Clinical and neuroimaging prognostic markers in Alzheimer's Disease and Lewy Body Dementia: The role of muscle status and nutrition

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Preface

This thesis is submitted in partial fulfillment of the degree Doctor of Philosophy (Ph.D.) requirements at the University of Stavanger, Norway. The research project was carried out at the Centre for Age-related Medicine (SESAM), Stavanger University Hospital, from January 2019 to June 2022. The compulsory courses attended have been given at the University of Stavanger. The Western Norway Regional Health Authority has funded the work by the grant F-12511/4800002096.

Miguel Germán Borda, June 2022

Abbreviations

AD: Alzheimer´s Disease

DLB: Dementia with Lewy bodies

LBD: Lewy body dementia

PDD: Parkinson's Disease Dementia

MCI: Mild cognitive impairment

ICD: International Classification of Diseases

TAU: tubulin associated unit

MRI magnetic resonance imaging

fMRI functional magnetic resonance imaging

PET positron emission tomography

iMAT: Intramuscular fat

SPPB: The Short Physical Performance Battery

TUG: timed up and go

ADL: basic activities of daily living

IADL: instrumental activities of daily living

MRI: Magnetic resonance imaging

FDG: fluorodeoxyglucose

NFL: Neurofilament light chain protein

DEMVEST: Dementia Disease Initiation

DDI: Dementia Disease Initiation

GLIM: The Global Leadership Initiative on Malnutrition

BMI: Body Mass Index

RDRS-2: Rapid

SAT: subcutaneous fat

HC: Healthy controls

ROIs: Regions of Interest

GDS: The Geriatric Depression Scale

COPD: Congestive Pulmonar Disease

NPI: Neuropsychiatric disease Inventory

CERAD-MC: Consortium to Establish a Registry for Alzheimer's Disease memory composite score

REK: Regional Etic committee

EEG: Electroencephalogram

MCR: Motor Cognitive Risk Syndrome

NIA-AA: National Institute on Aging and the Alzheimer's Association

IWG-2: International Working Group AD: Alzheimer disease

Abstract

Introduction

Alzheimer's Disease and Lewy body dementia are the two most common neurodegenerative dementias. They have a progressive course with devastating consequences for the people living with these diseases and their families, but there are large individual variations. Finding early markers and markers of progression and prognosis could promote actions to improve the quality of life of the people affected with these diseases. Nutrition and muscle status are closely related and have systemic functions and interactions that affect the brain. This thesis describes the role of nutritional and muscle status biomarkers in the prognosis of people diagnosed with mild Alzheimer's disease, Lewy body dementia, and mild subjective cognitive decline.

Methods

For the aim of this thesis, I used data from 2 community-based prospective Norwegian multicenter cohort studies: DemVest (The Dementia Study of Western Norway) and DDI (Dementia Disease Initiation). In DemVest, patients with mild dementia, defined as a Mini-Mental Status Examination (MMSE) score; equal or higher to 20 or Clinical Dementia Rating (CDR) global score equal to 1, with different types of dementia, were included. The DDI study was designed to investigate early cognitive impairment and dementia markers. DDI participants included in this thesis were those classified as having Subjective cognitive decline (SCD) according to the SCD-I framework. Comprehensive clinical assessments, including measures of cognition, daily functioning and anthropometric measurement, blood samples, and brain MRI were performed in both studies. Brain morphology was studied using FreeSurfer segmentation and muscle morphology using slice O-Matic software.

Results

This thesis findings first indicate that nutritional status has an essential role in the 5-year prognosis of people living with dementia in the capacity to perform daily life activities and mortality. Second, the quality

of the muscle, here the muscle of the tongue, and its amount of fat infiltration were associated with malnutrition onset in people with dementia. Finally, in patients with SCD, muscle function measured with the timed up and go test (TUG) was associated with cognitive decline. TUG, in addition, was associated with cortical thickness in areas related with cognitive and motor functioning.

Conclusion

Nutritional and muscular status predict prognosis in people with SCD and with dementia. These findings suggest that interventions focused on these areas may improve outcomes such as cognition, function, and survival in these groups.

Contents

List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

Paper I

Borda MG, Ayala Copete AM, Tovar-Rios DA, Jaramillo-Jimenez A, Giil LM, Soennesyn H, Gómez-Arteaga C, Venegas-Sanabria LC, Kristiansen I, Chavarro-Carvajal DA, Caicedo S, Cano-Gutierrez CA, Vik-Mo A, Aarsland D. Association of Malnutrition with Functional and Cognitive Trajectories in People Living with Dementia: A Five-Year Follow-Up Study. J Alzheimers Dis. 2021;79(4):1713-1722. doi: 10.3233/JAD-200961. PMID: 33459715.

Paper-II

Borda MG, Bani Hassan E, Weon J, Wakabayashi H, Tovar-Rios DA, Oppedal K, Aarsland D, Duque G. Muscle volume and intramuscular fat of the tongue evaluated with MRI predict malnutrition in people living with dementia: a five-year follow-up study. J Gerontol A Biol Sci Med Sci. 2021 Aug 2:glab224. DOI: 10.1093/gerona/glab224. Epub ahead of print. PMID: 34338751.

Paper III

Borda MG, Ferreira D, Selnes P, Tovar-Rios DA, Garcia-Cifuentes E, Jaramillo-Jiménez A, Kirsebom BE, Dalajer T, Oppedal K, Sønnesyn H, Fladby T, Aarsland D. Timed Up and Go in People with Subjective Cognitive Decline Is Associated with Faster Cognitive Deterioration and Cortical Thickness. Dement Geriatr Cogn Disord 51, 63-72 (2022).

1.4 Organization of thesis

The thesis is divided into eight chapters. Chapter 1 includes hypothesis and objectives, as well a summary of the scientific contribution of this

thesis. Chapter 2 will introduce the reader to the background necessary to understand the motivation behind the work presented. The chapter starts with a general introduction of cognitive decline and dementia, venturing into the two variants of dementia studied in this thesis. I then describe how and why other functions and systems in the body outside the brain have an effect in the progression of the neurodegenerative dementia process with a particular focus on muscle and nutritional status. Towards the end of the chapter, I introduce the imaging techniques and their role in dementia. Chapter 3 describes theoretical foundations of the thesis and particularly the gaps in the literature that my research aims to fill. In Chapter 4, the methodology used is described. I explain the characteristics of the population studied and the measurements and the techniques used to assess muscle, cognition, functional performance for daily life activities and brain structure. In chapter 5 there is a description of the findings, followed by chapter 6 where they are discussed. Chapter 7 includes the conclusions and a description of the future perspectives.

1 Introduction

1.1 Aims and Hypothesis

Overarching aim

To describe the role of malnutrition and muscle status in the progression of cognitive decline, functional decline, and mortality in people with subjective cognitive decline and with mild Alzheimer´s disease and Lewy body dementia.

Specific aims

1. Study the frequency of malnutrition and test the hypothesis that malnutrition can predict faster functional deterioration and mortality in people with mild Alzheimer´s disease and Lewy body dementia.
2. Test whether the muscular mass of the masseter and the tongue together with their intramuscular fat is associated with malnutrition in people with mild Alzheimer´s disease and Lewy body dementia.
3. Explore if the muscular function measured by the Timed-Up and Go test predicts cognitive decline and is associated with brain structure in older adults with subjective cognitive decline.

General Hypothesis

Malnutrition and muscle status influence the progression of cognitive decline, functional decline, and mortality in older adults in risk of dementia and with mild dementia.

Specific Hypotheses

1. Malnutrition is associated with faster functional decline and higher mortality in people with mild Alzheimer´s disease and Lewy body dementia.
2. Small tongue muscle and high intramuscular fat are associated with risk of having and developing malnutrition in people with mild Alzheimer´s disease and Lewy body dementia.
3. Muscular performance measured with **TUG** predicts a faster cognitive decline in people with SCD and it is associated with early changes in cortical thickness.

1.2 Contributions

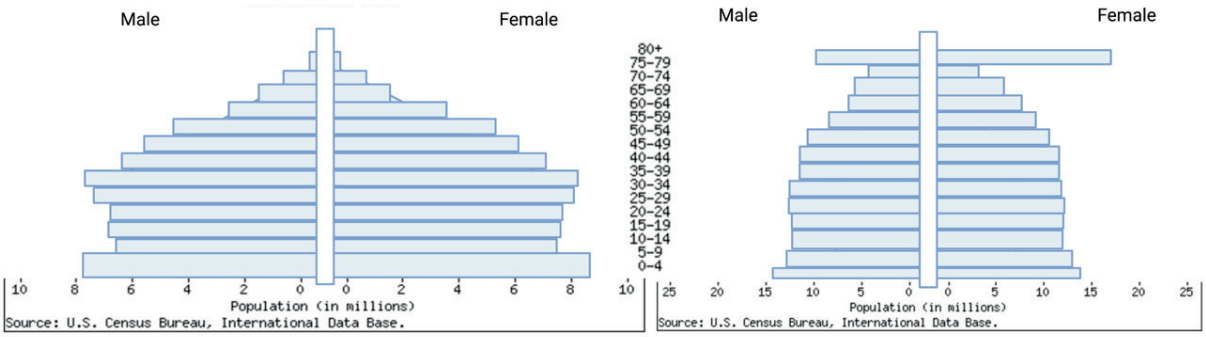
In Paper I, I describe the importance of malnutrition in older adults with early dementia and show novel an unexpected result regarding malnutrition. I show that malnutrition is associated with worse functional status and increases mortality. In paper II, I demonstrate that the tongue muscle can be an early biomarker that indicates and predicts malnutrition in people newly diagnosed with dementia. Finally, in Paper III I show that muscle function measured with an easy and accessible test can predict cognitive deterioration in people at risk of dementia. This muscular alteration is related to less cortical thickness.

My results open the door for a new area of research with the potential to find clinically relevant biomarkers and interventions for dementia, a big social and public health problem. Such results have not been shown before in a Norwegian cohort.

2 Background

There is a progressively marked increase in the older adult population relative to younger age groups (Figure 2.1). Therefore, chronic diseases and age-related problems such as neurodegenerative disorders and cognitive decline will likely become more prevalent. [1, 2]

Figure 2.1 Population pyramids 1950 vs. 2050



United states 2050 vs 2050. Taken and modified from: [3]

Age-related cognitive decline and dementia have a significant impact on the persons with the disease, their families, and society. Consequences of dementia include increased health costs, decrease in function and quality of life, frequent hospitalizations, pressure ulcers, infections, malnutrition, pain and in general represents suffering for patients and families. [4-9]

Neurodegeneration and cognitive decline have several stages, and normal cognitive aging needs to be differentiated from pathological cognitive ageing.[10]

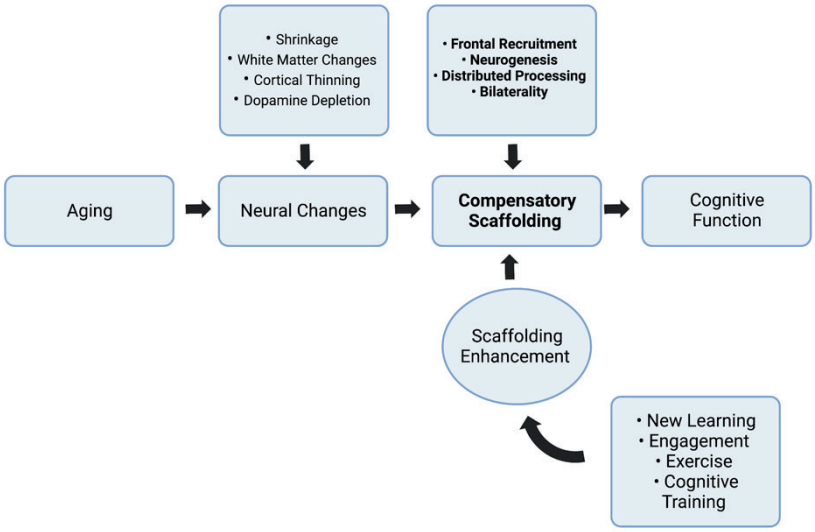
2.1 Cognition and Normal Ageing

Cognitive normal development after the age of about 21 years is characterized by two parallel processes: 1) A steady decline of fluid

intelligence, defined as the mental processes dependent on a biologically intact brain, such as working memory, attention, executive functions. This is clearly seen in reaction times, which increase linearly from the age of about 21 years. However, there is also 2) a steadily increase in crystallized intelligence, defined as knowledge and expertise. One aspect of this is vocabulary, which increases throughout the life-span. [11] With increasing age a phenomenon called scaffolding is invoked which compensates and maintains the function of important cognitive tasks. Scaffolding consists in the brain activation of associated compensatory circuitry as normal response to challenge in healthy cognitive aging and help in the maintenance of cognitive function as age-associated structural deterioration increases. [12, 13]

Normal aging alterations should not alter their daily life functioning, although it can affect some aspects of working life with special cognitive requirements. Figure 2.2.

Figure 2.2. Conceptual model of the scaffolding theory of aging



Taken and modified from:[13]

2.2 Subjective Cognitive Decline

Subjective Cognitive Decline (SCD) is a term that comprises a heterogeneous group of people presenting cognitive complaints without objective evidence of impairment. SCD has emerged as a possible initial stage in neurodegenerative diseases with the evolution towards dementia, especially in Alzheimer's disease. It seems reasonable to search for the earliest cases of Alzheimer's disease among subjects with cognitive complaints which do not present clinical signs of illness. Identifying a group of individuals in the pre-clinical stage has excellent utility for developing new preventive therapeutic strategies. For example, delaying the onset of dementia for just one year would mean a reduction in the global prevalence of 9 million dementia cases in the next 40 years. [14, 15]

2.3 Mild Cognitive Impairment

Throughout history, objective cognitive deficits not fulfilling criteria for dementia have received different names, such as age-related forgetfulness, age-related memory loss, etc. The term Mild Cognitive Impairment (MCI) appeared in the literature in 1990 and is defined as subjective impairment and mild difficulties in cognitive tests without significant alterations in the capacity to perform activities of daily living. [16] While not all MCI cases are progressive to dementia, the main utility of the concept is as a predictor of dementia development.

From a treatment and pharmacological point of view, it would be beneficial to identify interventions that can prevent or delay the passage from MCI to dementia. According to different observations, between 6 to 20% per year of people with MCI evolve towards a dementia syndrome. The estimated prevalence of mild cognitive impairment in

population-based studies ranges from 10 to 20% in persons older than 65. [17]

2.4 Dementia

When cognitive problems associated with brain pathology reaches a high degree of severity, it can be classified as dementia. Dementia is a leading cause of disability worldwide; It represents a great challenge since no curative or disease-modifying treatments are available. [18]

Dementia is also known as Neurocognitive Major Disorder. [19] According to the ICD-10, dementia is defined as ´´a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not impaired. `` Cognitive function impairments come together and sometimes preceded by deterioration in emotional control, neuropsychiatric symptoms, social behavior, or motivation. This syndrome occurs in Alzheimer's disease, cerebrovascular disease, Lewy body dementia and in other conditions primarily or secondarily affecting the brain. [20, 21] Due to the cognitive and emotional changes, impairments in activities of daily living will gradually occur.

Several diseases lead to dementia, and they can be classified according to their clinical manifestations, causes, and pathology such as vascular dementia, frontotemporal dementia, limbic-predominant, age-related TDP-43 encephalopathy or progressive supranuclear palsy but the most common neurodegenerative dementias are Alzheimer's disease and Lewy body dementia. [22]

2.5 Alzheimer disease

2.5.1 Epidemiology

Alzheimer's disease is the most common form of progressive dementia. and the prevalence worldwide is estimated to increase exponentially. There was over 55 million people worldwide living with dementia in 2020, and it is estimated that by 2050 it will rise to 139 million cases. In Norway, between 80,000 and 100,000 people live with dementia, and this prevalence is expected to increase to more than 140,000 in 2050. [23, 24, 9]

2.5.2 Pathology and mechanisms

Many are the mechanisms that have been suggested as protagonists of the pathogenesis of this disease. Among them are increased production and amyloid accumulation, microtubule hyperphosphorylation of the protein TAU, apoptosis phenomena, oxidative stress, inflammatory mechanisms, alterations in calcium homeostasis, and endothelial damage. Most of the research has focused on the hypothesis of the amyloid cascade and the TAU protein's hyperphosphorylation processes. [25, 26]

2.5.3 Clinical symptoms

Alzheimer's disease is a progressive disease which usually has memory deficit as its earliest and most pronounced symptoms. As the disease progresses, the patient progressively worsens, showing perceptual problems, language apraxia, and emotional changes. [7]

Alzheimer's disease can have typical, atypical, and mixed presentations. Some non-amnestic, atypical presentations are: Nonfluent primary progressive aphasia, logopenic aphasia, frontal variant of Alzheimer's disease, and posterior cortical atrophy. The latter two conditions are

pathologically distinctive and have typical clinical characteristics. [27] Mixed Alzheimer's disease defines those patients who fully meet the diagnostic criteria for Alzheimer's disease but have additional clinical and/or biological evidence of comorbid disorders such as cerebrovascular disease or Lewy body disease. [28, 29]

However, the most common clinical phenotype is early progressive episodic memory deficit, followed by or associated with executive dysfunction, language disorders, apraxia, agnosia, attention deficits, and complex visual and neuropsychiatric symptoms.

Depending on the age of appearance of the symptoms, the disease is classified into early-onset Alzheimer's disease, if the onset is before age 65 years, and late-onset Alzheimer's disease if it starts after age 65. These two forms are classified into two subtypes, familiar if there is a family history or Sporadic if there is no family history. [30]

The main consequence of this neurodegenerative disease is the loss of the capacity to perform activities of daily living and thus dependency and disability; this is a progressive process, that is typically broadly manifested on a late stage. Besides neurodegeneration, it has been described that Alzheimer patients present subtle motor changes that may occur from very early stages of the disease, such as loss of muscle mass or muscular function. [31, 32] The progression of those motor deficits together with cognitive decline and the onset of other comorbid conditions come together to determine the final functional prognosis. [33]

2.5.4 *Diagnosis and assessment*

For diagnosing Alzheimer's disease, several international consensus criteria exist, one of the most frequent and best validated criteria require the following: [10]

An early and significant episodic memory impairment

- The gradual and progressive change of memory for more than six months
- Objective evidence of significantly impaired episodic memory on testing that does not improve or does not normalize with adequate cueing or recognition testing

In addition, one or more of the following supportive biomarker features are required:

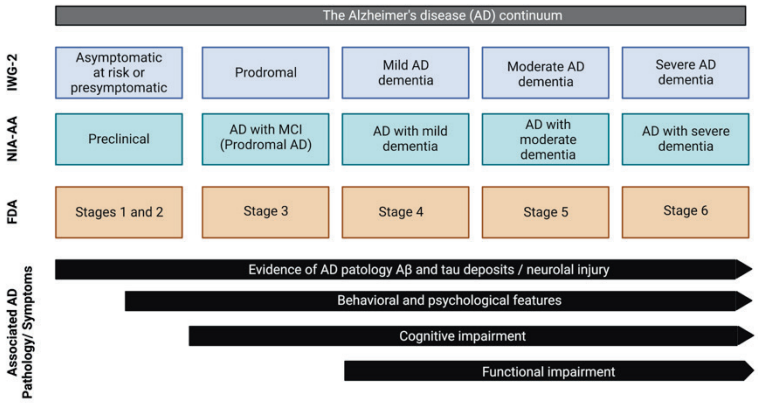
- Medial temporal atrophy on Magnetic resonance imaging.
- Abnormal spinal fluid concentrations of (1) amyloid, (2) total tau, or (3) phospho-tau
- Specific patterns of PET scanning producing hypometabolism of bitemporal parietal regions or Pittsburgh compound B
- Proven Alzheimer´s disease autosomal dominant mutation within the immediate family

In addition, one can exclude patients with:

- Sudden onset
- Focal neurologic defects
- Non-Alzheimer's disease dementia
- Major depression
- Cerebrovascular disease

According to the effects of reduced cognitive capacity reflected in the capacity to perform daily life activities, Alzheimer's disease can be classified in different stages Figure 2.3.

