
CSF t-tau (pg/mL)	91	327.0 (432.5)	62.0-2000.0
CSF p-tau (pg/mL)	91	39.8 (50.5)	14.7-400.0
Ratio p-tau/h-tau	91	0.15 (0.04)	0.04-0.24
Serum NfL (pg/mL)	145	18.5 (14.7)	3.91-149.00
CSF NfL (pg/mL)	91	785 (935)	209-10492

Legend: IQR=interquartile range; Min=minimum value for the variable; Max=maximum value for the variable; F=Female; M=Male; FI= Frailty Index; AD=Alzheimer's disease; P=positive; N=negative; ApoE4 = apolipoprotein E ε4 allele; CSF=cerebrospinal fluid; $A\beta_{1-42}$ = isoform β-amyloid 1-42; $A\beta_{1-40}$ = isoform β-amyloid 1-40; t-tau=total concentration of tau protein; p-tau=concentration of phosphorylated tau protein; NfL= neurofilament light chain.

Table 5 displays the distribution of the 40 FI items in the total sample (N = 146). The most frequent conditions were dyslipidaemia (42.47%), hypertension (34.25%), sleep disorders (27.40%), depressed mood (26.71%), irritability (23.97%), and gastrointestinal disorders (26.0%). Other conditions, such as peripheral oedema, difficulty walking more than 400 metres, and urinary urgency were not found in the sample.

Table 5 –Frequency of subjects with each item of the Frailty Index

Item of the FI	N = 146	
	patients with the condition	% with the condition
Hypertension	50	34.25%
Dyslipidaemia	62	42.47%
Neoplasms	20	13.70%
Osteoporosis	6	4.11%
Gastrointestinal disorders	38	26.03%
Renal insufficiency	1	0.68%
Thyroid disorders	20	13.70%
Respiratory diseases	7	4.79%
Arrhythmias	8	5.48%
Osteoarthritis	6	4.11%
TIA/Stroke	5	3.42%
Diabetes	8	5.48%
Heart failure	1	0.68%
Genitourinary diseases	16	10.96%
Sleep disorders	40	27.40%
Peripheral neuropathy	6	4.11%
Falls in the past 6 months	6	4.11%
Unintentional weight loss (≥4.5 kg in the past 6 months)	1	0.68%
Hearing loss	7	4.79%
Visual disorders (excluding presbyopia)	8	5.48%
Peripheral oedemas	0	0.00%
BMI > 30 or < 18.5 kg/m^2	5	3.42%
Dizziness	2	1.37%
Head trauma	5	3.42%
Difficulty maintaining balance	6	4.11%
Difficulty walking more than 400 meters	0	0.00%
Tremor	8	5.48%
Irritability	35	23.97%
Disinhibition	8	5.48%
Depressed mood	39	26.71%
Fatigue	2	1.37%
Headache	9	6.16%

Dyspnoea on exertion	1	0.68%
Sphincter incontinence	2	1.37%
Urinary urgency	0	0.00%
Difficulty using public transportation	2	1.37%
Difficulty managing money	6	4.11%
Difficulty managing the household	3	2.05%
Difficulty taking medications properly	3	2.05%
Difficulty using the telephone	1	0.68%

4.2. Cross-sectional correlations between FI and fluid biomarkers

4.2.1. Whole cohort

Figure 3 shows the correlation analyses measured with the Spearman coefficient, considering the entire cohort.

