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FACING FRAILTY FROM OTHER PERSPECTIVES: NEGLECTED PATIENTS,
FEATURES, AND NEW WAYS TO ADDRESS THEM.

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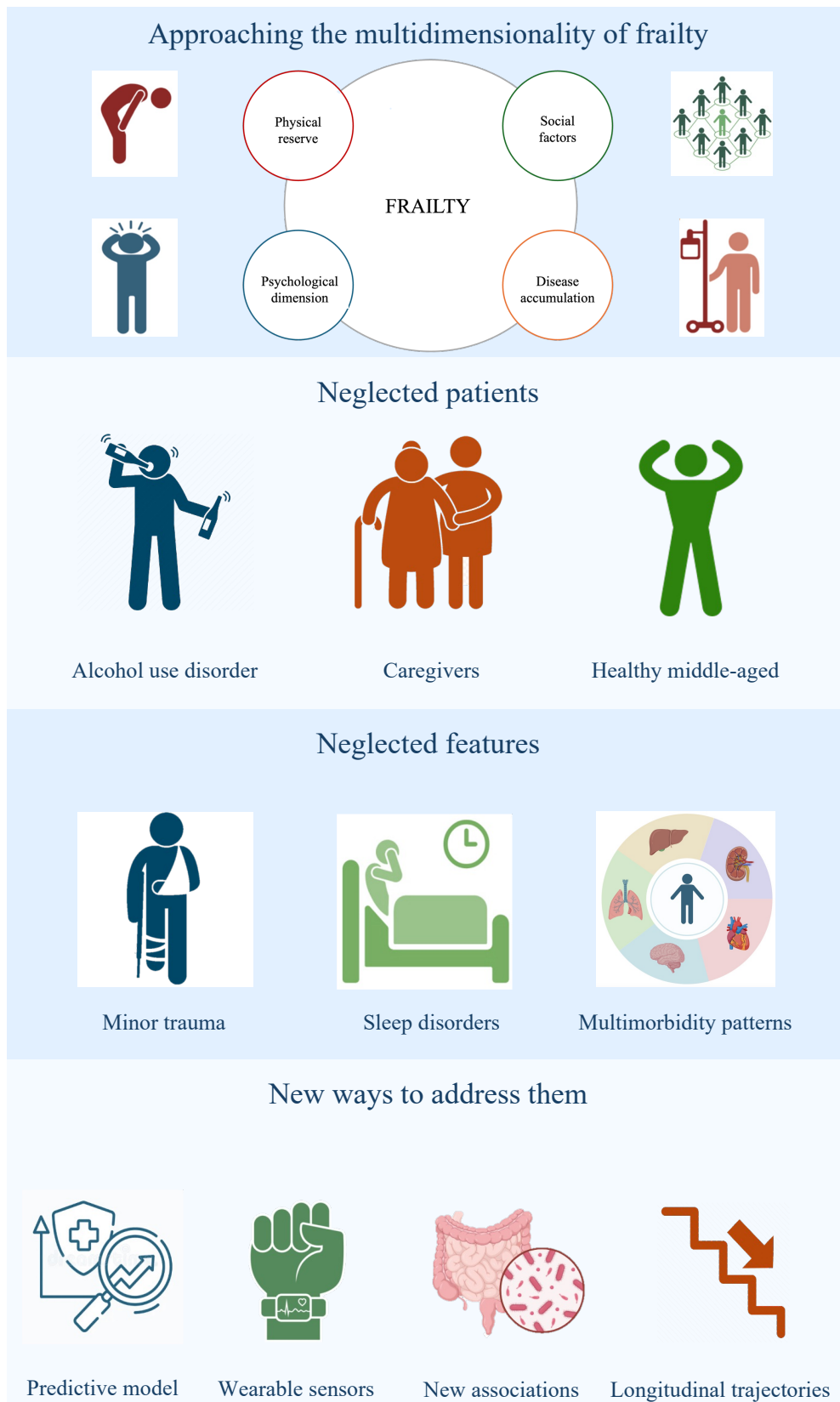
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Graphical abstract



Abstract

Frailty is a dynamic and multidimensional condition, with physical, psychological, and social factors playing a part in its development. The interaction between these domains is marked by considerable complexity. This thesis aimed to explore this complexity from other perspectives and broaden the debate on frailty towards 1) *neglected patients*, who may exhibit vulnerabilities not only because of aging; 2) *neglected features*, and 3) *new ways to address them*. This aim is addressed through the following individual studies:

Study I and **Study II** focus on young patients admitted to the emergency department with acute alcoholic intoxication (*neglected patients*), assessing their long-term mortality, evaluating among potential deaths predictors minor trauma and social vulnerability (*neglected features*), and developing a multivariable logistic regression model to predict 1-year readmission to the emergency department (*new ways*).