Figure 2.3. Stages within the Alzheimer's disease continuum



Alzheimer´s disease (AD) continuum, based on research classifications. Taken and modified from: [34] FDA: Food and Drug Administration NIA-AA: National Institute on Aging and the Alzheimer's Association IWG-2: International Working Group AD: Alzheimer disease

2.5.3.1 Biomarkers

Currently, Alzheimer´s disease hallmarks can be assessed in vivo by analyzing biomarkers in two main categories: 1) fluid biomarkers, including cerebrospinal fluid (CSF) and blood. The most relevant biomarkers in these categories are NFL and Aβ1–42. See Table 2.1. Further there are 2) imaging biomarkers, where structural MRI measures of the medial temporal lobe and the hippocampus are still the biomarkers most clinically validated, but other techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) offer great opportunities. [35-37]

Table 2.1 Classification of AD biomarkers

Source	Biomarker	Testing method
The retina of the eye	Retinal degenerative changes including ganglion cells and internal plexiform layers (GCIPL) and retinal nerve fber layer (RNFL; p indicates peripapillary)	Performed by optical coherence tomography (OCT) and spectral domain optical coherence tomography (SD-OCT)
CSF	CSF Biomarkers: biomarkers, CSF Aβ1-42, CSF P-Tau, CSF T-Tau, and Neurogranin	ELISA
Blood	AD pathogenic proteins: beta (Aβ)40 and Aβ42, P-Tau, T-Tau	SIMOA

	Inflammation: IL-1β and two soluble receptors sIL-1R1 and sIL-1R3, IL-8, SDF-1, intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion protein 1 (VCAM-1), progranulin, IL-33, and soluble interleukin 1 receptor-like (sST2).	ELISA, ECL, beas-based multiplex immnunoassays
	Neurodegeneration: neurogranin and neurofilament light (NFL)	SIMOA, ELISA
	Down-regulated miRNA miR-181c,-miR-125b and miR-103-miR-222, miR-26b-5p, miR26b, miR-31, miR-34a-5p, Let-7d-5p, miR-23a, miR26b, miR-103	RT-qPCR
	Up-regulated miRNA Mir-502-3p, miR-206,miR-132, miR-34c, miR-181c, miR-411	RT-qPCR

Taken and modified from: [37] CSF: Cerebrospinal fluid, ELISA; enzyme-linked immunosorbent assay, SIMOA: Single molecule array

2.5.4 Disease development and prognosis

Alzheimer's disease is a degenerative, irreversible, and progressive entity with an insidious onset. Its initial stages may not be detected by the person or family and is often erroneously classified as something normal in old age.

The first symptom in Alzheimer's disease is usually memory loss, which at first can be very subtle in aspects related to things that happened recently. Later, a difficulty in learning new things appears and the person may show a tendency to repeatedly ask about the same thing. As the neurodegeneration evolves, the brain pathology impairs other cognitive functions, such as executive tasks, procedural and semantic memory, and behavior. Eventually, the capacity to perform activities of daily living is

reduced, leading to disability and dependency, severely impairing quality of life. [25, 29, 8]

Unfortunately, sometimes people with Alzheimer's disease are often initially evaluated in advanced stages, when relatives detect the presence of very prominent symptoms such as disorientation, long-term memory failures, alterations in behavior, (apathy, depression, agitation, aggressiveness, alteration in hygiene, inappropriate behavior) alteration in language or urinary/fecal incontinence. [38]

Alzheimer’s disease mainly affects the brain, but the disease process goes hand in hand with a deterioration of other systems, such as the muscle and locomotor systems. The speed and sequencing of this process varies from person to person. However, the progression of this disease, from pre-prodromal phases, is gradual and the pathological changes often start up to 20 years before symptoms emerge. The presence of comorbidities, especially those of vascular origin, can precipitate and worsen the course of the disease. [6]

2.5.5 Management

Management of Alzheimer's disease consists of a series of interventions according to severity of the disease. There are pharmacological interventions and non-pharmacological interventions. [39]

2.5.5.1 A. Pharmacological interventions:

Although there is currently no drug that can permanently cure or stabilize Alzheimer´s disease, there are some groups of symptomatic drugs licensed for use.

1. Anticholinesterases (acetylcholinesterase inhibitors).

2. Glutamatergic transmission modulators (N-methyl-D-Aspartate receptor antagonists).

Huge efforts are directed towards disease modifying drugs for Alzheimer's disease. Aducanumab (Human monoclonal antibody that specifically binds beta-amyloid) has shown promising results and has been approved by the FDA, under the accelerated approval pathway, a decision that has been criticized. [40] Very recently a phase 3 medication Lecanemab, another monoclonal antibody that binds to soluble Aβ aggregates, met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months by 27%. [41]

In addition to disease-modifying drugs and drugs that targets cognition, other pharmacological interventions aims at ameliorating mood and behavior disorders. [42]

2.5.5.2 B. Non-pharmacological interventions:

Non-pharmacological interventions are consolidated as useful, accessible, and cost-effective tools to improve clinical manifestations for the patient and the caregiver. Some of the interventions include cognitive training, music therapy, education, exercise, and nutritional advice.[43]

2.6 Lewy body dementia

Lewy body dementia refers to different pathological and clinical conditions; the most common are Dementia with Lewy bodies (DLB) and Parkinson's Disease Dementia (PDD). [22]

2.6.1 Epidemiology

Dementia with Lewy bodies is a common type of dementia, representing 10-15% of dementia cases. [44, 45] Dementia is common in Parkinson's disease and develops in most patients surviving for more than ten years. [46]

2.6.2 Pathology and mechanisms

Lewy body dementia is characterized pathologically by abnormal deposits of the protein alpha-synuclein in the brain, called Lewy bodies. The pathological findings consist of abnormal protein deposits that disrupt the brain's normal function. The characteristic alpha-synuclein lesions form into aggregates inside neurons, becoming immunopositive with anti-alpha-synuclein antibodies. [47]. In many cases of DLB and PDD is frequent to have Alzheimer-type pathology, predominantly amyloid plaques, which can act as additive or synergistic with a-synuclein pathology. [48]

2.6.3 Clinical symptoms

The key symptoms of Lewy body dementia are cognitive impairment and parkinsonism. Dementia with Lewy bodies is characterized by a tetrad consisting of visual hallucinations, spontaneous parkinsonism, REM sleep behavior disorder, and dementia, with reduced capacity to perform daily living activities such as household tasks, personal care, and instrumental activities (shopping, cooking, handling finances, etc.). Dementia with Lewy bodies is diagnosed when cognitive impairment precedes parkinsonian motor signs or begins within one year from its onset. In contrast, in Parkinson's Disease Dementia, cognitive impairment develops in the setting of well-established Parkinson's disease. [49] In PDD, persons have a previous diagnosis of Parkinson disease first based on motor features and subsequently develop dementia. In DLB, dementia is present earlier on. For practical use, DLB diagnostic criteria suggested the 1-year rule, where DLB should be diagnosed if dementia appears before or within 1 year of parkinsonian motor symptoms. [50]

2.6.4 Diagnosis and assessment

Diagnosing Dementia with Lewy bodies can be challenging. Despite validated diagnostic criteria for DLB [51-53] only one in three cases are correctly identified. [54] Thus, the biggest challenge in diagnosing DLB is an early diagnosis and differentiation from Alzheimer's Disease. [22] The consortium diagnostic criteria for DLB have low sensitivity, with sensitivity and specificity of 32% and 95%, respectively, against autopsy-confirmed diagnosis. [55]. Differential diagnosis is still a concern, particularly in the early stages of the disease, since significant clinical and neuropathological overlap exists, mainly with Dementia with Lewy bodies, Alzheimer´s disease, and Parkinson's Disease Dementia.

DLB can be diagnosed as probable or possible, this is based on the assurance of the diagnosis. Probable DLB is determined with two of four core clinical symptoms, or one of four symptoms with abnormal indicative markers (i.e. DaT-Scan, myocardial IBG- scintigraphy, or polysomnography). Possible DLB can be diagnosed with one core symptom (not indicative marker), or one or more indicative markers (without a core symptom). [47]

Lewy body dementia leads to poor outcomes on crucial indicators, including quality of life (QOL), caregiver burden, nursing home admission, hospitalization, and mortality. [56] Therefore, more specific biomarkers are required to achieve better clinical therapeutic decision-making processes. Additionally, prognostic markers are not routinely available. However, there is wide variability within Lewy body dementia, with some patients having a very rapid decline and short survival. Thus, early identification of these patients is crucial to optimize management strategies and monitoring. [57]

2.6.4.1 Biomarkers

Cerebrospinal fluid (CSF) analysis, electroencephalography, blood, and imaging biomarkers are potential biomarker sources. However, results reported to date are nonspecific.

Current diagnosis guidelines include indicative biomarkers and supportive biomarkers. As indicative 1. Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. 2. Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy. 3. Polysomnographic confirmation of REM sleep without atonia. And as supportive 1. Relative preservation of medial temporal lobe structures on CT/MRI scan. 2. Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET imaging. 2. Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/ theta range. [47]

Reports in the literature demonstrated that low dopamine-transporter uptake on single-photon emission CT (DaTscan) improved sensitivity and specificity for diagnosing dementia with Lewy bodies compared with Alzheimer´s disease but did not help distinguish other parkinsonian dementia syndromes as progressive supranuclear palsy and corticobasal degeneration from dementia with Lewy bodies. [52, 58] DaTscan is also expensive and not widely available. On the other hand, biological fluid markers could be an arising option, widely available, cheaper, and with fewer safety concerns. Ideal potential biomarkers reflect a process similar to the particular disease; consequently, most studies in dementia rely on CSF markers candidates. CSF fluid α-synuclein concentration is significantly lower in patients with DLB than in those with Alzheimer´s Disease [59] but cannot distinguish between individual patients according to disease classification. Preliminary evidence also indicates that a low level of abeta42 in cerebrospinal fluid (CSF) is a predictor of faster decline in DLB. [60] Recent evidence has also shown that the α-

syn CSF RT-QuIC assay has the potential to detect underlying Lewy body disease at the mild cognitive impairment stage, including in those with possible mixed Alzheimer disease pathology. [61]

In addition, quantitative EEG measures of background rhythm frequency and relative power in the θ band have shown to have the potential to predict incident Parkinson's disease dementia. Arnaldi et al. showed that resting EEG and 123 I-FP-CIT-SPECT are good predictors of future cognitive worsening in Parkinson patients. [62-64] In addition, quantitative EEG has demonstrated good discriminative capacity for dementia with Lewy bodies. [65]

The disease, besides implying cognitive deterioration, is complicated by motor symptoms, including tremor, rigidity bradykinesia and postural imbalance, which together potentate disability, high burden of comorbidities, and other complications. Early detection and early interventions to prevent complications are essential.

In previous research by our group, it has been shown that several factors beyond cognitive impairment have an important role in the functional prognosis of those newly diagnosed with Lewy body dementia. The load of neuropsychiatric symptoms measured with the Neuropsychiatric Inventory (NPI) significantly associated with altered course of functional decline over five years. A higher score on the NPI was associated with faster functional loss. [66] Polypharmacy is a geriatric syndrome frequent in old age and even more in dementia. It was observed that the number of medications consumed by these patients was directly correlated with functional decline. [67] Finally, we documented that the prescription of benzodiazepines was frequent and increased with dementia progression and that alone or in combination with antidepressants increased the functional loss. [68]

Survival of individual patients after being diagnosed with dementia with Lewy bodies is challenging to predict, mainly due to comorbidity that is common in older adults and more common in dementia with Lewy

bodies, which contributes to a complex risk profile for mortality. A person diagnosed with LBD or DLB may live as long as 20 years or as short as two years after the onset of obvious dementia with Lewy bodies symptoms. However, research suggests most people live five to eight years with the disease and significantly shorter than those with Alzheimer´s. [56] Since dementia with Lewy bodies is closely connected with functional loss, hallucinations, and behavioral symptoms, it might be expected that these patients are more likely to be placed in a nursing home. In dementia with Lewy bodies the time to enter into a nursing home from the diagnosis was 1.8 years which was two years shorter than in Alzheimer´s disease. In addition, compared with Alzheimer´s disease, people living with dementia with Lewy bodies have worse quality of life and higher caregiver burden. [69, 56]

2.6.5 Management

There are no disease-modifying treatments available for Lewy body dementias yet. However, scientific societies agree that once available; such therapies should be initiated at an early disease stage, i.e., when there are still functioning neurons to salvage. [5] There is thus still a need for improved early detection of Lewy body dementia and the ability to distinguish between different neurodegenerative diseases. [56] Early diagnosis is also crucial for the implementation of clinical trials of potential novel drugs. Early management provides opportunities for better prognosis and quality of life, this based in education, control of neuropsychiatric symptoms, prevention of adverse events such as falls or malnutrition, promoting adequate medication and prevention of adverse effects associated with improper prescription, and initiation of non-pharmacological interventions, all to prevent a rapid functional decline and slow-down dependency and disability. [47, 56]

There are pharmacological interventions approved for the management of people living with Lewy body dementia. Cholinesterase inhibitors improve global cognitive function and reduce visual hallucinations and

other behavioral symptoms and is considered the first line of treatment. [70, 46] Memantine can be used in monotherapy if cholinesterase inhibitors are not tolerated or contra-indicated. Besides Memantine can be used also in combination with cholinesterase inhibitors, particularly if the effectiveness of the cholinesterase inhibitor is limited or is declining, or the disease is becoming more severe. The preferred pharmacological treatment of parkinsonism in Lewy body dementia is levodopa monotherapy, either co-careldopa (carbidopa/levodopa) or co-beneldopa (levodopa/benserazide hydrochloride) may be used. [46]

In addition, non-pharmacological interventions can be helpful, such as cognitive training, career, and patient education, physical activity, nutrition, and occupational therapy. [71]

2.7 Cognitive decline and neurodegeneration as systemic processes

Recent evidence supports that dementia and neurodegeneration are not processes limited to the brain, but their causes and evolution mechanisms often involve interactions of many body systems. [4, 72]

Dementia-onset and prognosis are determined by many factors that promote neurodegeneration. The most essential are systemic inflammation, endothelial damage, and oxidative stress. [72] There are studies linking chronic low-grade inflammation to changes in brain structure that could precipitate neurodegenerative changes. For example, Walker and collaborators described that people with increased levels of inflammatory proteins in the blood in midlife had higher risk of developing cognitive decline in the upcoming decades. [73] In addition, there has been described an association between chronic periodontitis and Alzheimer´s disease. [74]

In addition to the core pathological changes reported above, dementia could result from activating macrophages in the blood, microglia in the

brain, and subsequent secretion of pro-inflammatory cytokines. Further, neurotoxic final products of the tryptophan-kynurenine pathway are stored in astrocytes and neurons. These promote the release of inflammatory products and induce an elevated secretion of cortisol. In this case, cortisol has the capacity to inhibit protein synthesis, to reduce the synthesis of neurotrophic factors, and damage neuronal networks. [75] Plasma concentrations of several kynurenines are reported to be lower in patients with Alzheimer's. [76] Besides, elevated levels of cortisol have been related with hippocampal atrophy. [77] Diabetes Mellitus, hypertension, and other cardiovascular diseases are risk factors for developing dementia, in addition to lifestyle habits such as smoking and physical inactivity. All these entities have in common that they act on several systems in the body, are related to chronic inflammation, and have the potential to impair endothelial function. Vascular damage contributes to the formation of tau-containing neurofibrillary tangles and amyloid β (Aβ) plaques, and the Alzheimer pathology leads to cerebral hypoperfusion. [78, 79] When cerebral hypoperfusion happens, there is a metabolic energy crisis for the neurons, leading to acidosis and oxidative stress, promoting the hyperphosphorylation of tau proteins and, therefore, the formation of neurofibrillary tangles. [80]

Genetic studies of Alzheimer's disease and its risk factors also demonstrate inflammation as a potential first step in Alzheimer's disease pathophysiology. [81] Previous research reports that TNF-α plays a direct role in metabolic syndrome. [82] In short, patients with dementia and diabetes demonstrate high protein expression of TNF-α in skeletal muscle and increased TNF-α levels in plasma. [83] Elevated levels of tumor necrosis factor are evidenced in brains and cerebrospinal fluid of Alzheimer's disease patients. [84]

Exercise and physical activity have been proposed as protective against neurodegeneration. [82, 85] This effect may be related to the benefits at the cardiovascular level and the effects of stimulating the muscle, such as the production of anti-inflammatory myokines and other substances

that have shown to be neuroprotective. [86] It has been shown that sarcopenia causes cognitive decline through an imbalance of myokine secretion via a reduced skeletal muscle mass and that sarcopenia contributes to poor vascular homeostasis, leading to cognitive impairment. [87]

Physical activity promotes good muscle condition and, in addition, releases cytokines that reduce inflammation and the accumulation of ectopic adipose tissue, such as the visceral and intramuscular fat mass. Abdominal adiposity is associated with cardiovascular disease (CVD), type 2 diabetes, dementia, colon cancer, and breast cancer. [88, 89] In the absence of muscle contractions that stimulate the endocrine function of the muscle, malfunction of several organs and tissues of the body may also occur, implying increased risk of disorders such as cancer and dementia. [82]

Therefore, improving muscle condition through physical activity and nutrition could substantially benefit a broad group of chronic disabling conditions such as dementia.

2.8 Muscle status and dementia: The muscle as an endocrine organ

The locomotor system, also called the musculoskeletal system, comprises the bones, the joints, and the muscles. The bones provide the mechanical basis for movement, as they are the site of attachment for muscles and serve as levers to move. The joints relate two or more bones to each other in their contact zone. They allow the movement of those bones in relation to each other. And finally, muscles allow moving two parts of the body with respect to the other; therefore, it produces a physical displacement, which is called locomotion.

The muscle, besides being essential for locomotion, and other important tasks such as breathing and thermoregulation, is a primary site for

glucose uptake and storage. It is also a reservoir of amino acids stored as protein. In addition, recent evidence is accumulating, describing the capacity of muscle to produce myokines. [90] Myokines are any secreted protein produced in skeletal muscle, whether they act in an autocrine, paracrine, or endocrine manner. [91] They are made when the muscle is activated with physical activity. In the muscle, myokines are involved in many paracrine functions such as regulating angiogenesis, controlling adaptive and inflammatory processes, the oxidation of fatty acids, hypertrophy, and regulation of the extracellular matrix. On the other hand, myokines are also involved in endocrine functions such as regulating body weight, low-grade inflammation, insulin sensitivity, suppressing tumor growth, and improving cognitive function. [90]

Some of the expressed myokines include Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-15 (IL-15), and brain-derived neurotrophic factor (BDNF). [92] Interleukin-6 was the first described myokine. Originally it was classified as a pro-inflammatory cytokine; however, lately, it has been attributed with anti-inflammatory properties. It increases up to 100 times during physical activity, being stimulated by the contraction of the skeletal muscle fibers. IL-6 promotes the production of IL-1 other anti-inflammatory cytokine, also increases glucose uptake and fatty acid oxidation, and enhances insulin secretion. IL-8 is a chemokine that promotes angiogenesis, and its levels increase after muscle contraction. [93] IL-15 has an anabolic function in muscle growth, and elevated circulating levels of IL-15 result in significant reductions in body fat and increased bone mineral content. [94] The BDNF is strongly expressed in the brain and plays an important role in synaptic plasticity, regulating growth and neuron survival. [95] BDNF mRNA and protein levels are augmented in skeletal muscle in response to exercise and contribute to enhanced fat oxidation by activating AMPK. It has been reported that people with Alzheimer's disease have low plasma levels of BDNF. [96] In addition, low plasma levels of BDNF have been found in patients with depression, type 2 diabetes, and

other cardiovascular diseases. Besides, BDNF in the hypothalamus is a key factor in controlling body mass and energy homeostasis. IRISIN: Irisin is a membrane-bound protein in skeletal muscle that is induced by exercise. Irisin improves adiposity and glucose homeostasis.[97] Besides skeletal muscle, Fibronectin type III domain-containing protein 5 (FNDC5) is also expressed in skeletal muscle and the brain and increases hippocampal BDNF expression and ultimately neurogenesis in this brain region. [98] Systemic anti-inflammatory cytokine responses are more pronounced after exercise, due to more muscle damage. This is a regulatory mode of the cytokine network for adaptation against systemic inflammatory stress. [99] Table 2.2. Shows a summary of other important myokines.