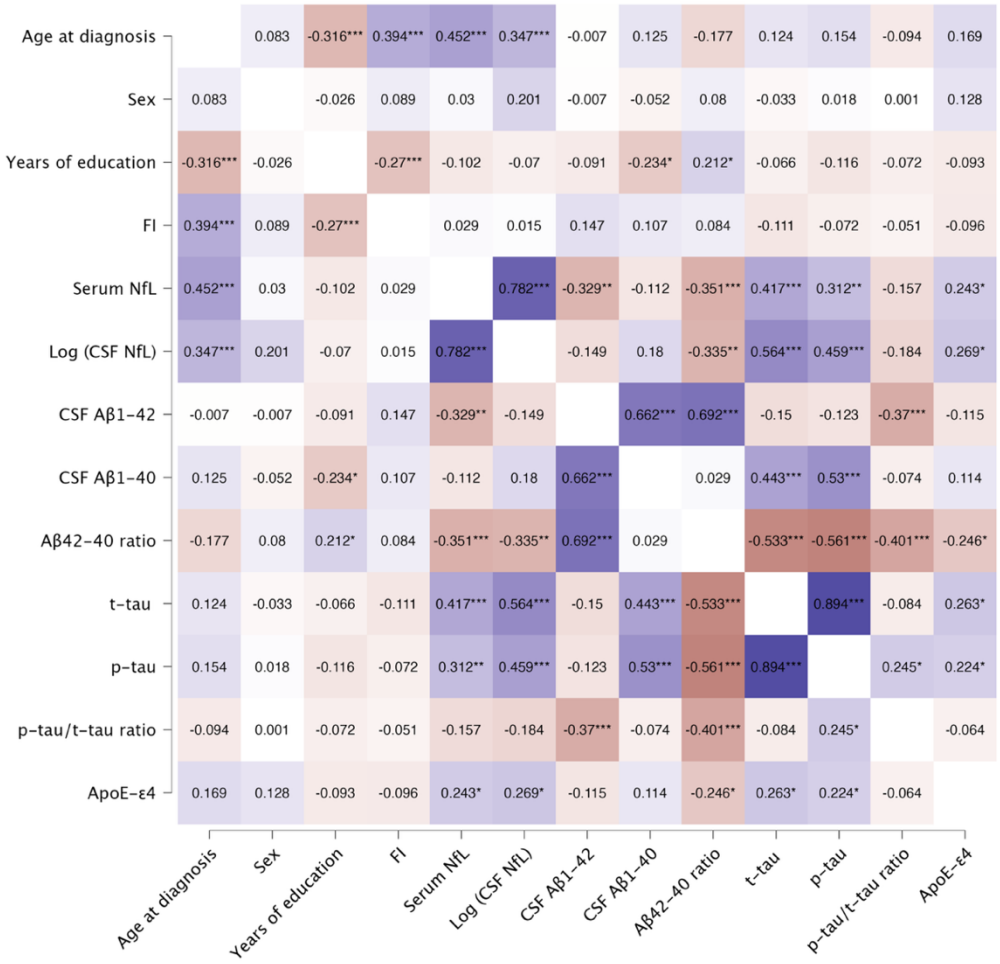

Figure 3 – Whole cohort correlations between FI, socio-demographic characteristics, and fluid biomarkers

Legend: FI=Frailty Index; NfL=Neurofilaments light chain; CSF=cerebrospinal fluid; Log (CSF NfL) = Logarithm of CSF NfL; $A\beta_{1-42}$ = isoform β-amyloid 1-42; $A\beta_{1-40}$ = isoform β-amyloid 1-40; t-tau=total concentration of tau protein; p-tau=concentration of phosphorylated tau protein; ApoE4 = apolipoprotein E ε4 allele; * p < .05, ** p < .01, *** p < .001.

In the whole sample of young-onset MCI participants, FI displayed a statistically significant moderate positive correlation with age (ρ = +0.39) and a statistically significant moderate negative correlation with years of education (ρ = –0.27). No statistically significant associations emerged between FI and any Alzheimer-related biomarker - namely CSF $A\beta_{1-42}$, $A\beta_{1-40}$, the $A\beta_{42/40}$ ratio, hTau, pTau, the pTau/hTau ratio. Similarly, FI was unrelated to sex, serum NfL, log-transformed CSF NfL, and APOE-ε4 carrier status.

4.2.2. Sub-group analysis

Within participants who met the biological definition of Alzheimer's disease, the negative association between education and frailty remained statistically significant (ρ = –0.41), whereas the age–frailty relationship decreased to a non-significant trend (ρ ≈ +0.31, p = .06). Crucially, FI did not correlate with any amyloid, tau or neurodegeneration marker, nor with ApoE-ε4 status (see Figure 4).