In **Study III** the first systematic map of the published evidence on the use of wearable sensors (*new ways*) in caregivers of people with dementia (*neglected patients*) is provided, mainly focusing on sleep disorders (*neglected features*).

Study IV investigates associations between Fried's frailty phenotype and sleep disorders (*neglected features*), evaluating possible associations with gastrointestinal symptoms (*new ways*) in hospitalized middle-aged adults with low comorbidities and without cognitive impairment (*neglected patients*).

Lastly, **Study V** explores the association between multimorbidity, evaluated through chronic disease patterns (*neglected features*) and physical performance tests by examining their longitudinal trajectories over 15 years (*new ways*) in a community-based cohort of older adults.

Frailty is not just a physical phenomenon. The findings of this doctoral thesis suggest broadening the discussion surrounding frailty by evaluating the interplay between physical, psychological, and social factors, and by shifting the focus to patient groups beyond older adults. Moreover, this doctoral thesis provides novel instruments to approach this interplay, aiming to foster resilience in patients and improve their ability to prevent functional decline through tailored prevention and person-centered care.

List of scientific works

The doctoral thesis is based on the following works, which will be referred to in the text as Study I, II, III, IV, V.

- I. Mortality and its association with chronic alcohol-related diseases in patients admitted to the emergency department for acute alcoholic intoxication: retrospective cohort study (**first author**, Intern Emerg Med. 2023 Jan;18(1):257-263. doi: 10.1007/s11739-022-03114-6);
- II. Development and internal validation of a multivariable model for the prediction of the probability of 1-year readmission to the emergency department for acute alcohol intoxication (**first author**, Intern Emerg Med. 2023 Jan;18(1):257-263. doi: 10.1007/s11739-022-03114-6);
- III. Wearable sensors for monitoring caregivers of people with dementia: a scoping review (**first author**, Eur Geriatr Med. 2024 Dec 3. doi: 10.1007/s41999-024-01113-8.);
- IV. Associations between gastrointestinal and sleep symptoms in pre-frail and frail hospitalized adults (**first author**, under review);
- V. Multimorbidity patterns and trajectories of physical performance: a population-based study (**first author**, under review);

Other scientific works related to the topic of the thesis

- The role of the circadian timing system in sarcopenia (**first author**, Eur Geriatr Med. 2025 Jan 2. doi: 10.1007/s41999-024-01129-0);
- Multimorbidity patterns and mental health outcomes in late life: a systematic review (**first author**, under review)
- Ethical and legal implications of the use of health monitoring wearable devices (Social Science & Medicine, 2025 Jan 8, doi: 10.1016/j.socscimed.2025.117685);
- Predictors of clinical trajectories of patients with acutely decompensated cirrhosis. An external validation of the PREDICT study (Liver Int. 2024 Jan;44(1):72-82. doi: 10.1111/liv.15734);
- Low haemoglobin level predicts early hospital readmission in patients with cirrhosis and acute decompensation (JHEP Rep. 2023 Feb 11;5(5):100698. doi: 10.1016/j.jhepr.2023.100698);
- COVID-19-Related Death in Patients with Alcohol or Substance Use Disorders (Eur Addict Res. 2023;29(1):67-70. doi: 10.1159/000527542);
- Relationship between muscle mass, bone density and vascular calcifications in older people with SARS-CoV-2 pneumonia (J Clin Med. 2023 Mar 19;12(6):2372. doi: 10.3390/jcm12062372);

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List of abbreviations and acronyms