Table 2.2. Additional important myokines and their endocrine effect

Protein	Tissue	Central effects
Identified and putative muscle-derived factors triggered by exercise		
Cathepsin B	Skeletal muscle	↑ Hippocampal neurogenesis + spatial memory ↑ Hippocampal BDNF + DCX
Irisin	Brain Skeletal muscle	↑ Hippocampal BDNF
L-Lactate	Skeletal muscle	↑ Vascularization ↑ VEGFA expression and vascularization
Additional factors (not necessarily induced by physical activity or derived from skeletal muscle)		
Kynurenin (KYN) Kynurenic acid (KYNA)	Liver Skeletal muscle (PA)	↓ KYN accumulation decreases stress-induced neurobiological mechanisms of depression

Taken and modified from Julien Delezie et al. 2018 [100]

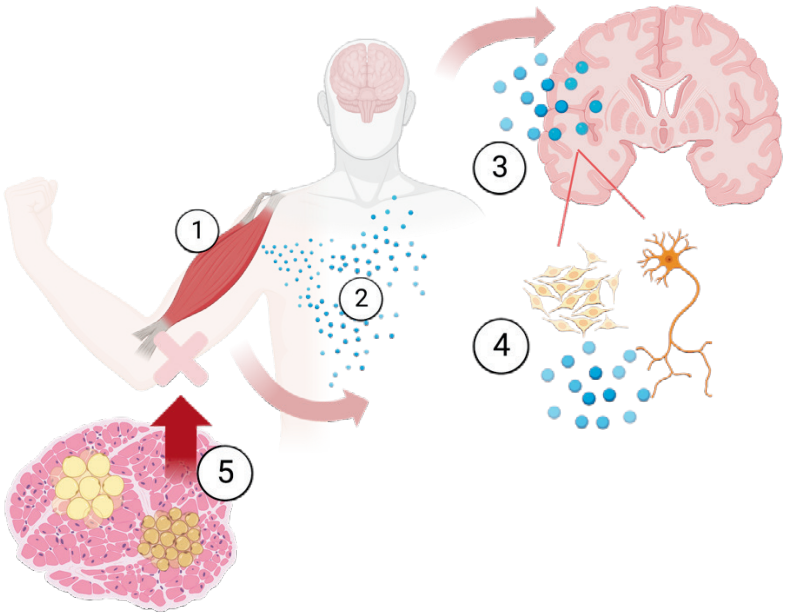
2.9 Intramuscular fat

Adipocytes can be deposited in several depots, the 5 traditional places are subcutaneous, visceral, intermuscular, and as intramuscular fat (iMAT). Intermuscular fat are adipocyte accumulations in spaces between the muscles, and iMAT consists of lipid droplets that exist near the mitochondria and are located inside skeletal muscle fibers. [101] iMAT serves as an energy store that can be used during exercise. Excess accumulation of intramuscular fat in humans has been associated with cardiovascular risk factors, inflammation, and conditions such as insulin resistance and type 2 diabetes. [102] In addition, high levels of iMAT are associated with loss of strength and mobility dysfunction. [103, 104] This harmful effect on muscle and mobility has been associated with stimulating the production of the proinflammatory cytokines related to iMAT accumulation. [105]

The genesis of the iMAT can be induced by age, diet, gender, fasting, genetics, and physical activity. [101] In addition diets with decreased protein intake might increase iMAT by increasing steroil-CoA desaturase activity. [102]

iMAT can be measured via computed tomography (CT) or magnetic resonance imaging (MRI). The estimation could have a clinical utility for healthy people to establish the risk of adverse outcomes or in people already with chronic diseases to establish a prognosis. [106] However, although iMAT may contribute to neurodegeneration, its role in dementia development has not yet been established. Figure 2.4.

Figure 2.4. Systemic interaction between muscle and brain



Muscles in the body produce Myokines, 2. These Myokines have systemic anti-inflammatory effects, 3. These effects are seen in the brain, 4. In the brain the myokines promote synaptic plasticity, cell survival and proliferation. 5. The muscle infiltrated by fat inhibits the production of anti-inflammatory myokines and increases systemic inflammation.

2.10 Malnutrition

According to the World health organization, malnutrition is the deficiencies, excesses, or imbalances in a person's energy intake and/or nutrients. However, the terms malnutrition and undernutrition has been used indistinctly to describe states related with low height and nutrient deficiencies or insufficiencies (starvation, cachexia/disease related malnutrition), and the term overnutrition to describe overweight or obesity.[107] According the European society of clinical nutrition and

metabolism, malnutrition is a state consequence of the lack of intake and uptake of nutrients, conducting to an alteration in the corporal composition and body cells, decreasing the mental capacity and clinical outcomes of the disease.[107]

Malnutrition is a frequent problem in older adults. However, it is often under-recognized and even assumed to be expected with age. Its relevance relies on the important negative consequences (see below). Therefore, adequate screening, identification, prevention, and intervention strategies for this condition are needed. [108]

The prevalence of malnutrition varies between studies due to the different measuring instruments and regions. In developed countries, the reports give an approximate prevalence of 15% in older adults in the community, between 23 and 62% in hospitalized patients, and about 85% or more in those living in nursing homes. [109, 110]

Malnutrition in older adults has multiple consequences, including impaired muscle function, decreased muscle and bone mass, immune dysfunction, anemia, cognitive decline, poor healing, poor recovery after surgery, increased risk of institutionalization, more extended hospital stays, frailty, mortality, and reduction in quality of life. [111]

The causes of Malnutrition are multifactorial and can be classified into two groups: [112]

1) age-related alterations in homeostasis: Taste, smell, and appetite generally decline with age, making it more difficult to enjoy and maintain regular eating habits. In addition, after a demanding catabolic event such as surgery, infection, or acute disease, older adults tend to take longer than young adults to regain lost weight. They remain malnourished longer and are more susceptible to subsequent diseases, such as infectious processes. Table 2.3.

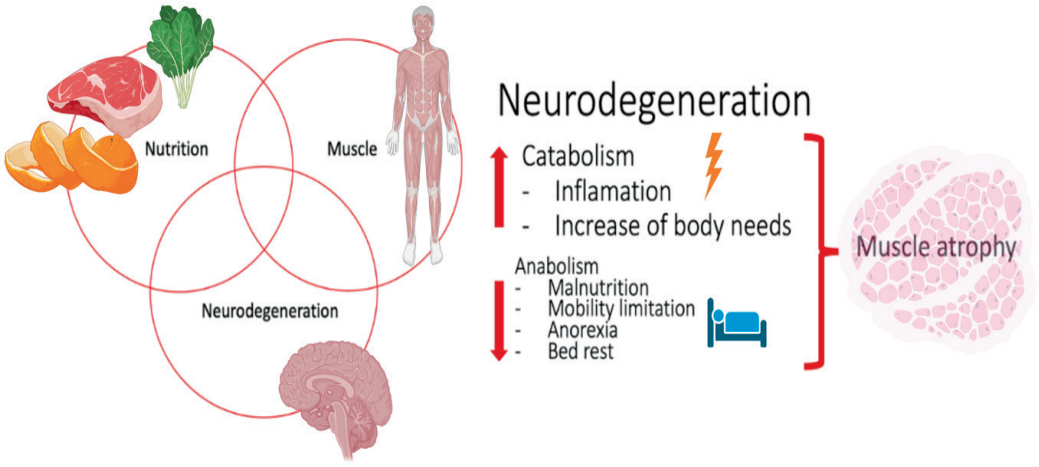
Table 2.3. Non-physiological causes of malnutrition:

Dementia	Forgetting to eat, not buying groceries, or other irregular food habits can result from behavioral or memory problems from dementia.
Parkinson's disease	Difficulty handling cutlery, excessive salivation, dysphagia.
Disability	Problems cooking, buying, and handling ailments due to functional disability and mobility problems
Eating function	Malnutrition can come from the impairment in the ability to eat, difficulty chewing, swallowing or limited capacity to handle tableware.
Medications	Medications have an important role, because they have to potential to affect appetite, taste or the absorption of nutrients.
Illness	Decline in appetite and changes in how the body processes nutrients can result from disease-related inflammation and illnesses
Oral health:	Oral ulcers, oral candidiasis, edentulism
Endocrine:	Hypothyroidism, hypoadrenalism, hyperparathyroidism
Restricted diets	Dietary restrictions for managing medical conditions — such as limits on salt, fat, or sugar — might also contribute to bad eating.
Limited access to food.	Problems and limitations in mobility may interfere with the food access or food with suitable nutrients.
Depression	Mood disorders specially depression are responsible of causing malnutrition due to loss of appetite, lack of motivation to shop or cook.
Poverty	Older adults may have trouble affording food with nutritional value
Reduced social contact/ loneliness	Eat alone might produce the not enjoyment of meals between older adults and therefore lose interest in cooking and eating. Also, this can get worst when depression is present.

Alcoholism	The digestion and absorption of nutrients can be affected by alcohol consume. In addition, misuse of alcohol can result in miss use of money destined for food, poor decisions about nutrition and poor eating habits.
Other medical conditions	Heart failure, chronic obstructive pulmonary disease, kidney failure, inflammatory arthropathies, infections, and tumors.

There are plenty of instruments to assess malnutrition in older adults; weight loss (greater than 5% in 3 months or 10% of habitual weight indefinite of time) [113] and anthropometric measurements such as the evaluation of the triceps fold or the circumference of the midarm. However, a drawback of these determinations is their dependence on reference values adjusted for age, sex, and race. Other alternatives are measuring cholesterol and plasma proteins such as albumin, prealbumin, or transferrin. [114] Further widely used methods, allowing rapid and practical application and implementation are the clinical scoring systems, such as the global subjective deterioration of the mini nutritional assessment. [115] Other helpful ways have been recently proposed, such as The Global Leadership Initiative on Malnutrition (GLIM) Index, which considers the Body mass index, age, and the current disease. [116, 117]. Figure 2.5.

Figure 2.5. Imbalance between catabolism and anabolism with ageing and dementia.



2.11 Sarcopenia

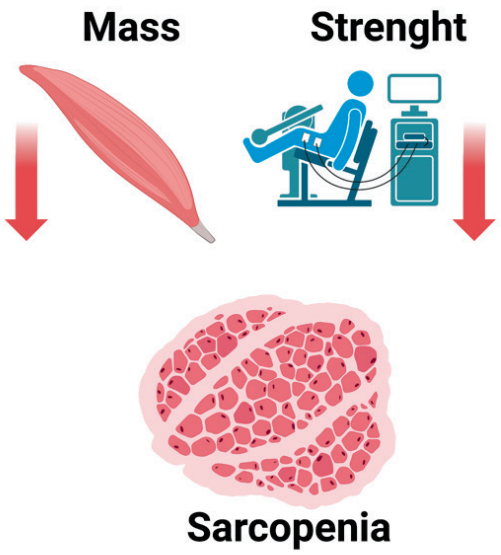
Sarcopenia is defined as the loss of muscle volume and function. The term sarcopenia was described for the first time in the late eighties, but, only until 2016 did the World Health Organization (WHO) include sarcopenia as a disease in its International Classification of Diseases and Health-Related Problems (ICD) with the ICD-10-CM code (M62.84). [118]

Sarcopenia is a prevalent disease in the population above 65 years of age. It occurs in 6-22% of older adults live in the community, and for those who reside in homes, 14-38%. [119] The prevalence increases with age; however, sarcopenia is caused by a combination of genetic and physiological and environmental factors. Lack of mobility, sedentarism, nutritional deficiency, and decreased caloric and protein intake in old age are the main drivers of muscle atrophy and the severity of sarcopenia. [120]

The European Working Group on Sarcopenia has established the diagnostic criteria of sarcopenia in Older People (EWGSOP2).

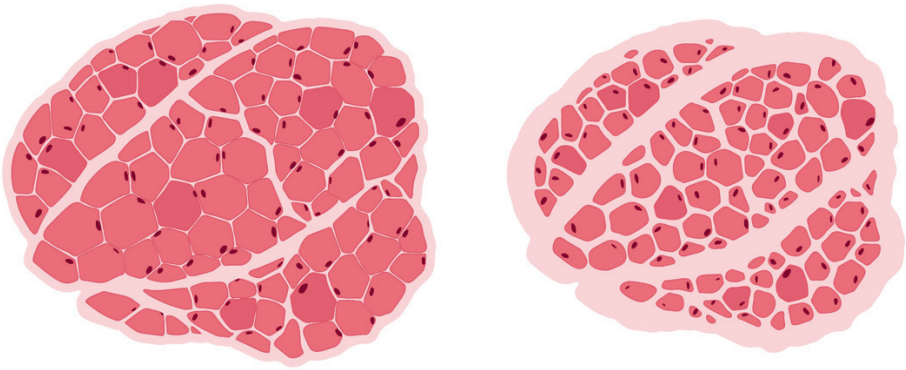
According to these criteria, sarcopenia is likely if there is low muscle strength, and the diagnosis is confirmed if there is added low quantity or muscle quality. [119] Figure 2.6.

Figure 2.6. principal components of sarcopenia definition



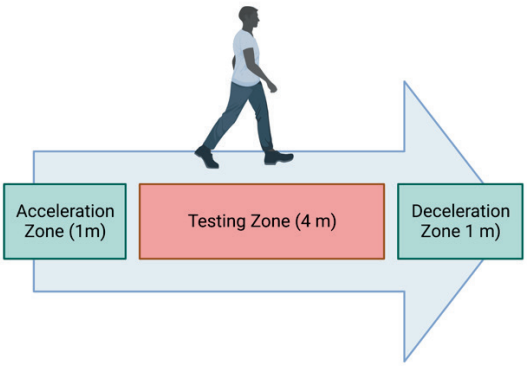
Muscle strength is commonly measured with grip strength using a dynamometer or by assessing the quadriceps strength with the test of rising from a chair (the amount of time needed for a patient to get up five times from seated without using the hands.) To measure muscle mass, it is recommended to use Dual-energy X-ray absorptiometry (DXA), Body MRI, computed tomography (CT), or ultrasound. [119] Figure 2.7.

Figure 2.7. Shows right a muscle cross-section with sarcopenia and in the left the same muscle of a 21-year-old person without sarcopenia



Several tests have been proposed to evaluate muscle performance due to their practicality and low cost; the most used is walking speed, which is a fast, safe, and trustworthy measure. The most used are four and 6-meter walk but several distances has been also used and validated. [119] Figure 2.8.

Figure 2.8. 6-meter gait speed test, person in instructed to walk 6 meters and time in seconds is measured in the testing zone.



The Short Physical Performance Battery (SPPB); is a test for screening physical function in older adults, which has been shown to have good predictive ability for death and nursing home admissions, future disability, and increased need for help. [121, 122] Finally, the timed up

and go (TUG) is the time measured in seconds that the participant uses to walk a distance of 3 m, turn, walk back to the chair, and sit down again. Longer time in the TUG is associated with greater dependency, nursing home admission, and greater cognitive decline. [123]

Treatment of sarcopenia is composed of two fundamental pillars: Nutrition and physical activity. Nutrition alone cannot reverse muscle atrophy and sarcopenia, fiber contraction stimulates protein synthesis in the muscle, and physical activity reduces muscle protein degradation. Aerobic exercise is beneficial for this. However, resistance exercise has shown the best results when reversing muscle loss. [124, 125]

2.12 Function as a comprehensive outcome in dementia

Functional capacity is defined as the ability of a person to meet their needs autonomously, independently, and satisfactorily. [126] The basic activities of daily living (ADL) are those aimed at self-care and mobility. Their deterioration is closely related to disability, frailty, frequent hospitalizations, nursing home admission, depression, multimorbidity, and death in older adults. [127] On the other hand, the instrumental activities of daily living (IADL) refer to the capacity of the individual to carry out actions that link them to the environment, such as making purchases and managing his finances, which allow him to use the resources of the community to supply your needs. [128]

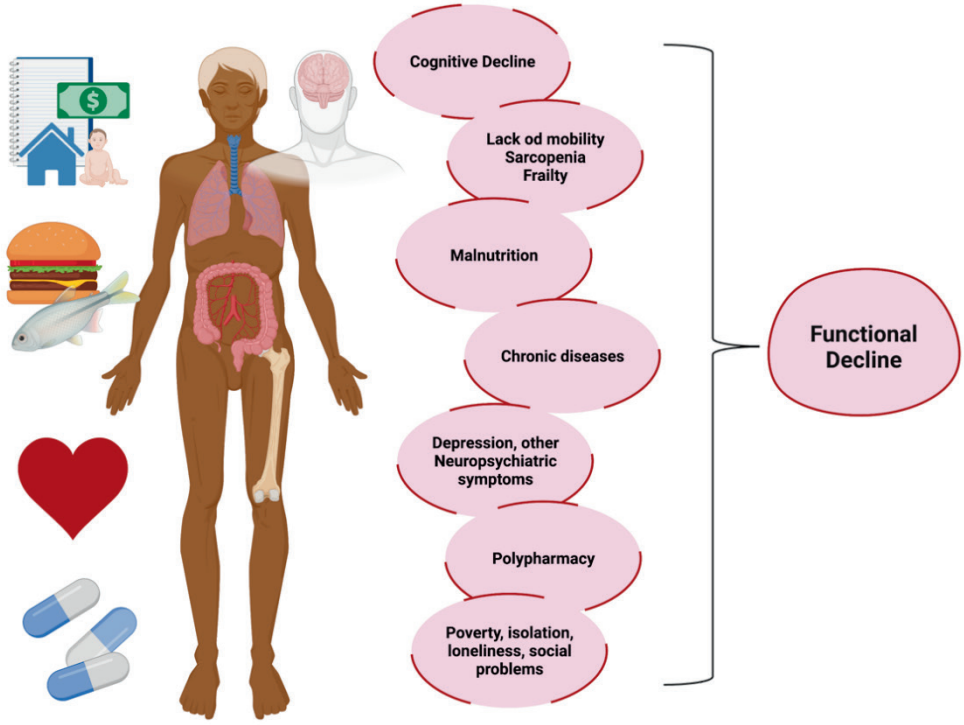
Functional status depends on multiple factors that are not adjustable, such as sociodemographic characteristics including sex and age. However, other factors are modifiable or partially modifiable, such as cognitive status, concomitant diseases, nutritional status, habits (e.g., physical activity, smoking, alcohol consumption), the number of medications taken, and the general state of health. [126]

Functional deterioration in older adults is becoming increasingly important as a significant public health problem. It is estimated that the

number of older adults with some degree of disability will triple by 2050 due to the aging population and the increasing prevalence of age-related diseases which lead to functional impairment. [129, 130] Functional loss and dependency severely impair the quality of life of the people. It also generates a significant burden for the social and health systems, avoiding an adequate distribution of resources among the population. [2, 18]

Dementia is one of the main drivers of functional loss, disability, and dependency. [131] In people with dementia, functional loss leads to dependence, nursing home admission, frailty, sarcopenia, mobility limitation, and pressure ulcers, among other frequent problems [132, 133, 126]. Cognitive impairment is the main factor leading to functional loss in dementia; however, it is not the only responsible factor. Functional capacity is very complex and depends on the person (e.g., co-morbidity, resilience, genetics) and the family/caregivers and environment. For example, people with dementia tend to be more inactive, which leads to muscular atrophy, loss of strength, sarcopenia, joint, and muscle pain, and functional loss. Likewise, those affected with dementia change nutritional habits and forget times for eating, which may lead to malnutrition and promote disability. [134, 135, 126] Figure 2.9.

Figure 2.9. Components that can affect the functional prognosis in a person living with dementia



Taken and modified from: [136]

2.13 Imaging

Imaging of the brain has a crucial role in the evaluation of a patient living with or with the suspicion of dementia.

Magnetic resonance imaging is based on the polarity of hydrogen atom spins that align extrinsically when exposed to the magnetic field generated by the resonator. Once aligned, these cells emit radiofrequency pulses generated by the antennas whose purpose is to accommodate the protons in the horizontal plane. When 63% of the protons spontaneously pass (recovery) to the vertical plane, images known as TI sequences are

obtained. The remaining 27% (protons still on the horizontal axis) generate the T2 sequence. [137]

MRI is the preferred imaging technique in the study of cognitive decline, due to that it provides more details about the person under study. MRI in addition to structural information, can provide functional information through diffusion/perfusion and spectroscopy.

Besides, CT can also be useful in the case the MRI is contraindicated or to discard causes that can be intervened with surgery. [138]

The main MRI sequences are: i) T1-weighted image in oblique coronal plane to evaluate the medial temporal lobe and hippocampal atrophy. ii) FLAIR and T2-weighted sequence to study infarcts and white matter hyperintensities. iii) Magnetic susceptibility sequence to detect micro bleeding such as amyloid angiopathy, calcifications and iron deposits.