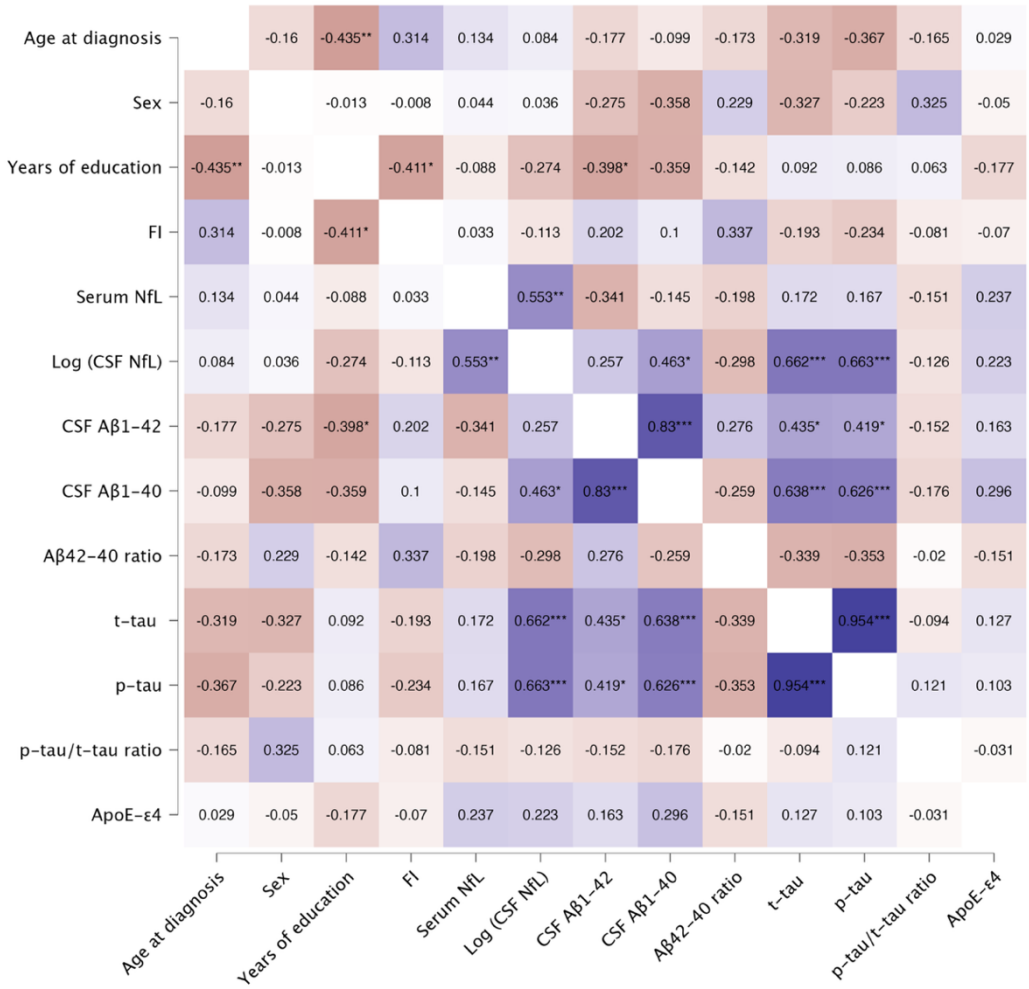

Figure 4 – Correlations between FI, socio-demographic characteristics, and fluid biomarkers in AD group

Legend*:* FI=Frailty Index; NfL=Neurofilaments light chain; CSF=cerebrospinal fluid; Log (CSF NfL) = Logarithm of CSF NfL; $A\beta_{1-42}$ = isoform β-amyloid 1-42; $A\beta_{1-40}$ = isoform β-amyloid 1-40; t-tau=total concentration of tau protein; p-tau=concentration of phosphorylated tau protein; ApoE4 = apolipoprotein E ε4 allele; * p < .05, ** p < .01, *** p < .001.

In the amyloid-negative group, frailty was strongly associated with age (ρ = +0.46) and modestly and inversely associated with education (ρ = –0.27), both correlations were statistically significant. As observed in the full cohort, FI showed no statistically significant relationship with any fluid biomarker tauopathy or axonal injury and remained unaffected by sex and APOE genotype (see Figure 5).