AAI	Acute Alcoholic Intoxication
AIC	Akaike Information Criterion
ANOVA	Analysis Of Variance
ANS	Autonomic Nervous System
ATC	Anatomical Therapeutic Chemical
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorder Identification Test
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
COPD	Chronic Obstructive Pulmonary Disease
DSM-IV	Diagnostic And Statistical Manual Of Mental Disorders, Fourth Edition
ED	Emergency Department
eFI	Electronic Frailty Index
ESS	Epworth Sleepiness Scale
FFS	Fried Frailty Score
FI	Frailty index
GDS	Geriatric Depression Scale,;
GOLD	Global Initiative For Obstructive Lung Disease
GSRS	Gastrointestinal Symptom Rating Scale
HGS	Hand-Grip Strength Test
HR	Hazard Ratio
ICD-10	International Classification Of Diseases Version 10
ICD-9	International Classification Of Diseases Version 9
IL-6	Interleukine-6
IQR	Interquartile Range
LF/HF	Low Frequency To High Frequency Ratio
LRM	Logistic Regression Model
MFP	Multivariable Fractional Polynomials
MM	Multimorbidity
MMSE	Mini Mental State Examination

MUST	Malnutrition Universal Screening Tool
NYHA	New York Heart Association
PSQI	Pittsburgh Sleep Quality Index
PY	Person Years
SARC-F	Sarcopenia Finding Tool
SD	Sleep Duration
SE	Sleep Efficiency
SF	Sleep Fragmentation
SL	Sleep Latency
SMR	Standardized Mortality Ratios
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SUD	Substance Use Disorder

SECTION I

1. FRAILTY

1.1. A multidimensional condition

Frailty is a clinically identifiable state of diminished physiological reserve and increased vulnerability to a broad range of adverse health outcomes [1,2].

Although the concept of frailty has been recognised for centuries, it was not until 2001 that a landmark attempt was made to standardise the definition of frailty via a description of the condition's core clinical presentations [3].

Since then, the concept of frailty has constantly evolved in the literature, with a progressive debate about how to define this condition [4]. This debate aside, some important factors have remained consistent over the past decades in the conceptualisation of frailty [4,5]. First, frailty is multidimensional, with several factors playing a part in its development [4] (Figure 1).