Both MRI and CT can provide evidence of ischemic damage, however, MRI is more sensitive. In addition, with the MRI is possible to obtain higher resolution of soft tissue images compared with other imaging techniques, this is very useful when evaluating the parenchyma of the brain and the posterior fossa. It is also superior to the CT when evaluating intracranial blood vessels, allowing separation of arterial and venous circulation. [139]

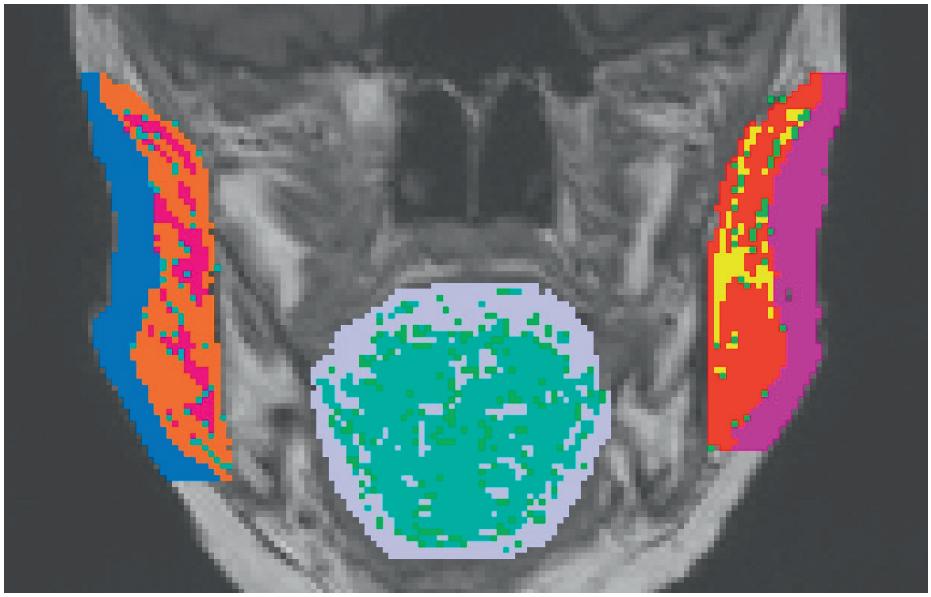
Depending on the type of dementia an atrophy pattern will predominate. For example, in Alzheimer's disease the temporo-parietal atrophy will be mainly present at least in the earliest stages.[140] On the other hand, in dementia with Lewy bodies imaging tests have evidence that images show a discrete diffuse cortical atrophy. There is greater atrophy of the mesencephalon and hippocampal-sparing as the most common pattern of atrophy in dementia with Lewy bodies. [141, 142]. Vascular changes are also very important to detect thus, in most of the cases are mixed with neurodegenerative changes corresponding to other neurodegenerative dementia such as Alzheimer disease. Changes commonly present usually

correspond to small vessel dementia, (Binswanger disease) or lacunar infarction.

The objectives of taking a brain image are; 1. Excluding a potentially reversible cause of dementia. [143] 2. Evaluate the specific subtype of dementia, in particular to differentiate the specific type of the dementia. 3. Quantify the stage of the disease to follow its response to treatment, and 4. Identify subjects who may respond to treatment. [141]

In addition of what we have mentioned above a standard brain MRI not only shows brain structures. Usually, it also evidences head bones, fat, and muscles. MRI has demonstrated good soft tissue resolution, high contrast between fat and water, and is free from ionizing radiation. [144] This last characteristic allows repetitive scans in specific longitudinal observations. MRI for muscle measure has been validated to reliably measure body compartments, at high accuracy. Figure 2.10.

Figure 2.10. In colors masseter and tongue muscle segmented from a normal brain MRI.



MRI image from Demvest study analyzed with Slice-o-matic sofware.

2.13.1 Additional imaging techniques

With molecular imaging, the brain can be studied using functional and quantitative metabolic nuclear medicine to provide additional important diagnostic information in the study of dementia. Recent developments have solidified cerebral positron emission tomography (PET) as a useful diagnostic tool for example: radiotracers, hybrid imaging, and quantitative computer-based algorithms.

The most common radiotracer used in PET is 2-deoxy-2-[F-18] fluoroglucose (FDG), a glucose analog. More FDG is up-taken by the cells with higher metabolic activity. In healthy subjects, the most intense FDG uptake occurs in the subcortical putamen, caudate nucleus, and thalamus, followed by high uptake in the cortical gray matter. [145] Two key structures to recognize are the cingulate gyrus and the overlying precuneus cortex, which are best appreciated on sagittal images of the medial hemispheres. The typical pattern of compromised metabolism in Alzheimer´s disease consists of the involvement of the precuneus, the posterior temporal and parietal lobes and the posterior cingulate gyri. [146, 147] For dementia with Lewy bodies studies have shown that patients with the disease have hypometabolism in the brain's parieto-occipital cortex and a relatively normal cingulate island sign a pattern of brain metabolism in the posterior cingulate that has the appearance of an island on scans. In a recent study, patients with mild cognitive impairment who progressed to dementia with Lewy bodies had widespread hypometabolism on FDG-PET compared with the normal group. In Lewy body dementia the cingulate island sign ratio was higher when comparing with Alzheimer's disease. [148] More definitive in vivo diagnoses, more targeted subject selection, and treatment monitoring in clinical trials with the objective of delaying or preventing the symptomatic phase of Alzheimer´s disease have been achieved thanks to molecular imaging techniques targeting amyloid and tau PET ligands.

The most common radiotracer used in dementia is FDG. However, there are several radiotracers such as carbon and fluorine-labeled amyloid- and tau-specific are used to study specific phenomena. [149]

On the other hand, it has been shown that other imaging procedures have clinical utility in the diagnosis of dementia with Lewy bodies specially when differentiating from Alzheimer´s. This is the case for The DaTSCAN. People with dementia with Lewy bodies have reduced levels of the dopamine transporter protein (DAT) in the corpus striatum, due to the loss of dopaminergic nigral neurons. Tracers that bind to the dopamine transporter CAN identify this reduction on certain brain scans (PET or SPECT). This is known as DAT imaging. it has shown diagnostic accuracy with good sensitivity and specificity to differentiate between Parkinsonian syndromes and diseases with non-dopamine deficiency etiology. [150-152]

2.13.2 Muscle Imaging

Magnetic resonance imaging and ultrasound offer excellent special resolution, this allows a very good evaluation of muscle microanatomy. MRI has a superior sensitivity in detecting structural changes and especially subtle injury, therefore MRI imaging is considered the diagnostic gold standard for most muscular conditions. [153] MRI muscle imaging has the potential to evaluate a wide range of conditions, intramuscular collections, neoplasia, acute or chronic muscle injury and secondary changes to injury. [154] In addition quantitative MRI has shown to be of great utility. Thus, has become an increasingly important tool for the initial diagnosis of muscular disorders, disease tracking, and for evaluation and follow-up of treatment efficacy. On the other hand, with whole-body MRI is possible to identify signature patterns of muscular involvement in large anatomical regions. [155]

With the aim of measuring muscle mass and diagnose sarcopenia different imaging techniques has been used. These tests aim to be cost effective, more accessible, and practical. Vertebral L3 computer tomography has shown to give practical and precise measures of body composition, and this measured has been tested in cancer patients and in the intensive care unit. [156, 157]. Mid-thigh imaging estimated by magnetic resonance of tomography has shown to be a good predictor of whole-body skeletal muscle. [158]. The psoas muscle measured with tomography has been reported in several studies however more evidence is needed to validate the use of this measure. Finally ultrasound is a reliable and valid method to identify muscle wasting, and also as a measure of muscle quality. [159] The measure of the quadriceps using this technique is becoming more popular has the potential to be implemented in the community. [160, 119] These methods has shown clinical impact for example the thickness of the quadriceps has been shown to predict rehospitalization or death, even in those patients without walking capacity, [161] Ulrish et al. reported that opportunistically using masseter muscle area from head images predicted early mortality following people who had suffered a severe traumatic brain injury. [162] In addition, Tanabe et al. described how masseter sarcopenia conferred independently increased hazards of death within one year of traumatic injury. [163] In the table 2.4. we display the different current used techniques to identify muscle quantity.

Table 2.4. Imaging alternatives for the assessment of sarcopenia

Commonly Used Parameters	**Pros**	**Cons**
DXA		
Whole-body lean mass	Inexpensive	Lack of portability
Appendicular lean mass	Low radiation	2-dimensional data

Appendicular lean mass/height squared	Short image acquisition time, simultaneous measurement of whole-body fat mass and bone mass	No differentiation between subcutaneous and visceral fat. Does not include trunk muscles
Computerized Tomography		
Muscle size (CSA, volume)	High accuracy and reproducible results	Expensive
Muscle echo intensity	Simultaneous measurement of lean body mass, visceral and subcutaneous fat Differentiate between fat and fat-free mass	High complexity and radiation exposure
Magnetic Resonance		
Muscle edema, atrophy, fatty infiltration	No radiation exposure	Expensive
Muscle size (CSA, volume)	Best spatial resolution	High complexity
Muscle adipose tissue content	Body mass composition differentiation Capable of detecting changes in muscle structure	Limited access, long time of acquisition and lack of standardized assessment protocol
Ultrasonography		
Muscle size (CSA, volume)	Inexpensive	Operator skills and training required
Muscle thickness	No radiation exposure	Reliability and accuracy depend on operator
Muscle attenuation	Short image acquisition time	Poor reproducibility and accuracy

Echo intensity	Portable and real time visualization of target structure	

Taken and modified from: [153] CSA = cross-sectional area, DXA = dual-energy X-ray absorptiometry, US = ultrasonography

3 Current evidence, research gap and need for new information

Previous research has shown how maintaining a good nutritional status has been an important intervention to preserve well-being and health in older adults, including those living with dementia. [164, 165]

While weight gain is the main problem in middle age, weight loss in late life has been strongly associated with disability, cognitive impairment, dementia severity, worse clinical progression, nursing home admission, and mortality. [166-168]

In older adults, several studies have studied the association between high BMI as a protective factor and many of the most common adverse outcomes. [169-171] However, BMI does not only refer to fat composition; between 36-45% of the body composition is represented by muscle. So, muscle weight and size are also contributing to measures such as the BMI. [172] In addition, during old age and when living with chronic conditions, there is increased systemic inflammation, which increases catabolism, overcoming the nutritional intake and anabolism. Therefore, a high BMI can be protective. These phenomena could explain the paradoxical findings in the older adult population; where some studies have found that even though the risk of certain diseases increases as the BMI rises, such as cardiovascular diseases or cancer, people tend to live longer. [169] Being a bit on the higher side of the WHO's BMI adult categories appears to give an extra protective effect in olde age groups. [173] Studies show that this may be different in older populations, where malnutrition is the main factor associated with adverse outcomes. Interestingly, evidence has pointed out that a "U-shaped" relationship exists between nutritional status and unfavorable consequences, where the people in the extremes of underweight and obesity represent the groups with a higher risk of morbimortality. [174]

A recent study showed that significantly lower BMI occurs beginning approximately 7 years before MCI diagnosis. [175]

In individuals with dementia, malnutrition is associated with sleep disturbances, psychological problems, immobility, frequent falls, increased hospitalization risk, and many other adverse events. [176, 177] In addition, adequate calory and protein intake are crucial for preserving muscle mass and function. Maintaining muscle quality and thus preventing sarcopenia is very important. Previous research has shown how sarcopenia is closely related to cognitive decline and how people with dementia and sarcopenia have more negative outcomes. [178] Berri and colleagues described how poor muscle function, but not reduced lean muscle mass, drives the association of sarcopenia with late-life cognitive impairment. [179] However, the loss of lean mass has been associated with AD-related brain atrophy. [180] Both conditions share common pathways; for example, elevated levels of circulating inflammatory mediators are detectable in patients with both sarcopenia and dementia. [181, 182]

Muscle function by itself has also shown to be relevant not only regarding prognosis but regarding the capacity to predict future dementia. In a meta-analysis of 6 studies including 8699 participants from the United States and Europe in people without memory problems, reduced gait speed (a measure of reduced muscle function) was associated with an increased risk of incident dementia by 2.1 to 3.6 times. Those with memory problems and gait impairment had a 5.2 to 11.7 times higher risk of developing dementia. [183] In addition, Dumurgier et al. examined the relationship between slow gait speed and the hazard of incident dementia in a community-dwelling of older adults. They described that gait was slower up to 7 years before the clinical onset of dementia. [184]

These changes in muscle mass and muscle performance have been partially related to brain changes. Yu et al. described significantly greater

atrophy in parietal gray matter in people with sarcopenia compared with a sarcopenia-free control. [185] Hsu and collages also share the same findings in Asian population, which describe that Sarcopenia is significantly associated with parietal atrophy in older adults. [186]

On the other hand, muscle performance evaluated with gait speed has also been associated with morphological changes in the brain. Callisaya et al. reported that white matter lessons and hippocampal atrophy were associated with a decline in gait speed. [187] In addition, Doi et al. described that increased dual-task gait speed was associated with a gray matter pattern of increased volume in the medial frontal gyrus, superior frontal gyrus, anterior cingulate, cingulate, precuneus, fusiform gyrus, middle occipital gyrus, inferior temporal gyrus, and middle temporal gyrus. [188]

As mentioned, maintaining functional capacity and independency are one of the most important goals in geriatric medicine and specially in people living with neurocognitive disorders, therefore we aimed in paper I to assess the impact of the nutritional status in trajectory of the functional capacity. Good nutrition leads to good muscle, and then higher body composition. Therefore, I consider there exist the following gaps:

A. There is not previous description of the nutritional status of the people living with mild dementia in Norway, likewise there is not a register of the negative implications that this condition has in this population. B. It exist few understandings of the importance of the muscle in the prognosis of chronic diseases specially in mild dementia, therefore it is also important to show the implications of having low muscle mass or function in this population, in crucial areas such as nutritional status, cognition and brain structure. D. Finally there has not been reports of practical ways to determine muscular volume in people with dementia, currently this process is costly and time consuming.

4 Methodology

To address the aims and hypotheses, data from two different studies were used. Article I and II are based on The Dementia Study of Western Norway (DemVest), and Article III is based on the Dementia Disease Initiation study (DDI).

4.1 The Dementia Study of Western Norway (DemVest)

4.1.1 Population

The Dementia Study of Western Norway (DemVest) is a longitudinal cohort study with annual assessments of patients referred to dementia clinics at the three main hospitals in Hordaland and Rogaland counties. [55] The different centers were contacted by certified mail before the beginning of the study and invited to refer all patients with suspected dementia to the study. All dementia diagnostic units (geriatric, neurology, and psychiatric) in the region recruited patients for the study. All area residents were covered by the same National Insurance Scheme with restricted copayment, thus allowing the representation of a general dementia population. Information regarding medical background, clinical assessment, blood, cerebrospinal fluid, and Magnetic resonance imaging was collected from each subject.

Inclusion criteria were people with mild dementia, defined as a Mini-Mental Status Examination score of 20 or more or a Clinical Dementia Rating global score of 1, and diagnosed with dementia. Exclusion criteria were the absence of previously diagnosed moderate or severe dementia, delirium, previous bipolar or psychotic disorder, terminal illness, or recently diagnosed significant somatic disease. All participants at baseline were living at home, and 57% had a partner living with them. Participants were followed up yearly with comprehensive clinical assessments.

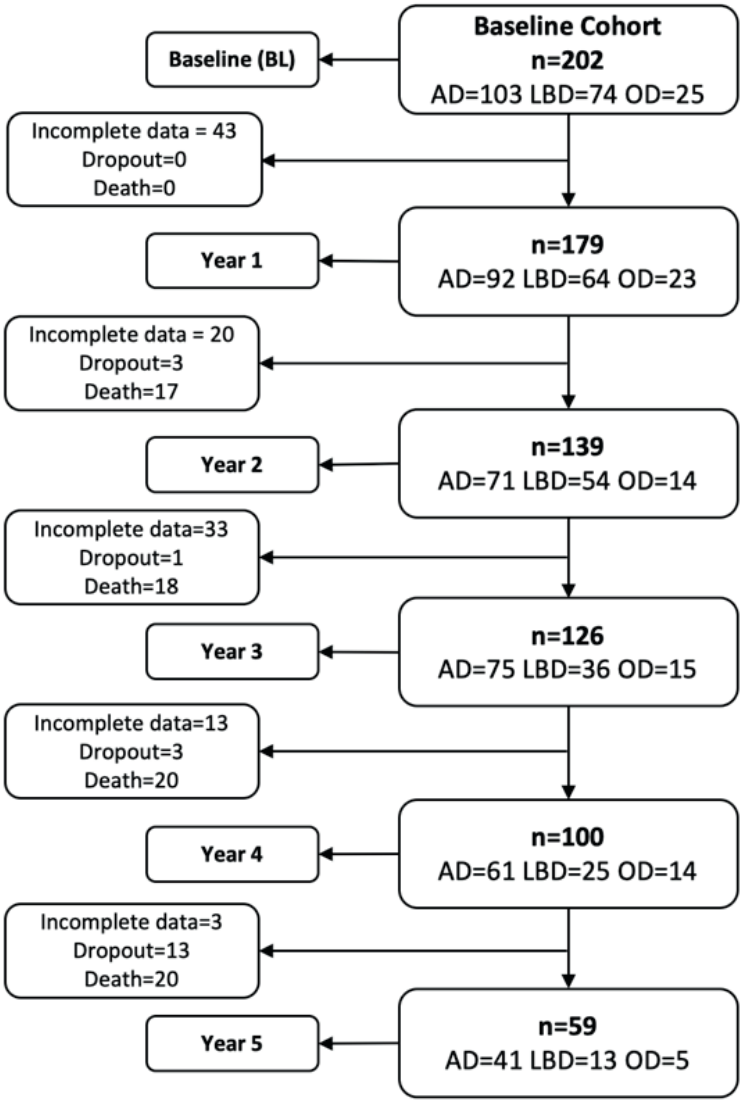
4.1.2 Diagnostic procedures

Diagnosis of early dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders. [19]Specific types of dementia were diagnosed according to the corresponding validated instruments. [189]. Alzheimer's disease was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria, [190] DLB according to the 2005 DLB Consortium criteria. [51] and dementia in Parkinson's disease according to the recommendations from the Movement Disorders task force. [191] Multidisciplinary diagnostic consensus meetings were performed at regular intervals. The first clinical diagnosis was made after the baseline visit and reviewed after both two and five years. The latter consensus process also involved an expert geriatrician. The revisions focused on participants with previous "possible" Alzheimer Disease or Dementia with Lewy bodies diagnoses, or an unexpected clinical course, for instance, slow cognitive decline. All available information, including neuroimaging and clinical information, (without neuropathology) were used in these revisions. In addition, pathological diagnosis was made on 56 participants of the DemVest cohort, with an accuracy above 80% compared to the clinical criteria. [192]

4.1.3 Sample and follow-up

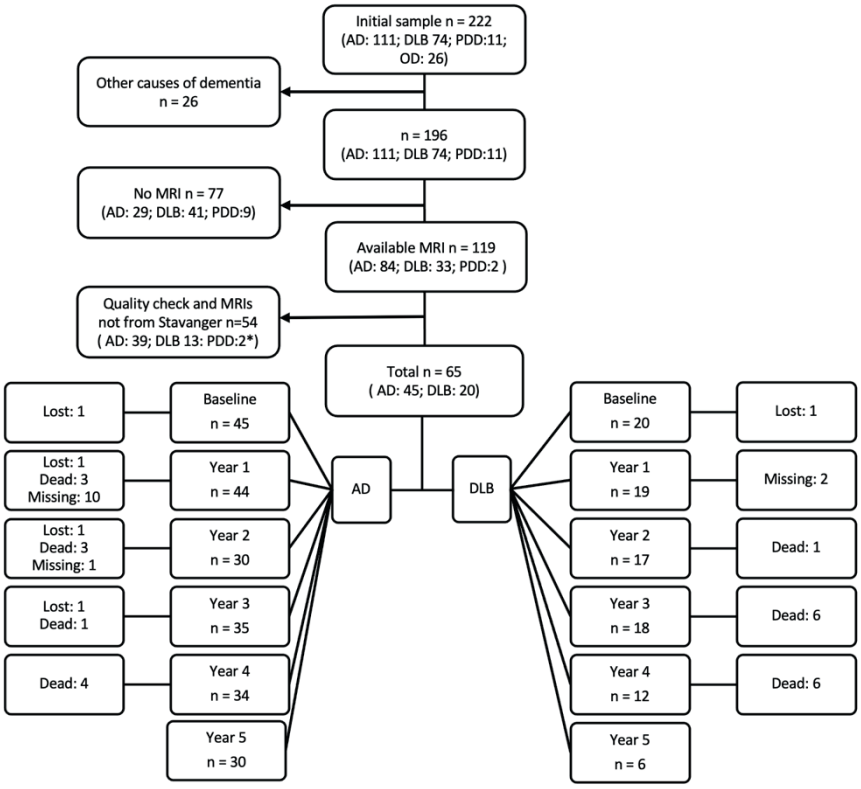
From an initial sample of 222 participants with different types of dementia, people diagnosed with mild Alzheimer's disease and dementia with Lewy bodies followed up for five years were selected for this thesis. The final sample used for the analysis corresponded to those participants with complete assessments. In the figures 4.1 and 4.2, it can be observed the data retrieval for both papers using DemVest data; note that they differed in the data availability, especially regarding imaging. The participation rate was very high throughout the study, and the drop-out was nearly entirely due to death.