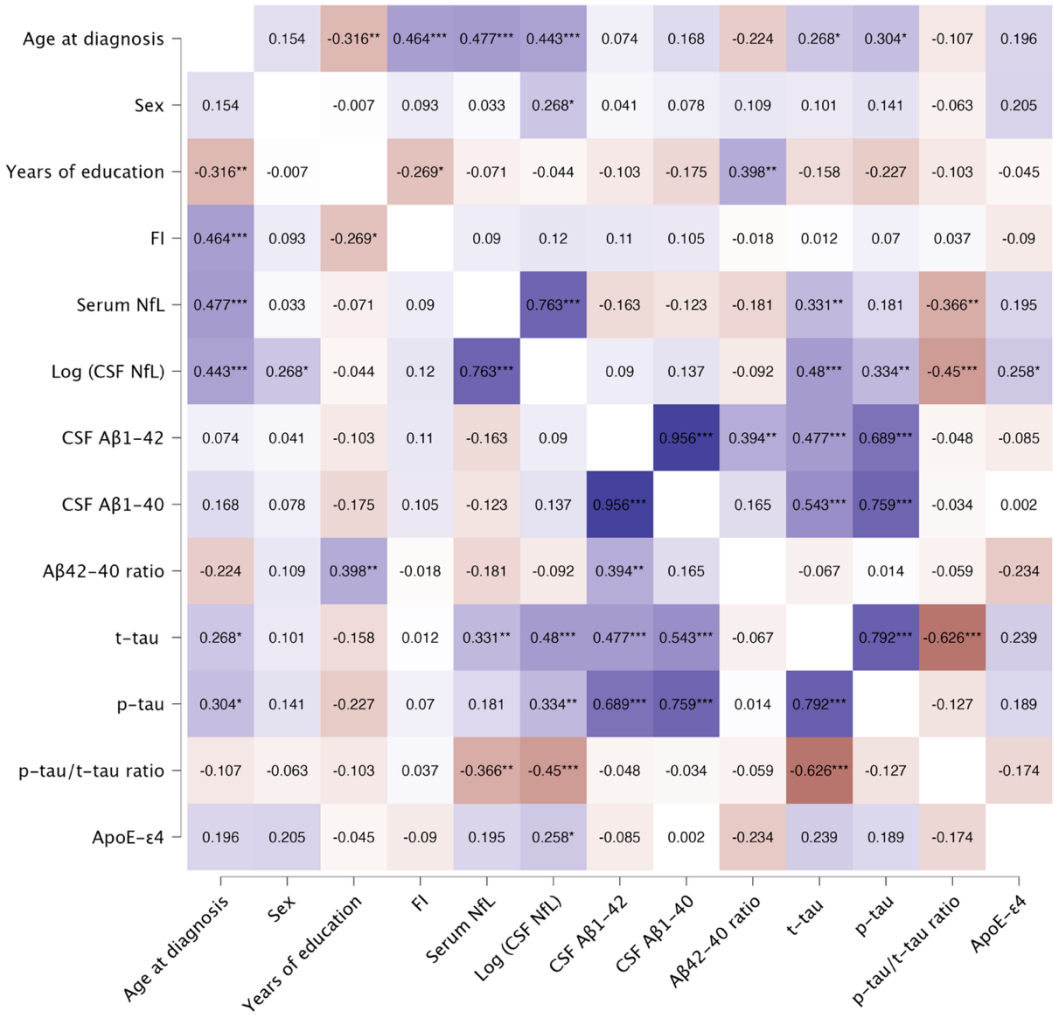

Figure 5 – Correlations between FI, socio-demographic characteristics, and fluid biomarkers in non-AD group

Legend*:* FI=Frailty Index; NfL=Neurofilaments light chain; CSF=cerebrospinal fluid; Log (CSF NfL) = Logarithm of CSF NfL; $A\beta_{1\text{-}42}$ = isoform β-amyloid 1-42; $A\beta_{1\text{-}40}$ = isoform β-amyloid 1-40; t-tau=total concentration of tau protein; p-tau=concentration of phosphorylated tau protein; ApoE4 = apolipoprotein E ε4 allele; * p < .05, ** p < .01, *** p < .001.

4.3.Neuroimaging

All voxelwise analyses were corrected for multiple comparisons with TFCE-FWE ($p < 0.05$) and were adjusted for age, sex and years of education. The frailty index (FI) acted as the explanatory variable; negative correlations therefore indicate lower grey matter volume (for VBM) or lower white

matter structural integrity measured as FA (for TBSS) with higher frailty, whereas positive correlations indicate higher volume or white matter integrity with higher frailty. We expected to find results from correlations indicating decreased volume or white matter integrity (positive correlations for VBM and FA, negative correlations for MD and RD) with increasing frailty, but also explored opposite correlations for completeness.

4.3.1. Voxel based morphometry analysis

Figure 6 illustrates the spatial distribution of Voxel-based morphometry (VBM). Whole-brain voxel-based morphometry demonstrated a negative association between frailty and grey-matter volume. More precisely, after correction for multiple comparisons, higher frailty scores were associated with bilateral atrophy in lobule VI and Crus I of the cerebellum, regions integral to cerebello-thalamic motor and cognitive loops. Within the left hemisphere, frailty also predicted reduced volume throughout the peri-rolandic sensorimotor belt—pre- and post-central gyri, the central and parietal opercula, and the anterior division of the supramarginal gyrus—extending into Heschl's gyrus. In addition, lower grey-matter density with increasing frailty was observed in ventral visual areas, encompassing the lingual gyrus and the occipital–temporal fusiform cortex bilaterally.