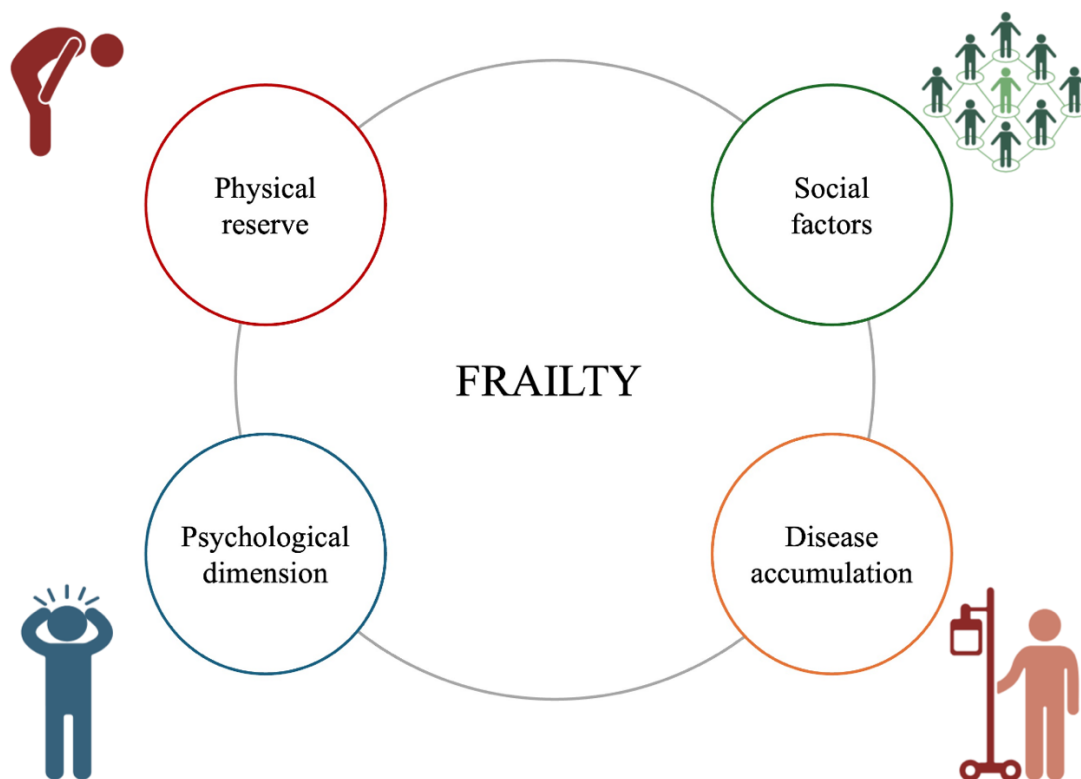


Fig. 1 – Frailty as a multidimensional condition

Second, frailty is dynamic, which means that an individual can fluctuate between states of severity of frailty [4]. Frailty is potentially preventable, up to a probable point of no return

when it becomes a pre-death phase [4]. Therefore, strategies to prevent and slow the progression of frailty are paramount [4] (Figure 2).

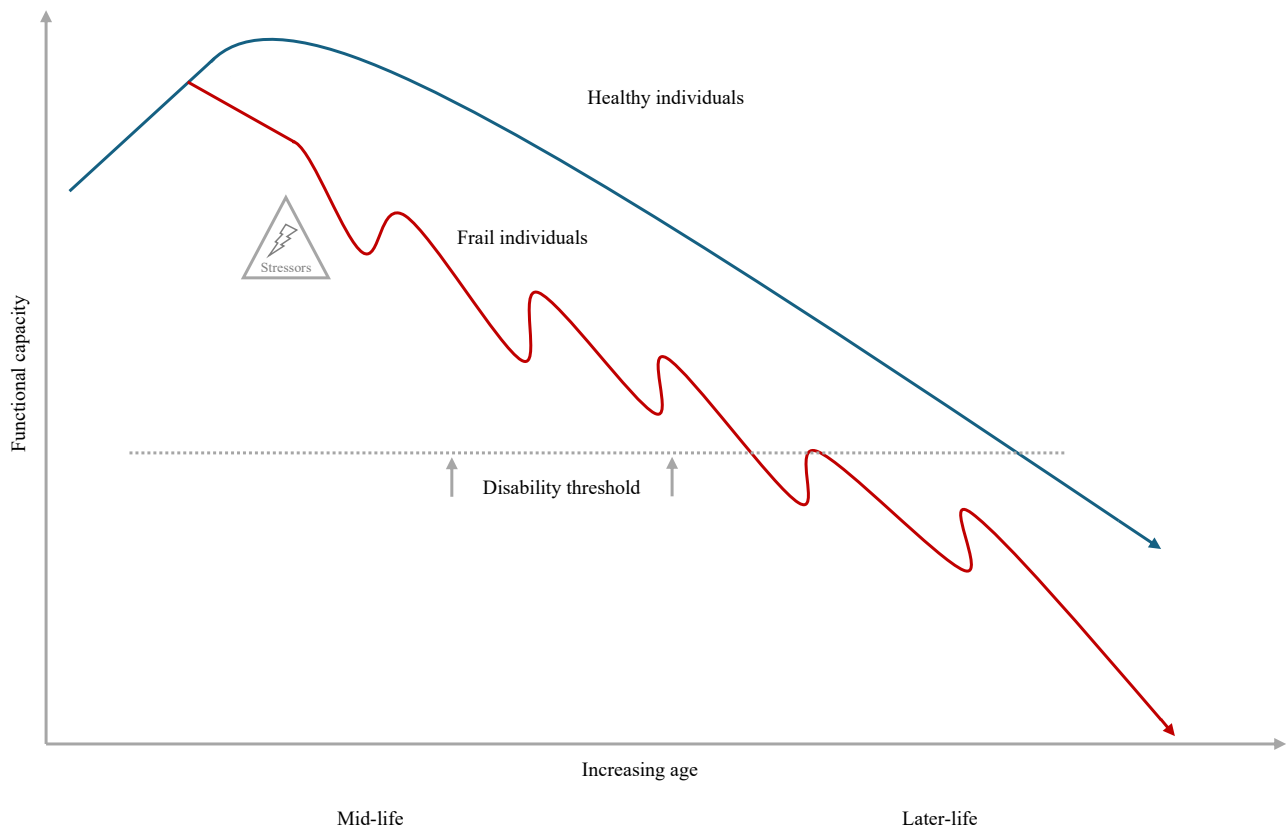


Fig. 2 – Usual trajectory of frail individuals across the lifecourse

However, as it is a comparatively new research discipline, many gaps in knowledge remain: no universal consensus exists on the definition of frailty or its assessment, and more robust, high-quality trials of strategies to prevent and manage frailty are needed [6].