Figure 4.1. Flowchart of the study design and data retrieval from Paper I (Borda MG 2020)



AD: Alzheimer disease, LBD: Lewy Body dementia, OD: Other dementias

Figure 4.2. Flowchart of the study design and data retrieval from Paper II (Borda MG 2021)



AD: Alzheimer disease, DLB: Dementia with Lewy bodies, PDD: Other dementias

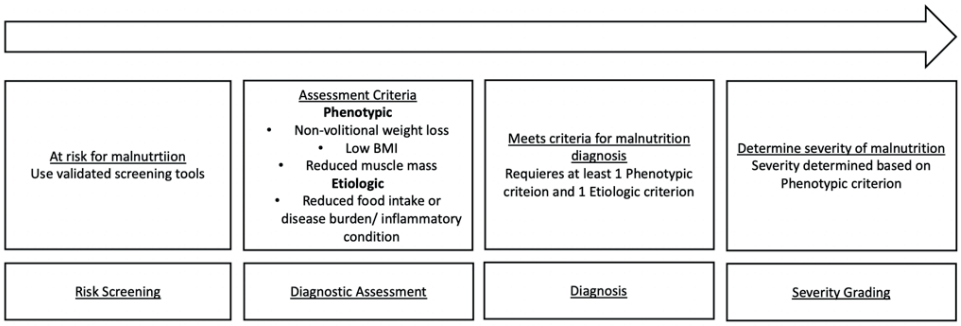
4.1.4 Outcome measurements

4.1.4.1 Nutritional assessment status

For papers I and II, nutritional status was the main variable of interest. We used the Global Leadership Initiative on Malnutrition (GLIM) index to determine the nutritional status. [116] It is a global initiative that targets the priority of adopting international consensus criteria so that

malnutrition prevalence, interventions, and outcomes can be compared throughout the world. It takes into consideration the BMI differences when the body ages and the importance of active inflammatory processes in the body. Furthermore, the GLIM Index has been shown to be a prognostic factor and predictor of incident mortality in several settings, including community-dwelling older adults and patients with inflammatory diseases such as cancer. [193, 194] Figure 4.3 shows the proses of malnutrition identification according to GLIM.

Figure 4.3. GLIM Criteria classification



Taken and modified from Cederholm (2019)

Following the inference rules, in my papers, BMI and age were used to categorize individuals into three possible nutritional status groups: severe malnutrition, moderate malnutrition, or adequate nutritional status. Individuals whose BMI was less than 18.5 and were younger than 70 years and with BMI less than 20 and 70 years or more were classified as severely malnourished. Participants with BMI less than 20 and younger than 70 years of age and BMI less than 22 and older than 70 were considered to have moderate malnutrition. Participants who did not fit into the established categories were considered as not having malnutrition. As a required etiologic criterion, all studied participants had a diagnosis of dementia. For the primary analyses, moderate and

severe malnutrition were analyzed together in a single group. We analyzed nutritional status at baseline and yearly during the five years of follow-up.

4.1.4.2 Cognitive assessment:

The cognitive test implemented in the papers I and II was the Mini-Mental State-Examination. Dr. Marshal Folstein initially developed this test in 1975, and it has been validated in many different languages. It is the most used cognitive scale in research. Therefore, it allows comparisons at an international level. The MMSE assesses the cognitive status in cognitive domains such as orientation, memory, attention, language, and execution/praxis. The original Mini-Mental State-Examination has a score range of 0 to 30. It allows to obtain a first estimate of the cognitive status quickly and is helpful for follow-up. Scoring/Interpretation: The questions can be scored immediately by summing the points to each completed task with a maximum score of 30 (no impairment). It is recommended to treat unanswered questions as errors. The recommended cutting point used to indicate cognitive impairment deserving further investigation is 23 or 24 out of 30. However, this instrument was used as a continuous scale in my analysis.

MMSE Test-retest reliability has been examined in many studies. Folstein reported in samples of psychiatric and neurological patients, ‘‘the test-retest reliability has not fallen below 0.89, and inter-rater reliability has not fallen below 0.82’’. In another study, the inter-rater reliability gave a Pearson correlation of 0.95 and a Kendall coefficient of 0.63 in a sample of 15 neurological patients. [195] (/instruct.uwo.ca)

4.1.4.2 Functional measurement

The functional capacity assessment was assessed in the paper I using the RDRS-2. This is a tool used to describe the functional capacity of older individuals with chronic conditions. The RDRS-2 contains eight

questions on activities of daily living, three on sensory abilities, three on mental capacities, and one question on dietary changes, continence, confinement to bed, and medication. The questions are rated on four-point response scales. Each question carries the same weight and is summed to provide an overall score that ranges from 18 to 72. Higher scores indicate a more significant disability. The authors have stated that typical scores for older adults living in the community with minimal disabilities average between 21-22, while 36 for those in nursing homes and hospitalized older adults averaged 32 (Linn & Linn, 1982). In the paper, we used the first 13 items which correspond to the activities of daily living: 1. Eating, 2. Making simple food (e.g., sandwiches), 3. Cooking dinner and adhering to a diet, 4. Mobilization - inside / outside (with or without aids), 5. Daily personal care (including brushing teeth, combing hair, and maintaining personal hygiene), 6. Bathing/showering, 7. Dressing (including finding clothes) 8. Toilet usage (including occasional clothing and cleaning), 9. Use of telephone 10. Buying food and other necessary items, 11. Handling money and paying bills, 12. Having a financial overview plan and writing tax returns, 13. Taking medications as prescribed. The Items were scored from 1 to 4 (Alone=1, with some help=2, with a lot of help=3, and cannot perform=4) and then divided over the number of items (0 minimum and four maximum total scores).

According to Linn & Linn, the item correlation reliability of this scale ranged from 0.62 to 0.98. The three lowest correlations were found amongst the questions on mental status. Test-retest reliability was found to be between 0.58 and 0.96. [196]

4.1.4.3 Confounding variables

Demographic factors included in the analysis were sex and age. Comorbidities were assessed using the Charlson Index and were registered based on participants and informant reports. [197]

Cognition was evaluated using the MMSE in its validated version in Norwegian. [198]

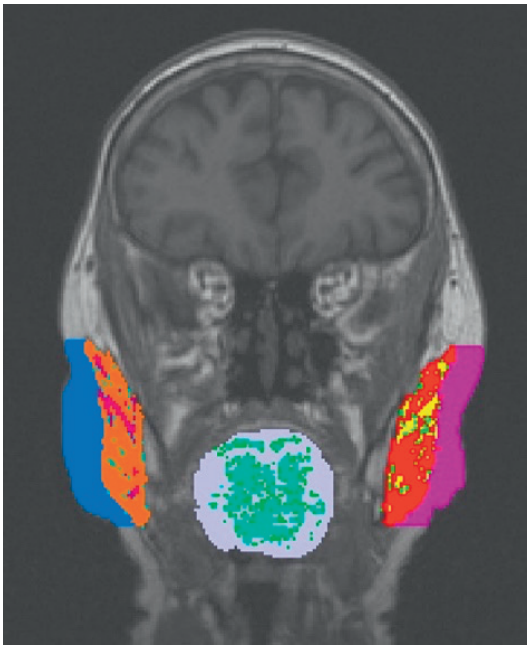
4.1.4.4 MRI calculations of iMAT and muscle volume

Baseline brain MRIs were acquired from a 1.5-T Philips Intera scanner using this acquisition protocol for a 3D T1-weighted sequence: repetition time/echo time 10.0/4.6 ms, flip angle 30.0°, 2-mm slice thickness with 1-mm spacing between the 3.10 slices (1-mm slices with no gap), number of excitations 2, matrix 256 × 256, and field of view 26 cm. We conducted a visual quality check procedure, discarding those with movement artifacts and inadequate image quality. A standardized preprocessing method for harmonizing multiple collections of MRIs was applied, which consisted of movement correction and intensity normalization.

Using the thresholds for tissues of interest, the volumes and volume ratios of muscle, iMAT, and subcutaneous fat (SAT) were manually tagged and quantified at the regions of interest using Slice- O-Matic (Montreal, CA) software (Figure 4.4) as previously described. The volumes of tissues and their signal intensity (e.g., in muscle, a possible indicator of intracellular fat infiltration) were quantified.

Because this is a new method, we had to calibrate and determine the tissue thresholds for each machine. Thus, to reduce variability data from the center, only the images from Stavanger were used. Therefore, images from other sites were excluded due to different scanners and acquisition techniques.

Figure 4.4. Segmentation of the tongue and masseter iMAT and muscle mass. This uses slice O-matic software.



MRI image from Demvest study analyzed with Slice-o-matic sofware.

4.2 The Dementia Disease Initiation study (DDI).

4.2.1 Population

The Dementia disease initiation study is a nationwide prospective, population-based, longitudinal multicenter cohort from Norway.

Participants were recruited from referrals to local memory clinics or self-referrals responding to advertisements in media, newspapers, or news bulletins. Healthy controls (HC) without subjective or objective cognitive problems were recruited from spouses of participants with either MCI or SCD and volunteers responding to media advertisements or news bulletins. Criteria for inclusion were age between 40 and 80

years and a native language of Norwegian, Swedish, or Danish. Exclusion criteria were dementia, brain trauma, stroke, severe psychiatric disorder, or any severe somatic disease that might influence cognitive functions, intellectual disability, or other developmental disorders. The cohort described here was recruited from 2013 to 2021 and participants were assessed approximately every two years. For further description of the DDI cohort and methods, refer to the study by Fladby et al. [199]

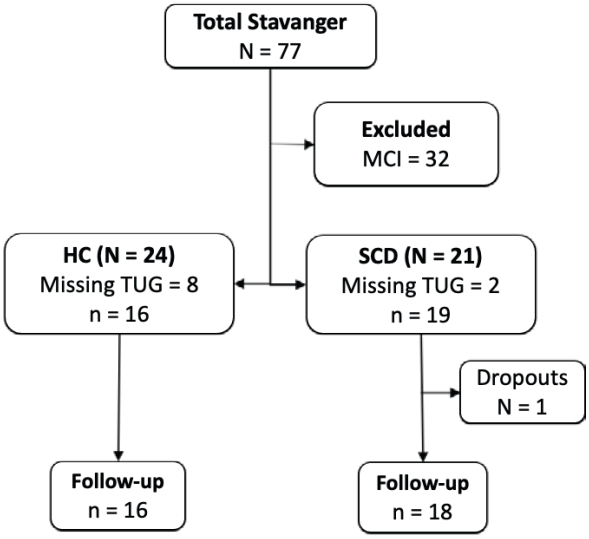
4.2.2 Diagnostic procedures

DDI uses a standardized protocol for participant selection, assessment, and disease-stage classification (SCD, mild cognitive impairment, and dementia) according to published and validated criteria. [200-202]. Participants were classified as SCD according to the SCD-I framework, which requires normal objective cognitive performance on formal neuropsychological testing, in combination with a subjectively experienced decline in any cognitive domain. [202]. MCI was classified as having subjective complaints and scoring below a threshold on at least one neuropsychological test. [16] In addition to a standardized clinical assessment, the diagnostic procedures also included structural and functional imaging and blood and CSF analysis. In this paper, only subjects with SCD from one of the centers were included.

4.2.3 Sample and follow-up

Participants were assessed at baseline and evaluated at follow-up (average 1.5, min 1.4 max 2.4 years). Data from 45 participants recruited and studied in one of the centers, Stavanger University Hospital, were analyzed to avoid scanner variability. [203] One participant did not continue in the study and was considered a dropout between baseline and year 2. See the Flowchart of the study sample in Figure 4.5.

Figure 4.5. Flowchart of the study sample (Paper III)



N= number of participants in the study; n= number of participants used for the analysis according to data availability.

MCI: Mild Cognitive Impairment, Others: Individuals with diagnosed dementia and Parkinson´s disease, SCD: Subjective cognitive decline. Missing: Subjects without TUG.

Clinical outcome measurements

Muscular performance: TUG

This test was designed in 1991 to measure basic mobility function. The test is quick, requires no special equipment or training, and is easily included in the routine medical examination. TUG is defined as the time measured in seconds that the participant used for walking 3 meters, turning, walking back to the chair, and sitting down again. [204]

Regarding functional mobility, participants who take less than 20 seconds to complete the test are independently mobile regarding basic transfers—tub or shower transfers, climbing stairs, or going outside alone. In comparison, those who take 30 seconds, or more are dependent

on help for basic transfers. Regarding predicting falls, participants who take longer than 14 seconds to complete the TUG have a high risk for falls. Podsiadlo and Richardson (1991) found that scores greater than 30 seconds were the best predictor of functional dependence in older adults with ranges of neuropathologies. However, in paper III, we use the test as a continuous variable.

TUG has excellent sensitivity (87%) and specificity (87%). It has concurrent and predictive validity in older adults. It correlates well with log-transformed scores on the Berg Balance Scale (r = -0.81), gait speed (r = -0.61) and Barthel Index of ADL (r = -0.78).

TUG has been shown to have good interrater reliability (ICC = 0.87–0.99). Good test-retest reliability- ICC = 0.97–0.99 and Spearman's rho = 0.93) have been demonstrated in many studies.

In paper III, the protocol to measure TUG was the following: The participant wore regular footwear and used customary walking aid (none, cane, or walker). No physical assistance was given. The participant started with their back against the chair, their arms resting on the chair's arms and their walking aid at hand. The participant was instructed that on the word “go," they may get up and walk at a comfortable and safe pace to a line on the floor 3 meters away, turn, return to the chair, and sit down again. The test was performed three times. The first execution makes the participant familiar with the exercise; the average time from the 2nd and 3rd execution is calculated and used for evaluation. The participant was allowed to rest for a few minutes between each trial of the test is performed.

For the cognitive outcome of this study, we used the previously described MMSE in its validated version in Norwegian, [205] and the CERAD memory composite score (CERAD-MC) constructed comprising subtests from The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). The composite included CERAD subtests for total learning, recall, and recognition and was constructed following an

established method for cognitive composites. [206, 207] and have previously been shown to detect prodromal Alzheimer's disease accurately.[208] Raw scores for the CERAD subtest total learning (30 items), recall (10 items), and recognition (20 items) were standardized to a score between 0 – 100. Then, these scores were summed and averaged to compute a 0 – 100 standardized composite score. [209, 210]

CERAD was created in 1986 by the National Institute on Aging for the clinical assessment of cognitive changes in Alzheimer's disease, including diagnosis and longitudinal assessment of cognitive deficits. The CERAD battery has been used to assess cognitive changes in pre-dementia and dementia stages, including AD, PD, frontotemporal dementia, or vascular dementia. The popularity and widespread use of the CERAD are due to its very good inter-rater agreement, its retest reliability, and its reliability when used for longitudinal follow-up assessments. [211]

In this article CERAD was selected due to its capacity to detect earlier changes when compared only with the MMSE and has previously shown to be accurate in detecting prodromal Alzheimer´s disease. [208]

Imaging analysis:

MRI images were collected on a 1.5T Philips Ingenia (Best, the Netherlands) at the Department of Radiology at Stavanger University Hospital with the same ds Head 16-channel coil. Head movement was minimized using foam cushions, and the participants were instructed not to move their heads during the whole session. There were no hardware updates during the study period. For the current data analyses we used a sagittal 3DT1 Turbo field echo (TFE) sequence (repetition time (TR) = 7.6 ms, echo time (TE) = 3.5 ms, flip angle (FA) = 8 degrees, inversion time (TI) = 939.5 ms, turbo factor (TF) = 237, 180 slices, slice thickness = 1 mm, field of view (FOV) = 240 mm, voxel size 1 x 1 x 1 mm 3 , time of acquisition (TA) was 6 min 20 s) and a transversal 3D Fluid attenuated inversion recovery (FLAIR) sequence (TR = 4800 ms, TE = 356 ms, FA

= 90 degrees, TI = 1660 ms, TF = 202, 240 slices, slice thickness = 1.2 mm, voxel size 1.15 x 1.15 x 1.2 mm 3 , TA = 5 min 50 s).

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 6.0 using the aseg atlas (Massachusetts General Hospital, Boston, MA). [212] This includes segmentation of the subcortical white matter, detecting white matter hypointensities and deep gray matter volumetric structures, and parcellation of the cortical surface according to a previously published parcellation scheme. [213, 212] These labels cortical regions and thickness values are calculated in the areas of interest (ROIs) (Subcortical= 3 (Volumes: white matter hypointensities and left and right hippocampus) ROIs Cortical= 30 ROIs (Cortical thickness)). In addition, intracranial volume based on FreeSurfer estimations was calculated.

Other variables considered for the analysis were sociodemographic factors (age, sex, years of schooling, and marital status) and body mass index (BMI). Depressive symptoms were assessed using The Geriatric Depression Scale (GDS) with a cut point of 6 for at least mild depression. The comorbidities (evaluated through a score, summing up hypertension, diabetes, COPD, stroke, myocardial infarction, arthritis, and cancer). [214]

4.3 Statistical methods

Paper 1.

- Objective: Study the frequency of malnutrition and test the hypothesis that malnutrition can predict faster functional deterioration and mortality in people with mild Alzheimer's disease and Lewy body dementia.

A descriptive analysis was performed by estimating percentages for categorical variables and means and standard deviations for quantitative

variables. We also evaluated the differences between the nutritional status groups using Pearson's chi-squared test for categorical variables and the Kruskal-Wallis test for quantitative variables. The baseline variables considered potential confounders were age, sex, the total number of comorbidities, and the NPI total score. The follow-up ADL (based on RDRS-2) and MMSE scores were considered for each nutritional state as the outcome. The normality distribution assumption for continuous variables was analyzed using the Shapiro-Wilk test. To investigate the association between baseline and longitudinal nutritional status and the outcomes (ADL and the MMSE scores), we conducted a linear mixed model adjusted by sex, age, comorbidities, and NPI. We merged the two malnutrition groups into one to provide larger groups and more statistical power.

In addition, we performed another model adjusting additionally by MMSE when using ADL as an outcome and vice versa. In the main analysis, such adjustments were not committed to avoid collinearity in the estimations because we have shown that MMSE and ADL are highly correlated with other variables already included as cofounders, such as the NPI. [20, 215] We also explored the associations in Alzheimer's disease and Lewy body dementia groups separately.

Time was evaluated with a quadratic term due to its relationship with the functional and cognitive scores. The models used random coefficients to control the variability between patients and time trajectories for each patient in the estimation procedures assuming an unstructured covariance matrix. MMSE was treated as a left- and right-censored variable and modeled by a Tobit linear mixed effect model to account for floor effect during follow-up. We carried out a Kaplan-Meier analysis to evaluate the possible impact of malnutrition on mortality status during the follow-up. We used a Fine-Gray Competing Risk Analysis to estimate Sub-Hazard Ratios in the presence of attrition controlled by the previous cofounders at baseline, including the ADL score. We fixed the

significant probability at 0.05 to evaluate the influence of the covariates in the models using STATA 15®.

Paper 2.

- Objective: Test whether the muscular mass of the masseter and the tongue together with their intramuscular fat is associated with malnutrition in people with mild Alzheimer's disease and Lewy body dementia.

A descriptive analysis was performed by estimating percentages for categorical variables and means and standard deviations for quantitative variables. We also evaluated the differences between groups using Pearson's chi-squared test for categorical variables and the Kruskal-Wallis test for quantitative variables. The baseline variables considered potential confounders were age, sex, the MMSE score, and the Charlson Index score for comorbidities. The normality distribution assumption for continuous variables was analyzed using the Shapiro-Wilk test.

To analyze the association between baseline nutritional status as an outcome and tongue, left, and right masseter muscle measures as covariates, we conducted a logistic regression adjusting by the cofounders listed above and the type of dementia (AD/DLB) due to the possibility that any diagnosis, especially dementia with Lewy bodies could have a more significant influence on the outcome, based on its reported poorer prognosis. [66] We performed the same analysis using the longitudinal nutrition status using a mixed logistic model. To determine whether these MRI analyses could predict future malnutrition, we completed the analyses excluding participants without malnutrition at baseline. We fixed the significant probability at 0.05 to evaluate the covariates' influence in the models using R version 3.6.0.

Paper 3.

- Objective: Describe if the muscular function measured by the Timed Up and test predicts cognitive decline in older adults with subjective cognitive decline.