No regions showed a positive correlation with frailty.

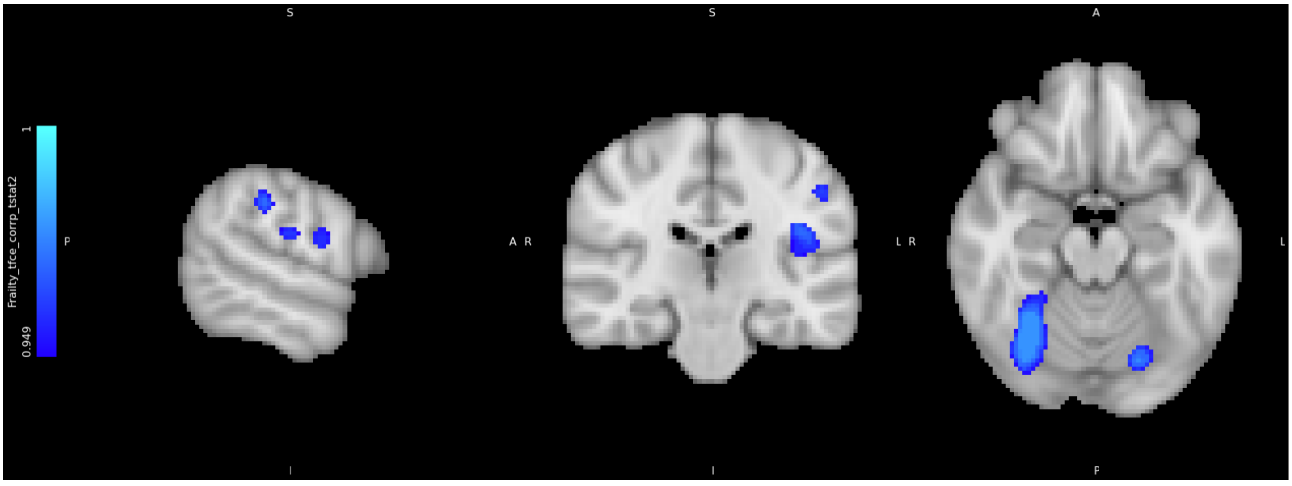

Figure 6 – Spatial distribution of VBM correlations

4.3.2. Fractional anisotropy analysis

Analysis of fractional anisotropy (FA) revealed widespread microstructural white matter degradation associated with higher frailty. Significant reductions in FA spanned commissural fibres (genu, body, and splenium of the corpus callosum; fornix), projection pathways (bilateral corticospinal tracts, internal and external capsules, anterior and posterior corona radiata, cerebral peduncles, and superior cerebellar peduncle) and long-range association tracts (cingulum in the right cingulate gyrus, bilateral superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, sagittal stratum). The middle and inferior cerebellar peduncles were likewise affected (see Figure 7).

No tract exhibited higher FA with increasing frailty.

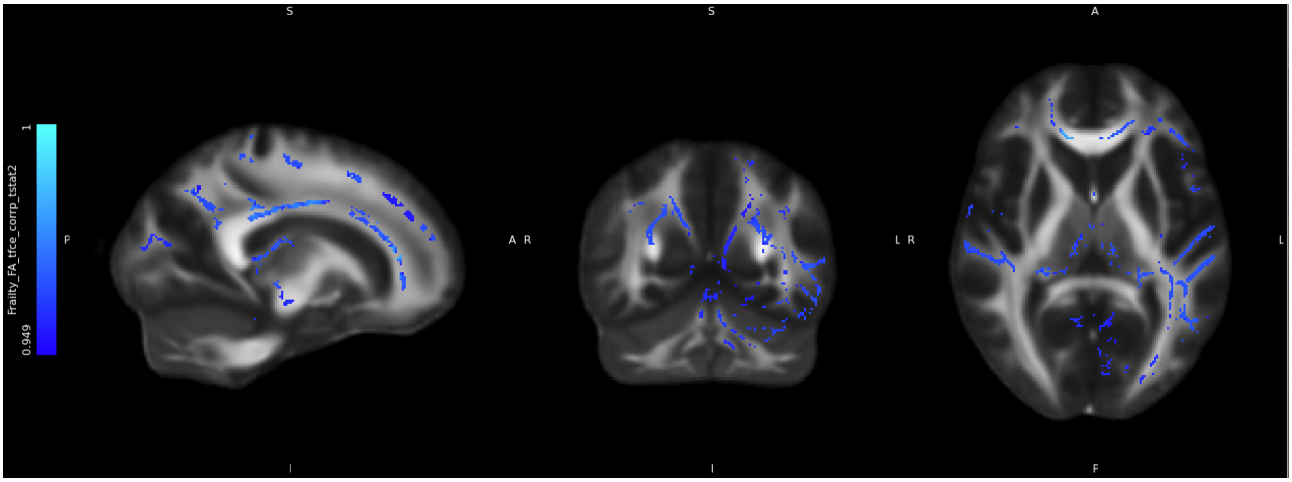

Figure 7 – Regions with FA reduction associated with higher frailty

4.3.3. Mean diffusivity analysis

Mean diffusivity (MD) showed a positive correlation with frailty, denoting greater extracellular water content and tissue disorganisation in participants with higher frailty scores. Significant clusters were confined to right-lateralised anterior white-matter, including the anterior corona radiata, external capsule, inferior fronto-occipital fasciculus and corticospinal projection fibres of the internal capsule, together with the left anterior thalamic radiation and the fornix.

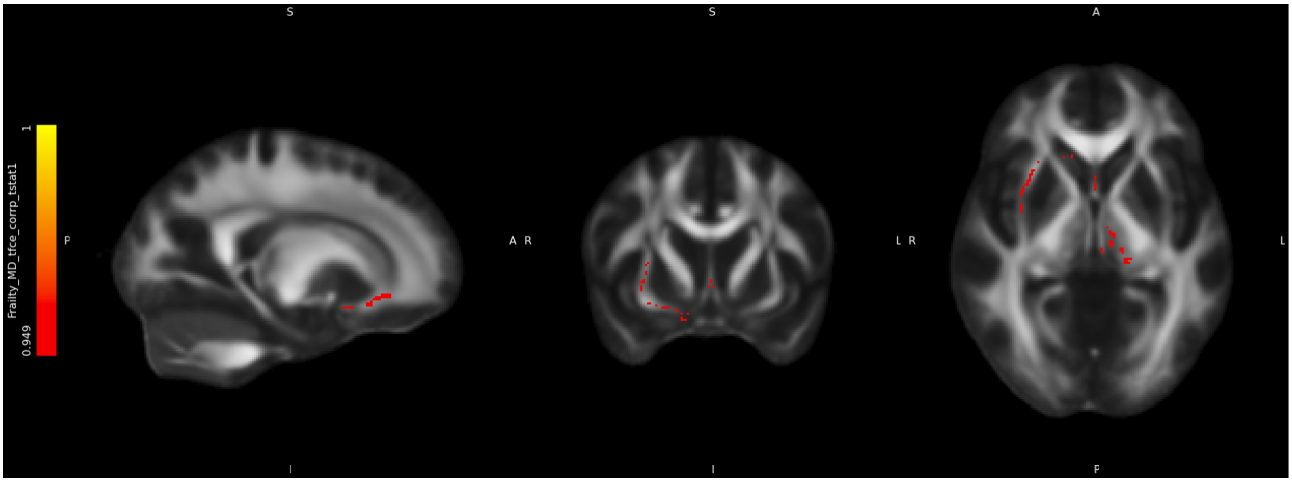

Figure 8 – Localization of regions with increased MD

4.3.4. Radial diffusivity analysis

Radial diffusivity (RD) demonstrated the most extensive positive associations with frailty. Beyond the regions identified for MD, elevations in RD encompassed virtually the entire corpus callosum, the posterior segments of the corona radiata and thalamic radiations, the superior corona radiata, the superior longitudinal fasciculus and the uncinate fasciculus, predominantly within the right hemisphere. These findings indicate myelin and axonal sheath compromise in a broad fronto-temporal–parietal network as frailty increases.