The variables were described using means with standard deviations or frequencies with percentages, as appropriate. Participants were classified into HC and SCD groups, and baseline characteristics were compared using a t-test for means and a chi-squared or Fisher exact test for frequencies. To assess the longitudinal effect of TUG in the progression of MMSE and CERAD, linear mixed-effect models with a random intercept were conducted. For modeling, the squared root of 30 - MMSE was used to obtain a better approximation to the normality assumption, while the CERAD-MC measure was used in its original scale. We performed a stepwise procedure as adjustment variables based on the AIC criteria and the likelihood ratio test, considering initially gender, age, BMI, year of education, marital status, number of comorbidities, and the GDS score for depression, adjusting finally only by years of education. All models considered the variability between subjects as a random intercept. We graphed the results of the adjusted models for HC and SCD using the original scale for the MMSE and the CERAD-MC at 1.5 years average of follow-up.

In addition, linear regression models were performed to explore potential associations between TUG and regional cortical thickness adjusting by age and sex and subcortical brain volumes adjusting by age, sex, and intracranial volume. These models included normalized brain volume as the dependent variable and TUG at baseline as the independent variable. P-values lower than 0.05 were considered statistically significant for this analysis. No corrections of the p-values were carried out since multiple comparisons were not made within the different models. All statistical analysis was performed using R version 4.0.3. [216]

4.4 Ethics and legality

The Regional Committee approved the Demvest REK 2010/633 and DDI study REK 2013/150. The patients provided written informed consent to participate after the study procedures had been explained to the patient and a caregiver, who was usually the spouse or son/daughter.

All data from both studies are kept according to Norwegian requirements on data privacy, and they were anonymized to as high a degree as possible. At specific points, such as obtaining data from the National Death Registry, the data must be re-personalized.

All participants had capacity to consent for research. The DDI participants did not have dementia, and the DemVest cohort had mild dementia at baseline only and thus still capacity. A family member also consented and supported the participants as they progressed to more advanced stages.

Patients received the usual treatment or standard of care. The treatment may have been better than normal because of the annual study assessments compared to off-study patients who would normally be followed by nursing home staff.

5 Results

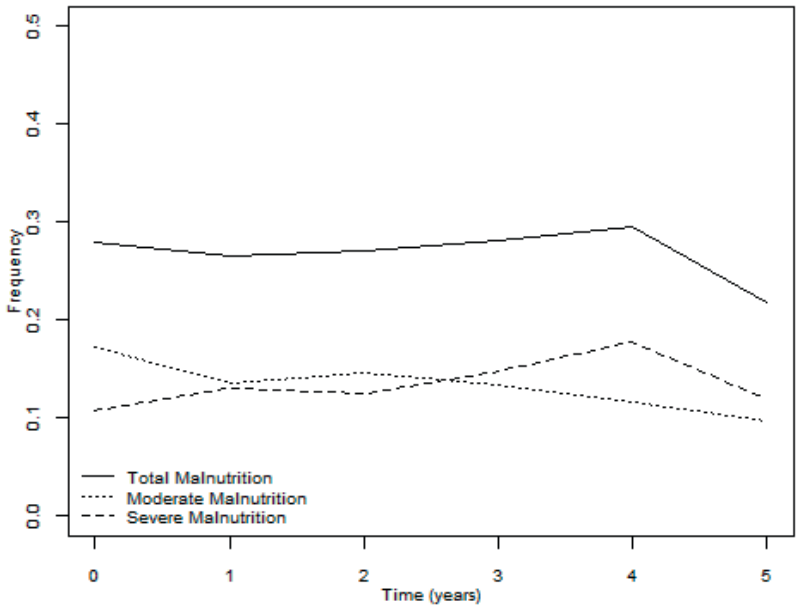
5.1 Paper 1:

Association of Malnutrition with Functional and Cognitive Trajectories in People Living with Dementia: A Five-Year Follow-Up Study.

5.1.1 Nutritional status

At baseline, the frequency of malnutrition was 28.70%, with 17.32% classified as moderate and 11.38% as severe malnutrition. The proportion of malnutrition was similar in Alzheimer's disease (28.16%) and Lewy body dementia (28.38%), but the Alzheimer's disease group had a higher prevalence of severe malnutrition (14.29%) compared to Lewy body dementia (9.72%) (p = 0.1517. Figure 5.1 shows the proportion of malnutrition during the 5-year study period. As can be seen, the proportion of malnutrition was relatively stable.

Figure 5.1. Malnutrition during follow up



5.1.2 Malnutrition during follow up

5.1.2.1 Association with ADL

Malnutrition was significantly associated with functional decline during the follow-up. Having malnutrition during the follow-up was associated with impairment of the RDRS score by 0.159 units (4%), compared to not having malnutrition (Coef. 0.159, SE 0.051, IC 95% 0.058, 0.260, $p = 0.0020$).

5.1.2.2 Association with cognition

There was no statistically significant association between cognitive decline and malnutrition during follow-up (Coef. –0.585, SE 0.365, IC 95% –1.305, 0.135, $p = 0.111$)

5.1.3 Malnutrition at baseline

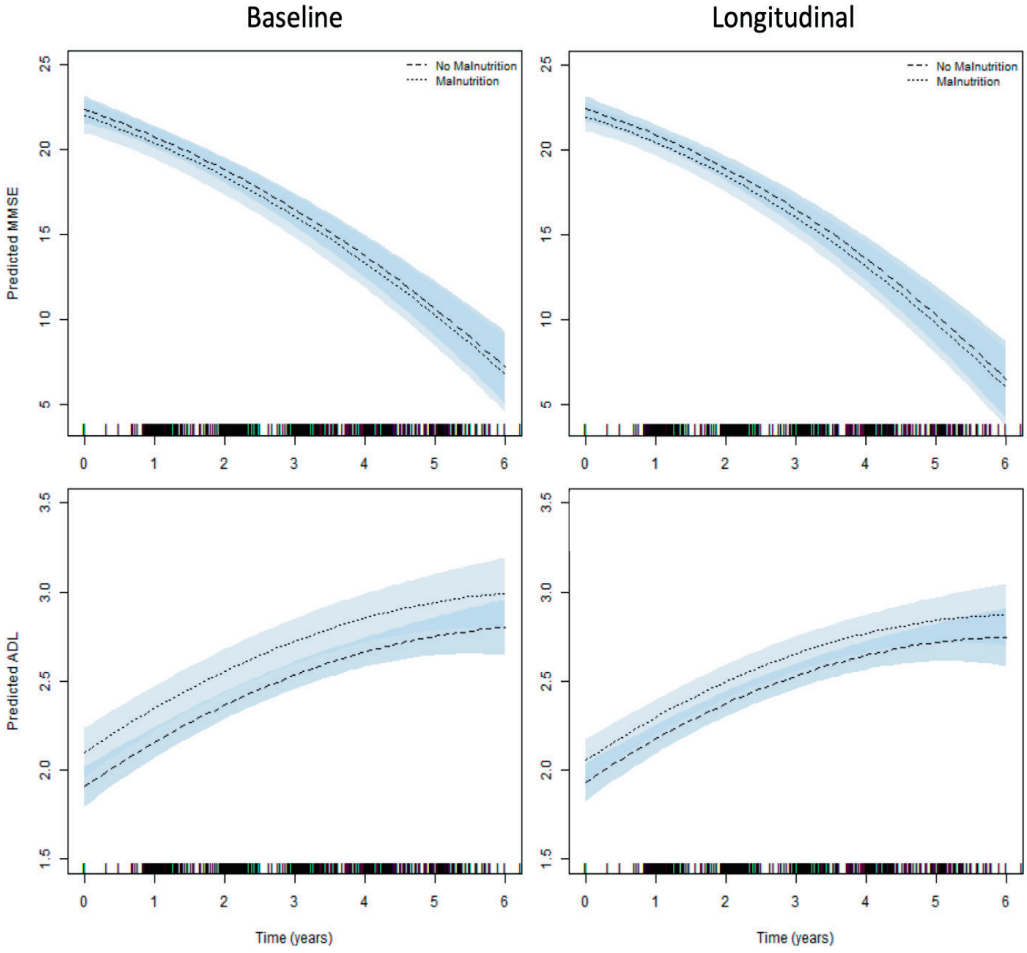
5.1.3.1 Association with ADL

Having malnutrition at baseline was associated with impairment of the RDRS score by 0.309 units (8%), compared to not having malnutrition (Coef. 0.309, SE 0.086, IC 95% 0.139, 0.478, $p \leq 0.0001$) Figure 5.2.

5.1.3.2 Association with cognition

There was no statistically significant association between cognitive decline and baseline malnutrition (Coef. –0.408, SE 0.498, IC 95%– 1.383, 0.568, $p = 0.413$).

Figure 5.2. The figure presents the Cognitive (MMSE) and Functional (ADL) trajectories across time (5y) for individuals with and without malnutrition.



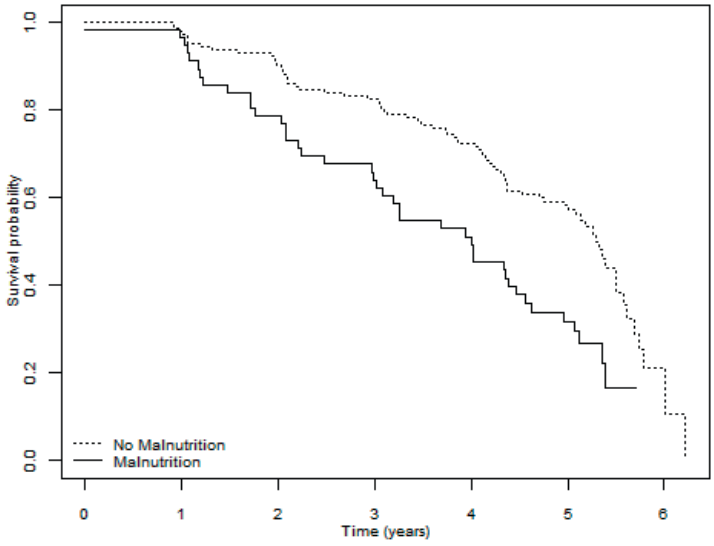
MMSE: Minimental State-examination, ADL: Activities of daily living

MMSE= Mini-mental State Examination (low scores indicate worst performance). ADL= Activities of daily living (High scores indicate worse performance.)

5.1.4 Mortality

Subjects with malnutrition had an increased mortality compared with those without malnutrition. SHR = 1.73 (CI 95% = 1.04 – 2.87; p = 0.033) Figure 5.3.

Figure 5.3. Mortality related with malnutrition

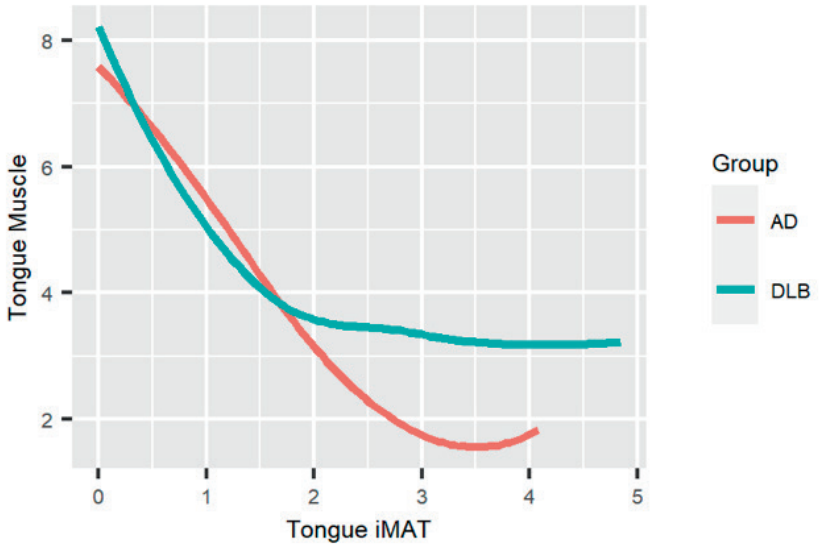


5.2 Paper 2

Muscle volume and intramuscular fat of the tongue evaluated with MRI predict malnutrition in people living with dementia: a five-year follow-up study.

Twenty-seven participants (41.54%) were men, 38 (58.46%) were women, and the mean age was 76.27 ± 6.70. There was an inverse relationship between muscle volume and iMAT; when muscle volume decreases, iMAT increases. Figure 5.4.

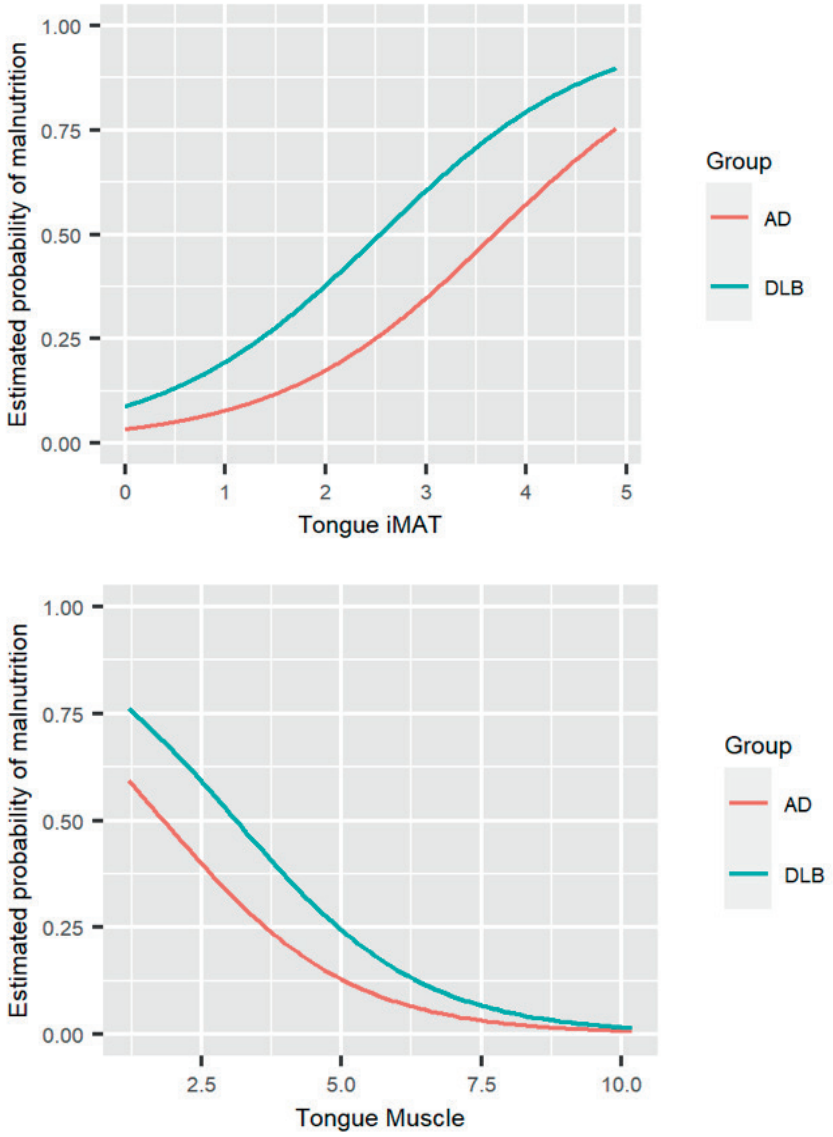
Figure 5.4. Relationship between muscle volume and iMAT



AD: Alzheimer´s Disease, DLB: Dementia with lewy bodies, iMAT: Intramuscular fat

At baseline, people with malnutrition had lower muscle volume (odds ratio [OR] 0.60, standard error [SE] 0.20; p = .010) and higher iMAT (OR 3.31, SE 0.46; p = .010) in the tongue. During the 5-year follow-up, those with lower muscle volume (OR 0.55, SE 0.20; p = .002) and higher iMAT (OR 2.52, SE 0.40, p = .022) in the tongue had a higher probability of malnutrition Figure 5.5.

Figure 5.5. Relationship between tongue muscle and iMAT with malnutrition



AD: Alzheimer´s Disease, DLB: Dementia with lewy bodies, iMAT: Intramuscular fat

Subsequently, we performed an analysis excluding those with malnutrition at baseline. We found that the tongue muscle volume was significant as a predictor of malnutrition development during the follow-up (OR 0.63, SE 0.21; p = .027).

The masseter iMAT and muscle volume were not associated with malnutrition in any adjusted models.

5.3 Paper 3:

Timed Up and Go predicts cognitive decline in Subjective cognitive decline and is associated with cortical thickness.

5.3.1 Baseline characteristics of the sample

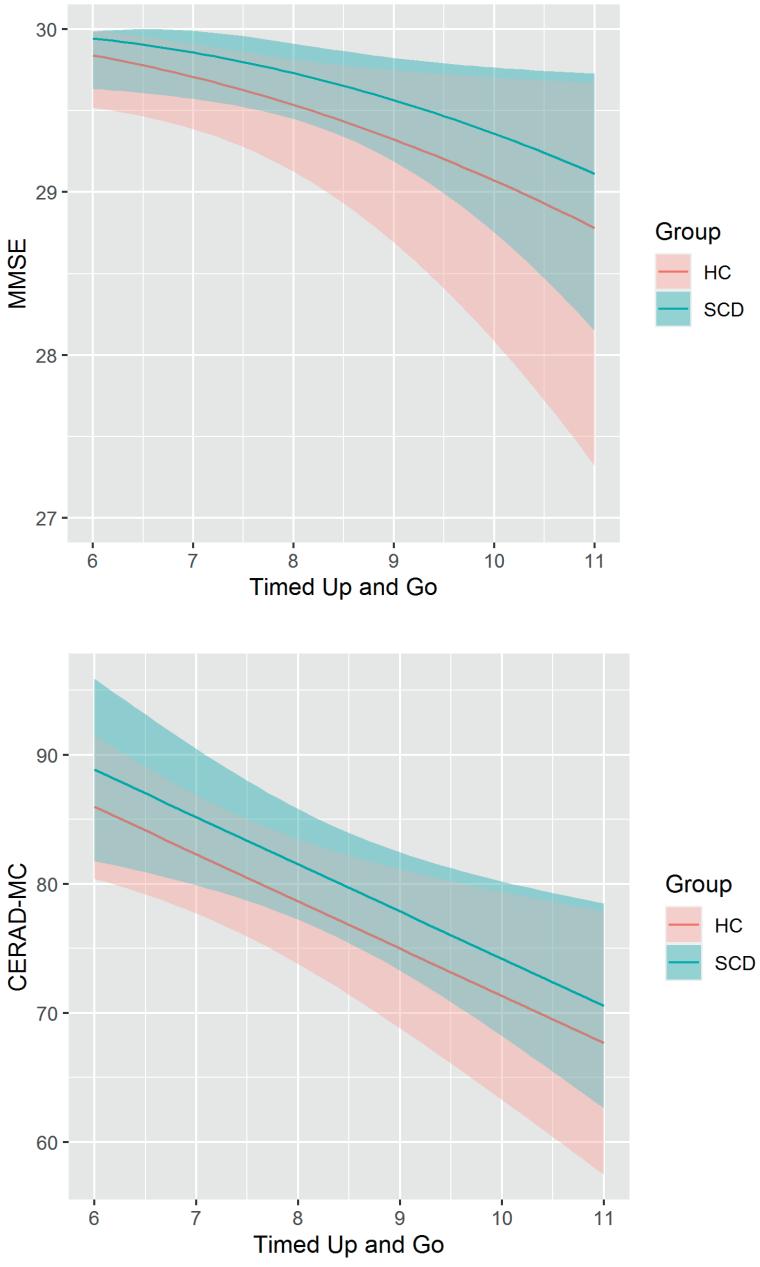
The final sample consisted of 19 SCD and 16 healthy control (HC) participants. The mean follow-up period was 1.50 ± 0.70 years (HC 1.59 ± 0.64 and SCD 1.39 ± 0.78 p-value 0.4562).

The TUG time at baseline was longer in SCD; 8.35 ± 1.34 vs. HC 7.42 ± 1.05 (p-value 0.028).

5.3.2 Cognitive performance associations with TUG

After adjustments, the TUG was associated with faster cognitive decline in subjects with SCD and HC. For the MMSE (Est. 0.14 Std. Err. 0.06 p-value 0.039), there was an average decrease in the score of 0.21 for SCD and 0.17 for HC by each second that the TUG increased. For the CERAD-MC (Est.-3.66, Std. Err. 1.24, p-value 0.006), there was an average decrease in the score of 3.66 for each second increase of the TUG for SCD and HC. The higher TUG at baseline, the lower the MMSE and CERAD-MC performance in the follow-up. Figure 5.6.

Figure 5.6. Association of TUG at baseline MMSE and CERAD-MC performance in the follow-up.