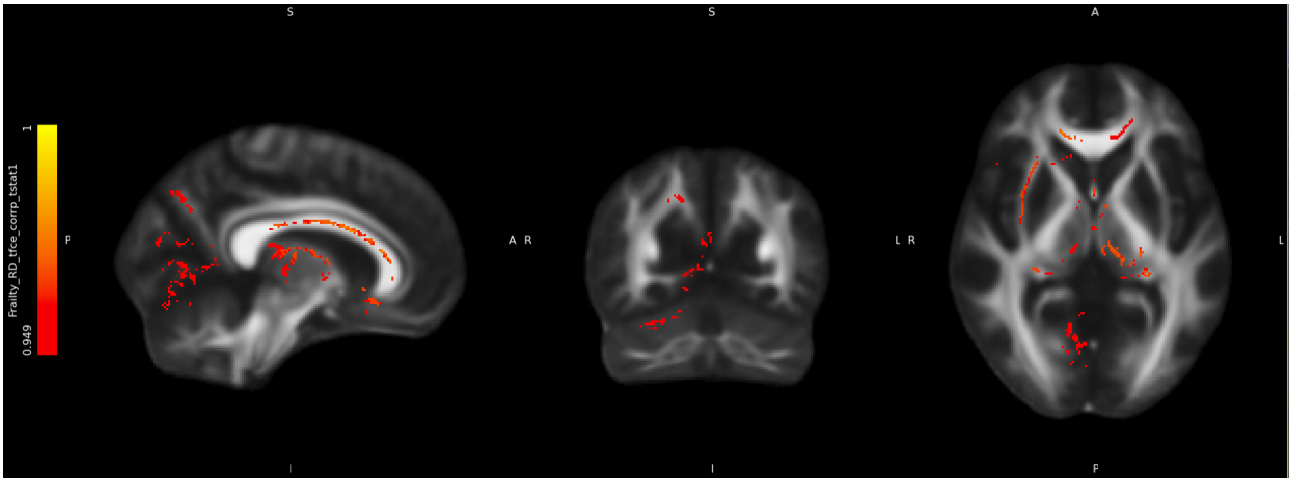

Figure 9 – Regions where RD was increased in association with frailty

5. Discussion

5.1. Frailty and fluid biomarkers of AD and neurodegeneration

The present study expands the still-limited evidence on frailty in young-onset cognitive decline by showing that, in a cohort of individuals with mild cognitive impairment aged < 65 years, physical frailty is uncoupled from CSF biomarkers of Alzheimer's disease[20] and other blood/CSF biomarkers of neurodegeneration .

Across the entire sample, frailty correlated only with socio-demographic factors - moderately increasing with age and decreasing with years of education - while displaying no association with CSF amyloid-β, phosphorylated and total tau, or serum/CSF neurofilament light chain.

These findings align with reports from older cohorts in which frailty has been linked to cognitive decline chiefly through vascular and lifestyle pathways rather than through amyloid-tau mechanisms[104,105]. They also complement experimental data suggesting that the biological substrates of frailty (e.g., inflammatory and metabolic dysregulation) are at least partly distinct from those underlying Alzheimer pathology[41,90,106].

Stratified analyses further emphasised this dissociation. Among amyloid-positive participants, frailty remained independent of biomarker burden and was driven almost exclusively by lower educational attainment. Conversely, in amyloid-negative individuals, frailty rose steeply with age, indicating that the accumulation of multisystem deficits still follows a time-dependent course when Alzheimer pathology is absent.

Importantly, neither subgroup showed a significant frailty–neurodegeneration link, underscoring that elevated neurofilament light chain - the most sensitive marker of axonal damage - does not yet translate into measurable frailty in mid-life in patients with cognitive decline.

This pattern suggests that systemic frailty and central neurodegeneration progress along partially independent trajectories during the prodromal phase and that their eventual convergence, often documented in late-life dementia, may represent a later phenomenon.
From a clinical standpoint, the data imply that frailty captures a distinct dimension of vulnerability rooted in life-course exposures - particularly educational and possibly socioeconomic factors - that may modify cognitive reserve and resilience. Screening for frailty in this age group therefore retains relevance, but principally as an index of general health and potential treatment tolerance.

However, interpreting our results is primarily constrained by four methodological issues. *First*, its cross-sectional design precludes any causal inference or temporal ordering between frailty progression and biomarker alterations, restricting interpretation to contemporaneous associations. *Second*, statistical power is limited: although the total cohort numbered 146, the subset with complete CSF data fell to 91 and the amyloid-positive subgroup to merely 37, rendering the analyses under-powered to detect small-to-moderate effects. *Third*, the frailty construct was operationalised with an index validated for older adults; in mid-life populations its properties remain less established, and the lack of objective physical-performance measures (e.g., grip strength) may have attenuated sensitivity. *Fourth*, amyloid status was determined with heterogeneous methods (CSF or PET), and although harmonised cut-offs were applied, methodological variability could have introduced misclassification and diluted true relations between frailty and amyloid burden.

Future cross-sectional and longitudinal work should go beyond these limits and determine whether frailty accelerates biomarker progression over time or, conversely, whether emerging Alzheimer pathology precipitates frailty in later stages.

5.2. Frailty and neuroimaging biomarkers

The present imaging analyses reveal that, even in mid-life individuals with mild cognitive impairment, systemic frailty is mirrored by discernible alterations in both grey- and white-matter architecture.

Grey-matter findings localise chiefly to lobule VI and Crus I of the cerebellum and to a contiguous strip of left peri-rolandic cortex. The cerebellum is now recognised as a hub not only for motor coordination but also for executive and affective regulation[107]; volume loss in these lobules has been linked to gait instability, slowed processing speed and impaired set-shifting, domains that overlap

with clinical constructs of frailty[91]. Likewise, atrophy within the pre- and post-central gyri and parietal operculum dovetails with the motor-performance and balance components embedded in the frailty index.

Measures of white-matter microstructural integrity showed even larger associations with frailty, further reinforcing this interpretation. Fractional-anisotropy reductions with increasing frailty extended across commissural callosal fibres, long association bundles such as the cingulum and inferior fronto-occipital fasciculus, and projection systems that link cortical motor regions with subcortical and brain-stem nuclei. The same tracts show parallel increases in radial and, more focally, mean diffusivity, a pattern generally considered to denote demyelination and extracellular fluid expansion rather than purely axonal loss[21,108].

Taken together, these convergent grey- and white-matter alterations suggest that frailty in young-onset MCI is not an epiphenomenon of Alzheimer molecular pathology but rather indexes a distinct neuro-anatomical vulnerability that centres on cerebello-thalamo-cortical and sensorimotor networks, and on demyelination rather than axonal damage.

The findings complement the scarce correlation between frailty and fluid biomarkers reported earlier, implying that structural brain changes constitute a more sensitive neural footprint of multisystem decline at this life stage. Whether these alterations arise from shared upstream mechanisms - such as systemic inflammation, vascular dysregulation or reduced physical activity - remains to be clarified.

Two main caveats qualify the interpretation of our neuro-imaging findings. *First*, the analyses relied on cross-sectional data from a modest subsample of the cohort, reducing statistical power to detect subtle associations and precluding causal inferences regarding the temporal interaction between frailty progression and brain changes. *Second*, the absence of complementary vascular imaging prevents us from determining whether the observed structural alterations reflect disuse, microvascular compromise, or neuro-inflammatory processes that are common in frailty.

Longitudinal follow-up, ideally coupled with interventional trials targeting mobility and aerobic capacity, will be necessary to determine whether ameliorating frailty can decelerate the observed cerebellar and fronto-parietal tissue loss or, conversely, whether progressive neurodegeneration drives further frailty accrual.

6. Conclusion

This thesis demonstrates that, in individuals who develop mild cognitive impairment before the age of sixty-five, the frailty construct applies and represents a dimension that is largely independent of canonical Alzheimer biology yet already embodied in the brain's macro- and micro-structure.

Across the full cohort, the frailty index correlated with age and educational attainment but showed no association with CSF amyloid-β, tau or neurofilament light chain, and it did not differ between amyloid-positive and amyloid-negative cases. Multimodal MRI revealed that higher frailty is linked to selective grey-matter atrophy in cerebellar and peri-rolandic regions and to diffuse microstructural compromise of commissural, projection and association fibres, with the most pronounced changes captured by decreased fractional anisotropy and increased radial diffusivity suggesting an association between frailty and myelin rather than axonal damage.

Taken together, these findings indicate that frailty and Alzheimer molecular pathology follow partially divergent trajectories in the prodromal phase, yet frailty is not a purely peripheral phenomenon: it is reflected in structural alterations of networks subserving motor control, visuo-spatial integration and executive regulation.

Clinically, the results underscore the potential value of frailty as an independent marker of functional reserve and treatment tolerance also in young-onset cognitive decline. Future longitudinal studies should clarify whether interventions that reduce frailty can mitigate the pace of diverse causes of cognitive decline. Such work will be essential for integrating frailty assessment into precision-medicine frameworks that account for both systemic and neurobiological dimensions of brain health.

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