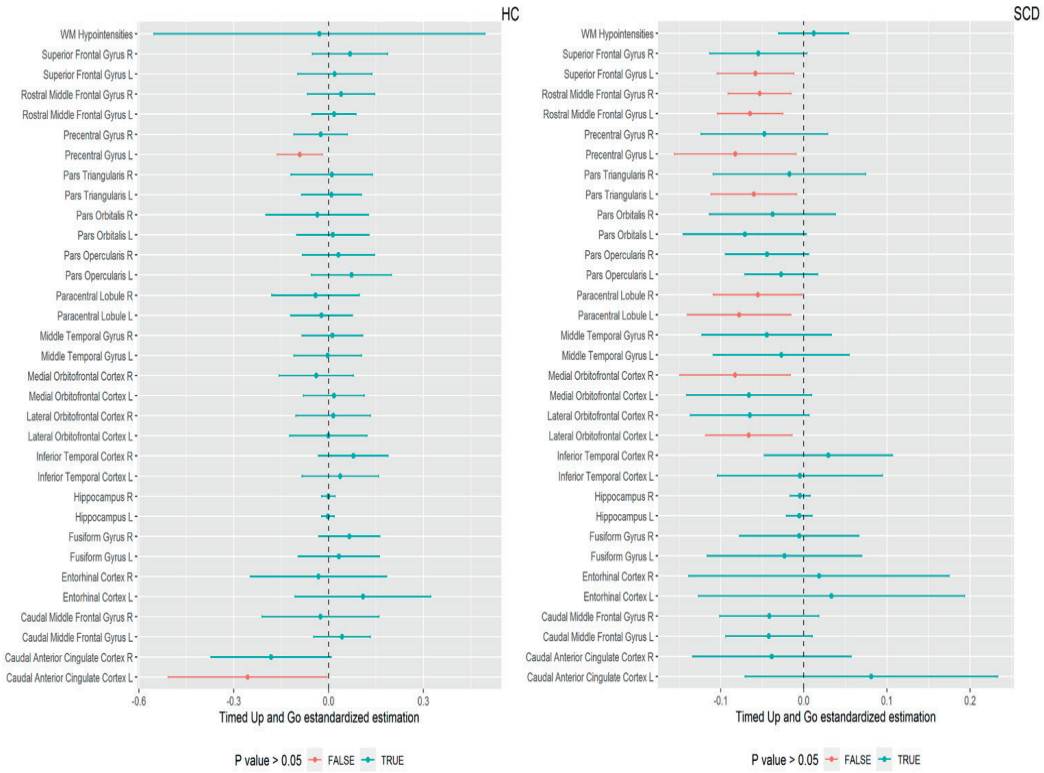


HC: Healthy Controls, SCD: Subjective cognitive decline, CERAD-MC: Consortium to Establish a Registry for Alzheimer's Disease memory composite score, MMSE: Minimental State-Examination

5.3.3 Cortical thickness associations with TUG

After adjustments, in HC, we found a negative association between TUG and cortical thickness in the left precentral gyrus and the left caudal anterior cingulate cortex. In SCD, the TUG test was negatively associated with cortical thickness in the left superior frontal gyrus, left lateral orbitofrontal cortex, left precentral gyrus, left pars triangularis, right and left paracentral lobule, right and left Rostral Middle Frontal Gyrus, and right medial orbitofrontal cortex. See Figure 5.7.

Figure 5.7. TUG and Brain Imaging measures



Adjusted models * SCD: Subjective cognitive decline, HC: healthy controls.

6 Discussion

Under the general hypothesis that dementia is more than a disease limited to the brain, I provide some evidence showing that dementia is indeed a systemic condition. Manifestations in other parts or systems of the body have relevant implications for dementia onset and prognosis. The thesis aims to show the important role of nutritional and muscle status in dementia. In the following I will outline the results of each paper and then show how that come logically together in my thesis and its implications. Following on this, I will discuss the limitations and strengths of the thesis and evaluate the existing evidence and how my results fill existing knowledge gaps, but also open opportunities for new research.

6.1. Nutrition as a dementia prognostic marker

As previously explained, nutrition is essential for adequate body functioning and specialty for normal muscle condition. In paper I, I report that malnutrition is a frequent problem. In people with mild Alzheimer's disease and Lewy body dementia, we found a prevalence of malnutrition of 28.7% at baseline using the GLIM Index. Other studies in Norway report malnutrition prevalence 22% in home-dwelling older adults and 13% in older adults diagnosed with dementia. [217, 218]. Thus, the prevalence of this problem in our findings was relatively high. However, the studies have wide heterogeneity due to the different definitions of malnutrition, the variety of existing scales and instruments, living situation, age, and diverse dementia severity staging at inclusion.

Few studies of malnutrition exist in Lewy body dementia. In older Japanese adults with dementia with Lewy bodies, the reported prevalence of malnutrition was high, ranging from 13% to 57%. [219, 220] Identifying malnutrition in people with Lewy body dementia is important, as compared with AD, this group has a worse prognosis, higher comorbidity, frailty, and mortality. [55, 56, 221]

In the main analysis of paper 1, we show how malnourished people with mild dementia had a more rapid functional decline over five years, even after adjustment for potential confounders. Presenting malnutrition at baseline was associated with a decrease in the ability to perform ADL of 8%, and having malnutrition during the follow-up with a 4% decrease. These effects on ADL of having malnutrition, especially at diagnosis, call attention to detecting malnutrition and acting from early stages. [222]

Adequate nutrition is crucial to maintaining good health and quality of life, and this is particularly true in older adults since nutritional status has been related to important outcomes. [223] Malnutrition is common in older adults and even more in those with dementia for various reasons, including forgetfulness, lack of appetite, apathy, depression, changes in taste and smell, tooth loss, poor oral hygiene, and swallowing disorders disorders. [224] Many of these symptoms are particularly common in Lewy body dementia. [225]

In dementia, the decline in the capacity to perform daily life activities is a key diagnostic and prognostic parameter. [226] Per definition, the principal cause of functional deterioration in dementia is cognitive impairment; however, other factors besides cognition may contribute to a faster functional loss. Our results show that, in people living with dementia, malnutrition plays an independent role in the functional prognosis. Some reports show similar results: Sanders et al. (2016) found that worse nutritional status was associated with greater impairment on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-sb) throughout dementia. [227].

On the other hand, the relationship with cognitive decline was not statistically significant.

There are several possible explanations for our results. At baseline, the prevalence of malnutrition was already high. At the same time, the compromise of functional activities was low, and we believe that, at least

initially, the directionality is that malnutrition worsens function. This might happen via various mechanisms, e.g., muscle wasting, decreased immune system, fatigue, low mood and energy, confusion, and reduced mobility. [228, 229] However, functional impairment can also potentiate malnutrition. [230] For example, functional loss generates food access, purchase, and cooking barriers.

Additionally, people with swallowing disorders may need to change to food with different consistency, leading to a poorly balanced diet. Thus, a bidirectional relationship across the follow-up is likely to explain the association between malnutrition and functional decline in people with dementia. In addition, with dementia progression, the interaction between these variables can contribute to other conditions such as frailty, which is frequent in dementia, and its prevalence increases together with the severity of the disease disease. [221]

6.2. When nutrition and muscle come together

Good nutrition with enough protein and calory supplementation must be ensured to maintain a good and healthy muscle. [124, 119, 125] Sarcopenia is one of the main consequences of malnutrition, and this condition is characterized by the loss of muscle volume and muscle function. Therefore, in paper II, I aimed to show if in older adults living with dementia the muscular volume, using the maseter or the tongue, (two very easily visible muscles in the brain MRI) could predict the onset of malnutrition. Here tongue muscle volume and iMAT were independently associated with a higher probability of developing malnutrition in people with mild dementia. This finding was especially relevant when evaluating people without malnutrition at baseline, where the muscle volume of the tongue significantly predicted malnutrition. Following our results, iMAT and particularly muscle volume of the tongue offers a unique opportunity for early prediction of malnutrition in dementia, thus providing the possibility of new highly needed biomarkers that help predict prognosis (e.g., higher risk of malnutrition)

and promote early actions in older persons with dementia. However, this study just opens a door to further investigation of this causal relationship with methods specifically adapted and controlling for important cofounding factors.

To our knowledge, this is the first study analyzing the association between muscle mass measured with head muscles and malnutrition in people living with dementia. However, previous studies have reported similar results in older adults, focusing on muscle but not fat volumes.

Norwegian research detected lingual atrophy in more than 1/3 of the hospitalized older adults using morphological measures. Here tongue atrophy was associated with anthropometric variables related to nutrition, serum concentrations of ascorbic acid, cholesterol, calcidiol, and general malnutrition. [231] In addition, using ultrasonography, Tamura et al. reported an association between tongue thickness and nutritional status. [232]

By contrast, we did not find associations between malnutrition and iMAT or muscle volume in the masseter muscle. Hwang et al. showed a significant correlation between the masseter muscle area analyzed via computed tomography anthropometry and the abdominal muscle area, weight, and age. This study differs from our study in many aspects, such as the imaging technique, segmentation, and assessment of the study variables. [233] Hashida et al. recently showed that geniohyoid muscle, but not masseter muscle, was associated with swallowing function after salvage surgery and radiotherapy in head and neck cancer, indicating that the tongue muscle is more critical than masseter muscle for swallowing. [234] It is then worth considering that masseter muscle volume can be altered by conditions not evaluated in the current study, such as bruxism, dental prosthesis, defective or missing teeth, the habit of chewing gum, temporomandibular joint disorder, or congenital and functional hypertrophies; common conditions in people living with dementia. [235-237]

6.3 Muscle function related with neurodegeneration

Muscular status is evaluated assessing muscle volume and muscle function. We have already shown how muscle volume seems to have a relevant role in the prognosis of people with dementia. Therefore, in paper 3 we explored the relevance of muscle function in pre dementia stages, and we assessed the association of muscle function with further cognitive impartment in people with SCD. In this study, we found that motor slowing, measured by longer time to perform the TUG test was associated with faster cognitive decline in both groups of participants; SCD and HC during a mean follow-up of 1.5 years. In addition, we report that longer time performing the TUG especially in SCD was negatively associated with cortical thickness in several brain regions.

This research provides evidence suggesting that gait speed and mobility using the TUG can be a useful measure that might predict a subsequent faster decline in cognitive performance in subjects with SCD and HC and identify neurodegenerative process at an early stage.

The performance in TUG has been reported to be also affected in people with MCI. [238] However, the evidence of the TUG is limited concerning the risk of faster cognitive decline in persons living with SCD. People with SCD have no objective cognitive decline in neuropsychological tests and have preserved function in activities of daily living. However, persons with SCD are at an increased risk of cognitive decline and dementia. SCD is considered a pre-Mild Cognitive Impairment or predementia stage. [239] Thus, identifying factors that can help to detect those subjects with SCD with a greater risk of dementia is clinically relevant. Recent studies have reported relevant associations between TUG and cognitive decline, including associations with dementia diagnosis; Lee JE et al, found an association of TUG with dementia incidence in a national registry in Korea. Moreover, Katsumata et al. reported that TUG was associated with global cognitive function in Japanese community-dwelling older adults. [240] Also, slower TUG

performance has been associated with poor performance in domains such as memory and executive function. [31, 241, 242]

Research is growing regarding physical measures and the prediction of risk of cognitive impairment. [32] There is evidence that slowing of gait speed (GS) occurs early in the disease course and may precede declines on cognitive tests. [243]

In addition, we found associations in special brain areas that seem to support this phenomenon. For example, the left precentral gyrus is the part of the brain's neocortex responsible for executing voluntary movements. In this study, low left precentral gyrus was associated with slower TUG in both groups, HC and SCD. Previous studies have shown relevant atrophy of this area in people diagnosed with Parkinson's disease with freezing of gait. [244] In addition, we found a negative association between cortical thickness and time to complete TUG. Thinner cortex in some ROIs was associated with a longer time to complete TUG, these areas are related with working memory, motor, somatosensorial, executive, and integration tasks. [245] A previous publication in persons with documented cognitive decline and gait impairment have reported volume loss in the superior frontal gyrus, superior parietal gyrus, precuneus, thalamus, and cerebellum. [246] The evidence regarding changes in people with SCD in gait or motor tasks is scarce.

Some cross-sectional studies investigating Motor Cognitive Risk Syndrom (MCR), (which by definition includes SCD), have shown that MCR is associated with lower gray matter primarily in the prefrontal cortex, and supplementary motor area. [247-249, 246] results that also support our current findings. Like some of the other studies, we did not find associations between TUG and hippocampal volume. [247] However, hippocampal degeneration may occur later in the degeneration process, reported mainly when cognitive symptoms are more pronounced. [250]

Some possible mechanisms behind the associations described in paper 3 include the following: First, high-level cognitive abilities are associated with specific brain regions with the capacity to regulate motor activities such as those involved in the TUG. [251]. We found associations in specific areas that seem to support this mechanism. Second, there are factors other than cortical integrity such as sarcopenia, hearing disorders, peripheric nerve alterations, skeletal and joint disorders that are involved in motor performance, these factors change with aging, interfering with normal motor performance, and therefore with mobility and also balance. [252] Muscle function (gait) is a proxy measure of good muscular status. Muscle per se, has endocrine functions that reduce inflammation and thus have the potential to reduce damage caused by inflammation in the brain. [100] Thus, for example, physical inactivity can potentiate muscle loss and increase inflammation by interfering with the anti-inflammatory properties of the muscle leading to neurodegeneration. [72] In fact, interventions such as physical activity and nutritional supplementation targeting muscle, mobility, and sarcopenia have shown positive effects on cognition and brain structure. [85, 253]

6.4 Special considerations in Lewy Body dementia

Within this thesis (Paper I and II), there is special focus to people with Lewy body dementia. Lewy body dementia is a frequent dementia, and it is frequently under-diagnosed and therefore undertreated. There is a lack of information regarding this disease and its systemic and functional consequences. Lewy body dementia is under and mainly misdiagnosed, therefore patients with this disease are more prone to polypharmacy and secondary adverse events, also to not receiving enough education about the disease and therefore this leads in a worst prognosis. People living with this disease are of special interest, because form early stages they have already a higher burden of conditions due to the presence of parkinsonism, neuropsychiatric symptoms and functional impairment.

[47, 66] In my papers, we show that people with Lewy body dementia have more comorbidity, more muscle atrophy, and tend to have the worst prognosis. Therefore, action is needed to provide better care to this population.

6.5 Limitations

In papers I and II, our results may have potential recruitment bias because of referrals of primary care patients, which may have led to an increased number of patients with complicated dementia or poorer health status. However, GPs were invited to refer any patients with suspected dementia. Furthermore, we used MMSE, which is less sensitive to the earliest changes. However, the sensitivity to change of MMSE is comparable to other screening instruments in Lewy body dementia. [254] Patients were treated according to recommendations for pharmacological and non-pharmacological treatment, which may influence the course of functional impairment and cognition. Also, the concomitant treatment and diet of the participants were not included in the analysis. Medications such as acetylcholinesterase inhibitors are associated with gastrointestinal complaints and anorexia. [255-257].

GLIM Index was used to identify malnutrition in this study. It is a global initiative that targets the priority of adopting international consensus criteria so that malnutrition prevalence, interventions, and outcomes can be compared throughout the world. [116] It takes into consideration the BMI differences when the body ages and the importance of active inflammatory processes in the body. Furthermore, the GLIM Index has been shown to be a prognostic factor in several settings. [117, 194] Nevertheless, it does not allow for identifying patients with risk of malnutrition, excludes the possibility that people with obesity can also have malnutrition, and does not assess actual nutrient intake. [116] Besides, the DemVest study did not include anthropometric objective beyond weight and height. Aa more detailed nutritional evaluation would have provided a more accurate measurement.

We used the first 13 items of the RDRS-2 questionnaire to assess ADL, due to those questions are the items that better describe daily functioning. This abbreviated form of the scale may not elucidate the full spectrum of capacity to perform daily life activities. The number of people with available anthropometric information varies between the different years of measurement. Despite deaths and dropouts in years 2 and 3, the number of Alzheimer's subjects increased during this period because more anthropometric data were available. We adjusted the analysis by neuropsychiatric symptoms for both primary outcomes; neuropsychiatric symptoms and especially depression, apathy, and appetite disturbance are highly related to nutrition. [258] Nutrition may be associated with the living situation. They were all living at home at baseline, and 57% had a partner living with them. During the study period, many moved to a nursing home. The exact number who lived with a partner or alone during the study period was not available, which might have influenced the findings.

When analyzing the muscles, it is important to know that muscle volumes can be altered by conditions that were not evaluated, such as missing teeth, bruxism, or dental prosthesis. The automatic segmentation method had limitations, such as determining thresholds and the operator’s experience. However, Slice-O-Matic measurements have been previously validated against gold standards, demonstrating a high inter-and intra-rater reliability and reliability and validity. [259] The concomitant treatment of the participants was not accounted for in the analysis. Persons under optimal treatment could have better condition. In addition, there are certain medications that can alter appetite and nutritional status.

Variables selected for the models´ adjustments, such as cognition or comorbidities, were chosen given their influence on nutritional status. [258] Model adjustments by BMI were not directly performed because the outcome (malnutrition) contains this variable. [116] An important issue is that the final sample from the DemVest included in the analysis

was relatively small, decreasing the power of this study. The sample was significantly reduced at the 5-year of follow-up because of mortality rates. Particularly in dementia with Lewy bodies, a high mortality rate was observed after year 3, which could have biased the estimates in the longitudinal mixed-effects models on malnutrition. [260]

Although the analyses were adjusted for critical factors that predict attrition, such as sex, age, comorbidities, and Neuropsychiatric symptoms, in line with the missing at random assumption, [260] the possibility that other factors related to mortality might have influenced the findings cannot be excluded.

In paper III, the main limitations were the small sample size and short follow-up duration, and thus the statistical power was relatively low. This was since we included only data from one centre to avoid scanner variability.

We could not establish the risk of progression to MCI or Dementia. Due to the study still counts with few MCI and dementia incident cases. Also, the number of variables to include in the models was limited. [261]. Therefore, we did not adjust for multiple comparisons. Thus, we consider the MRI finding as exploratory.

6.6 Strengths

The strengths of this thesis include the longitudinal datasets with long follow-up time and annual assessments with structured validated instruments. In the case of the Demvest from the time of dementia diagnosis until death. The latter allowed assessment and analysis of cognitive and ADL trajectories, from mild to severe dementia. Also, diagnostic procedures were rigorous and highly accurate; In Demvest the neuropathological diagnosis was available in a subgroup demonstrating that the clinical diagnosis was accurate. [192]

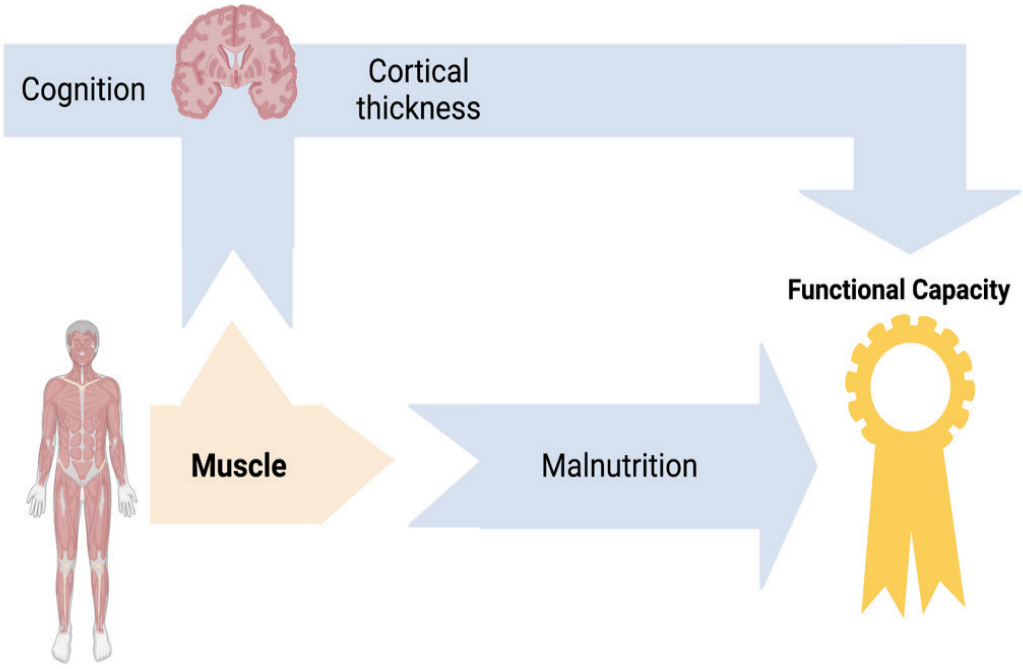
Further strengths are in addition that this thesis elucidates the importance of nutrition and muscle for the prognosis of patients with dementia and cognitive decline. Which is very relevant right now because there are available therapies that can have a positive effect in these areas. Paper II is one of the first studies to investigate the association of the iMAT and muscle volume of tongue and masseter in dementia. This study also provides the possibility to further study a potential new tool to determine muscle volume in a more practical way within the dementia diagnosis process. Also, this study give insight in new relevant prognostic biomarkers. Likewise, paper III this study shows the utility of cheap and accessible method, the TUG, to predict cognitive deterioration in people at pre dementia stages.

7 Conclusions

Muscle volume and function measured in practical and cost-effective ways show significant associations with the prognosis of people at risk or with stablished dementia and thus represent promising prognostic markers.

In paper one malnutrition showed a direct relationship with the functional prognosis. In paper II muscle volume was related with malnutrition and in paper III Muscle function was found to be related with cognition and brain cortical thickness, which are known to be hallmarks related with dementia and neurodegeneration prosses leading to functional capacity loss. With these findings it can be concluded that muscle has a central role for functional capacity in people with dementia. These results identify the muscle as a potential intervention target for future studies. Figure 7.1.

Figure 7.1. Relationship of this thesis findings with the ultimate goal in geriatrics.



7.1. Future Perspective

To provide evidence of the importance of a good nutrition and muscle can help health providers to improve awareness for prevention, detection and treatment of malnutrition and sarcopenia. Likewise, open a door for future diagnostic and interventional studies that will improve treatment opportunities, prognosis, and quality of life.

Allowing to detect muscle loss using an already existing brain MRI save time and resources to the patient. And allows the health provider to start early actions against sarcopenia.

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Appendices

Appendix 1 – First entry

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Association of Malnutrition with Functional and Cognitive Trajectories in People Living with Dementia: A Five-Year Follow-Up Study

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Original Article

Muscle Volume and Intramuscular Fat of the Tongue Evaluated With MRI Predict Malnutrition in People Living With Dementia: A 5-Year Follow-up Study

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Research Article

Timed Up and Go in people with subjective cognitive decline is associated with faster cognitive deterioration and cortical thickness

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Abstract:

Introduction:

Early markers of neurodegeneration provide an opportunity to detect, monitor, and initiate interventions in individuals who have an increased risk of developing dementia. Here, we investigated whether the 'Timed Up and Go test (TUG) is associated with early brain neurodegeneration and whether the TUG test could be a marker of cognitive decline, in people with Subjective Cognitive Decline (SCD).

Methods:

This is a longitudinal analysis of the Dementia disease initiation (DDI) study, a prospective, community-based, cohort study from Norway, designed to investigate early markers of cognitive impairment and dementia. Participants were classified as SCD and healthy controls (HC). The main studied variables were the TUG test and cognition as measured with the Mini-mental state examination and CERAD memory composite score (CERAD-MC). Additionally, we investigated the crossectional association of brain morphology with the TUG using 1.5T-MRI.

Results:

The sample included 45 participants (SCD=21, HC=24) followed during a mean time of 1.50±0.70 years. At baseline, the cognitive performance did not differ between the groups, but TUG was longer in SCD. Slower baseline TUG was associated with a faster cognitive decline in both groups and it was also associated with reduced cortical thickness especially in motor, executive, associative, and somatosensory cortical regions in people with SCD.

Discussion/Conclusion:

TUG predicted cognitive change in individuals with SCD, and there was a negative association between TUG and cortical thickness. TUG is a promising cheap and non-invasive marker of early cognitive decline and may help initiate interventions in individuals who have an increased risk of dementia.

Introduction

Dementia and cognitive impairment are growing issues in public health causing a high rate of disability and social costs.[1] With increasing life expectancy, the challenge will grow in the future.[2] The slow early development of neurodegenerative diseases provides a unique opportunity to detect, monitor, and intervene in individuals at predementia stages. Subjective cognitive decline (SCD) is a frequent condition occurring in 10-15% of people aged 65 or older. SCD is defined as a self-experienced persistent decline in cognitive capacity, compared with a previously normal cognitive status, which is unrelated to an acute event, and represents one of the earliest symptoms of dementia [3, 4]

The assessment of physical mobility is an essential component of the geriatric assessment of older adults.[5] Muscle mass, strength, performance, and balance in older adults have been associated with the development of unfavorable outcomes, including falls, future disability, and mortality.[6-8] Some indicators of reduced muscular function, such as gait speed and the Timed Up and Go (TUG) have also been shown to be associated with faster cognitive decline and progression to dementia in people with mild cognitive impairment[9-13]. Indeed, alterations in gait speed have been shown to precede cognitive decline by several years before the clinical onset of dementia [14, 15]. TUG involves tasks that require central nervous system coordination[16, 17] and involves physical measures that indicate muscle wellbeing, sarcopenia, and frailty.[18] To perform the TUG, the person in evaluation is asked to rise from a standard armchair, walk to a line on the floor 3 meters away, turn, return, and sit down again. Therefore, this test is quick, requires no special equipment or training, and can be easily included as part of a routine medical examination.[19]

However, longitudinal research regarding the role of the TUG in individuals with SCD is limited, and early markers indicating risk factors of cognitive decline progression in people with SCD are needed. In this study, firstly, we studied whether the TUG test could be a marker of cognitive decline in people with SCD. Secondly, we investigated whether TUG is associated with early brain changes.

Materials and Methods:

Design, participants, and setting

This is a longitudinal analysis of the Dementia disease initiation (DDI) study, a prospective, population-based, longitudinal multicenter cohort study from Norway. The DDI was designed to investigate early cognitive and biological markers to detect and track cognitive deterioration.

DDI uses a standardized protocol for participant selection, assessment, and disease-stage classification (SCD, mild cognitive impairment (MCI), and dementia) according to published and validated criteria.[20-22]. Data collected include the nature of cognitive decline (cognitive domain, onset), concerns and worries, including feeling worse compared to age-matched peers, and informant confirmation of decline (when available). Participants were classified as SCD according to the SCD-I framework, which requires normal objective cognitive performance on formal neuropsychological testing, in combination with a subjectively experienced decline in any cognitive domain.[22]

Participants were recruited from referrals to local memory clinics or self-referrals responding to advertisements in media, newspapers, or news bulletins. Healthy controls (HC) without subjective cognitive complaints were recruited from spouses of participants with either MCI or SCD and volunteers responding to media advertisements or news bulletins. Criteria for inclusion were age between 40 and 80 years and a native language of Norwegian, Swedish, or Danish. Exclusion criteria were dementia, brain trauma, stroke, severe psychiatric disorder, or any severe somatic disease that might influence cognitive functions, intellectual disability, or other developmental disorders. The cohort described here was recruited from 2013 to 2021. For further description of the DDI cohort and methods, refer to the study by Fladby et al. (2017).[23] Participants were assessed at baseline and again evaluated at follow-up (average 1.5, min 1.4 max 2.4 years). Data from 45 participants recruited and studied in one of the centers, Stavanger University Hospital, were analyzed to avoid scanner variability.[24] One participant did not continue in the

study and was considered as a dropout during baseline and year 2. See the Flowchart of the study sample in Supplemental Material.

Measurements

TUG was defined as the time measured in seconds that the participant used for walking a distance of 3 meters, turn, walk back to the chair, and sit down again. The protocol to measure TUG was the following: The participant wore regular footwear and used customary walking aid (none, cane, or walker). No physical assistance was given. The participant started with the back against the chair, the arms resting on the chair's arms, and his/her walking aid at hand. The participant was instructed that on the word “go", he/she may get up and walk at a comfortable and safe pace to a line on the floor 3 meters away, turn, return to the chair, and sit down again. The test was performed 3 times, the first execution is to make the participant familiar with the exercise. The average time from the 2nd and 3rd execution is calculated and used for evaluation. The participant was allowed to rest for a few minutes between each trial of the test.

For the cognitive outcome of this study, we used the Mini-Mental State Examination in its validated version in Norwegian (MMSE)[25], and the CERAD memory composite score (CERAD-MC) constructed comprising subtests from The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). The composite included CERAD subtests total learning, recall, and recognition and was constructed following an established method for cognitive composites. [26, 27] and have previously been shown to be accurate in detecting prodromal AD.[28] Raw scores for the CERAD subtest total learning (30 items), recall (10 items), and recognition (20 items) were standardized to a score between 0 – 100. Then, these scores were summed and averaged to compute a 0 – 100 standardized composite score. [29]

Imaging analysis:

The data were collected on a 1.5T Philips Ingenia (Best, the Netherlands) at the Department of Radiology at Stavanger University Hospital with the same ds Head 16-channel coil. Head movement was minimized using foam cushions and the participants were instructed not to

move the head during the whole session. There were no hardware updates during the study period. For the current data analyses we used a sagittal 3DT1 Turbo field echo (TFE) sequence (repetition time (TR) = 7.6 ms, echo time (TE) = 3.5 ms, flip angle (FA) = 8 degrees, inversion time (TI) = 939.5 ms, turbo factor (TF) = 237, 180 slices, slice thickness = 1 mm, field of view (FOV) = 240 mm, voxel size 1 x 1 x 1 mm 3 , time of acquisition (TA) was 6 min 20 s) and a transversal 3D Fluid attenuated inversion recovery (FLAIR) sequence (TR = 4800 ms, TE = 356 ms, FA = 90 degrees, TI = 1660 ms, TF = 202, 240 slices, slice thickness = 1.2 mm, voxel size 1.15 x 1.15 x 1.2 mm 3 , TA = 5 min 50 s).

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 6.0 using the aseg atlas (Massachusetts General Hospital, Boston, MA). [30] This includes segmentation of the subcortical white matter, detection of white matter hypointensities and deep gray matter volumetric structures, and parcellation of the cortical surface according to a previously published parcellation scheme [31, 30]. The cortical regions and thickness values are calculated in regions of interest (ROIs); 3 subcortical volumes= white matter hypointensities and left and right hippocampus and 30 cortical thickness ROIs. In addition, intracranial volume based on FreeSurfer estimations were calculated.

Other variables considered for the analysis were sociodemographic factors (age, sex, years of schooling, and marital status) and body mass index (BMI). Depressive symptoms were assessed using The Geriatric Depression Scale (GDS) 15 items, with a cut point of 6 for at least mild depression. The number of comorbidities (evaluated employing a summary score, summing up hypertension, diabetes, COPD, stroke, myocardial infarction, arthritis, and cancer) were recorded.[32]

Statistical analysis:

The variables were described using means with standard deviations or frequencies with percentages, as appropriate. Participants were classified into HC and SCD groups, and baseline characteristics were compared using a t-test for means and a chi-squared or Fisher

exact test for frequencies. To assess the longitudinal effect of TUG in the progression of MMSE and CERAD, linear mixed-effect models with a random intercept were conducted. For modelling, the squared root of 30 - MMSE was used to obtain a better approximation to the normality assumption, while the CERAD-MC measure was used in its original scale. As adjustment variables we performed a stepwise procedure based on the AIC criteria and the likelihood ratio test, considering initially gender, age, BMI, year of education, marital status, number of comorbidities, and the GDS score for depression, adjusting finally only by years of education. All models considered the variability between subjects as a random intercept. We graphed results of the adjusted models for HC and SCD using the original scale for the MMSE and the CERAD-MC at 1.5 years average of follow-up.

In addition, linear regression models were performed to explore potential associations between TUG and regional cortical thickness adjusting by age and sex and subcortical brain volumes adjusting by age, sex, and intracranial volume. These models included each normalized brain volume at baseline as the dependent variable and TUG at baseline as the independent variable. P-values lower than 0.05 were considered statistically significant for this analysis. No corrections of the p-values were carried out since multiple comparisons were not made within the different models. All statistical analysis was performed using R version 4.0.3.[33]

Ethics

The regional medical research ethics committee approved the study. Participants gave their written informed consent before taking part in the study. The study was in line with the guidelines provided by the Helsinki declaration of 1964, revised 2013, and the Norwegian Health and Research act.

Results:

Baseline characteristics of the sample

The final sample consisted of 19 SCD and 16 healthy controls (HC). Both groups were comparable and there were no significant differences in the CERAD-MC or MMSE at baseline. Baseline characteristics of the sample are displayed in Table 1. The mean follow-up period was 1.50 ± 0.70 years (HC 1.59 ± 0.64 and SCD 1.39 ± 0.78 p-value 0.4562). The time performing the TUG at baseline was longer in SCD; 8.35 ± 1.34 vs HC 7.42 ± 1.05 (p-value 0.028).

Cognitive performance associations with TUG

After adjustments, higher TUG was associated with faster cognitive decline in subjects with SCD and HC. For the MMSE (Est. 0.14 Std. Err. 0.06 p-value 0.039) there was an average decrease in the score of 0.21 for SCD and 0.17 for HC by each second that the TUG increased. For the CERAD-MC (Est.-3.66, Std. Err. 1.24, p-value 0.006) there was an average decrease in the score of 3.66 for each second that TUG increased for SCD and HC. The higher TUG at baseline the lower the MMSE and CERAD-MC performance in the follow-up. See Table 2 and Figure 1.

Cortical volume associations with TUG

After adjustments, in SCD the TUG test had a negative association with cortical thickness in the left superior frontal gyrus, left lateral orbitofrontal cortex, left precentral gyrus, left pars triangularis, right and left paracentral lobule, right and left Rostral Middle Frontal Gyrus and right medial orbitofrontal cortex. In HC, a longer time to complete the TUG test was negatively associated with cortical thickness in the left precentral gyrus and the left caudal anterior cingulate cortex. See Table 3 and Figure 2.

Discussion:

In this study, we found that motor slowing, measured by longer time to perform the TUG test was associated with faster cognitive decline in both groups of participants; SCD and HC during a mean follow-up of 1.5 years. In addition, we report that longer time performing the TUG especially in SCD was negatively associated with cortical thickness in several brain regions.

This research provides evidence suggesting that measuring gait speed and mobility using the TUG can be a useful measure that might predict a subsequent faster decline in cognitive performance in subjects with SCD and HC.
The performance in TUG has been reported to be also affected in people with MCI [10]. However, the evidence of the TUG is limited concerning the risk of faster cognitive decline in persons living with SCD. People with SCD have no objective cognitive decline in neuropsychological tests and have preserved function in activities of daily living. However, persons with SCD are at an increased risk of cognitive decline and dementia. SCD is considered a pre-Mild Cognitive Impairment or predementia stage [34, 35]. Thus, identifying factors that can help to detect those subjects with SCD with a greater risk of dementia is clinically relevant.

While no baseline difference in cognitive performance was shown between HC and SCD, we found that TUG performance was slower in SCD cases. However, when assessing TUG and cognition during the follow-up, reduced performance on CERAD-MC and MMSE was associated with slower baseline TUG in both groups. CERAD has been related to higher sensitivity for small changes compared to MMSE, [36] although in this study both tests were affected in both groups which strengthen the utility of TUG to predict cognitive decline in early stages

Recent studies have reported relevant associations between TUG and cognitive decline, including associations with dementia diagnosis; Lee JE et al, found an association of TUG with dementia incidence in a national registry in Korea. Moreover, Katsumata et al. reported that TUG was associated with global cognitive function in Japanese community-dwelling older adults.[9] Also, slower TUG performance has been associated with poor performance in domains such as memory and executive function [37-39].

Research is growing regarding physical measures and the prediction of risk of cognitive impairment [15]. There is evidence that slowing of gait speed (GS) occurs early in the disease course and may precede declines on cognitive tests[40]. A previous study by our group found a cross-sectional association of walking speed with cognitive testing using the

Trail Making (TMT) A and B tests and a gradual worsening in the GS starting from the normal controls, SCD, and to MCI[41].
Additionally, the GS and the TUG have been combined with cognitive tasks in the dual-task paradigm. Research in this area has shown that the dual-task can reveal subtle motor impairments that are not detected during single-task test conditions, and that these motor impairments represent a higher risk for cognitive deterioration in healthy older adults[42]. Montero-Odasso reported that in subjects with MCI, the dual-task gait test predicted the risk of dementia incidence [43].

Further, the Motor-cognitive risk syndrome (MCR) is also considered a condition of increased risk for dementia development defined as impaired gait speed in subjects with SCD[44]. There is evidence that this condition is a risk factor not only for cognitive decline but also for falls, disability, frailty, and increased mortality has been found in different populations [44-46]

GDS depression score at baseline was higher in the SCD group (but below the cut-off of mild depression (GDS>6): mean 2.63 ± 2.5). Depression may relate to cognitive and motor deficits, therefore it was considered as a possible confounder.[47, 48]. However, it was discarded in the final model after a stepwise procedure of variable selection.

In addition, we found a negative association between cortical thickness and time to complete TUG. Thinner cortex in some ROIs was associated with a longer time to complete TUG, these areas are associated with working memory, motor, somatosensorial, executive, and integration tasks. [49] A previous publication in persons with documented cognitive decline and gait impairment have reported volume loss in the superior frontal gyrus, superior parietal gyrus, precuneus, thalamus, and cerebellum.[50] The evidence regarding changes in people with SCD in gait or motor tasks is scarce. We here provide new evidence of reduced integrity in brain areas related to very early TUG alterations.
Some cross-sectional studies studying MCR, (which by definition includes SCD), have shown that MCR is associated with lower gray matter primarily in the prefrontal cortex, and supplementary motor area[51-53, 50] results that also support our current findings. Like

some of the other studies, we did not find associations between TUG and hippocampal volume [51]. However, hippocampal degeneration may occur later in the degeneration process, reported mainly when cognitive symptoms are more pronounced.[54]

Some possible mechanisms behind the associations described in our study include the following: First, high-level cognitive abilities are associated with specific brain regions with the capacity to regulate motor activities such as those involved in the TUG[55]. We found associations in specific areas that seem to support this mechanism.
For example, cortical thickness of the left precentral gyrus was related to longer time for TUG completion on both HC and SCD and is central for the execution of voluntary movement. Previous studies have shown thinning of this area in people diagnosed with Parkinson's disease with freezing of gait.[56]
Second, factors like mobility, muscle mass, and strength are also involved in motor performance. These factors change in the course of normal aging and especially in neurodegeneration, having the potential to interfere with normal motor performance.[57] Muscle function (gait) is a proxy measure of good muscular status. Muscle tissue is central e.g. in glucose and insulin metabolism and may reduce inflammation with possible links to metabolic and inflammatory changes associated with brain neurodegeneration.[58] [59, 60]. Thus, for example, physical inactivity can potentiate muscle loss and increase inflammation by interfering with the anti-inflammatory properties of the muscle. In fact, interventions such as physical activity and nutritional supplementation targeting muscle, mobility, and sarcopenia have shown positive effects on cognition and brain structure [61, 62]
This research has some limitations. Due to the small sample size and short follow-up duration, the statistical power is relatively low and we could not establish the risk of progression to MCI and Dementia. Also, the number of variables to include in the models was limited.[63]. Therefore, we did not adjust for multiple comparisons, thus we consider this an exploratory study. Available multicenter data from the DDI study was not used at this stage of analysis, to avoid scanner variability. The Cognitive-TUG was not used in the study. Instead, we assessed cognitive performance using a different validated and

comprehensive neuropsychological protocol. However, it would be relevant to use Cognitive-TUG in future studies in order to have a dual-task dynamic measure.

Conclusion:

Using longer time when performing the TUG test was associated with faster cognitive deterioration in the participants with SCD and HC. In addition, in HC and SCD there was a negative association between TUG and cortical thickness. This research provides evidence that measuring mobility using the TUG could be a marker of risk of progression in subjects with SCD.

Statements

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Statement of Ethics

This study was approved by the regional ethics committee (approval code: REK 2013/150) for the collection of medical data. All data was handled and kept under national health and data privacy protocols. All participants signed an informed consent form before inclusion in the study.

Conflict of Interest Statement:

The authors have no potential conflicts of interest to declare regarding research, authorship, and/or publication of this article.

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Author Contributions

Miguel Germán Borda: Conception of work, Formal analysis, Methodology, Visualization, Writing- Reviewing and Editing.

Daniel Ferreira, Per Selnes: Preparation of the initial draft, manuscript writing, review and approval

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Data Availability Statement

The data that support the findings of this study are not publicly available for containing information that could compromise the privacy of research participants but can be provide upon reasonable request to the PI DA dag.aarsland@kcl.ac.uk.

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Fig. 1. MMSE AND CERAD-MC progression according to TUG

MMSE and Baseline TUG, c. CERAD-MC and Baseline TUG. SCD: Subjective cognitive decline, HC: healthy controls. Marginal estimation at 1.5 years of follow-up.

Fig. 2. TUG and MRI measures

Adjusted models * SCD: Subjective cognitive decline, HC: healthy controls.