1.2. Measurement of frailty

Despite the existence of various definitions, two concepts of frailty predominate: frailty as a syndrome and frailty as a state of accumulated health deficits [1]. The two concepts identify different subpopulations as frail. The Fried frailty phenotype delineates a clinical syndrome resulting from altered metabolism coupled with abnormal stress responses [3]. Characteristic features are exhaustion (first manifestation), weakness, slowness, physical inactivity, and weight loss (last manifestation) [3]. The presence or absence and degree of frailty are determined by the number of features presented: a person is considered to be “robust” if none

of the features are present, “prefrail” if one or two are present, and “frail” if three to five are present. The presence of all five features indicates a critical transition, with the risk of death rising sharply and the chance of reversal diminishing [1]. The Fried frailty phenotype is distinct from the presence of multiple coexisting disorders and disability [7].

The concept of frailty as deficit accumulation focuses on a state of poor health mainly due to compounded age-related deficits [8]. The selection of deficits for evaluation depends on the context and available information (e.g., survey results, a comprehensive geriatric assessment, electronic medical records, administrative data, or biomarkers) and can include diagnoses, cognitive and physical impairment, disability, poor nutritional status, and laboratory abnormalities [9]. The degree of frailty is quantified by means of a frailty index (FI), which is the number of deficits present as a proportion of the total number of deficits assessed, with at least 30 assessed [10].

1.3. Multimorbidity

The presence of multiple co-occurring diseases within the same individual, i.e. multimorbidity, is commonly observed, in particular in older people [11–13]. Multimorbidity carries a critical burden at both the individual and societal levels, particularly in healthcare systems designed to handle individual diseases rather than multiple conditions [14].

Individuals affected by multimorbidity are at a higher risk of experiencing a lower quality of life, as well as increased rates of disability and mortality [11,15]. Additionally, psychological well-being may suffer as a consequence of multimorbidity, as individuals may experience increased stress, anxiety, and depression due to the physical and emotional burden of managing multiple health conditions [16,17]. Multimorbidity also places a heavy burden on the healthcare system as it contributes to unplanned hospitalization and healthcare utilization [14]. Notably, it is not only the rising count of multiple health conditions that raises the probability of unfavorable outcomes (‘quantity’), but also their specific combinations (‘quality’), which is believed to express the synergistic effects of diseases and their treatments.

Over the past two decades, researchers have developed several operationalizations of multimorbidity that are intended to provide a more accurate description of diverse morbidity phenotypes, as opposed to the original conceptualization based on a threshold of two or more diseases that has been shown to have limited discriminative power in older adults [13,18]. The number of diseases is widely used to measure the burden of multimorbidity [14]. A higher number of diseases has been linked to various health outcomes, including disability, physical

performance, and mortality [19,20]. However, this approach may not accurately reflect the impact of severe conditions, such as dementia, on overall health. To address this, weighted indices have been developed, including the Charlson Comorbidity Index and the Cumulative Illness Rating Scale (CIRS), which have been implemented in geriatric care [21,22]. Moreover, individuals with multimorbidity exhibit considerable heterogeneity based on their specific combinations of diseases. Diseases tend to cluster in specific patterns rather than occurring randomly [13,14]. Among individuals with at least two diseases, clusters of cardiometabolic, neuropsychiatric, and musculoskeletal diseases have been consistently identified [23]. Understanding how diseases cluster is crucial for uncovering specific mechanisms that can be targeted through treatment or prevention interventions [20].

2. NEGLECTED PATIENTS

2.1 Not merely a geriatric syndrome

The prevalence of frailty has increased in recent years largely because of population ageing [1]. However, frailty is not limited to older people. Frailty and prefrailty can exist in individuals younger than 65 years, particularly among those with multimorbidity [6]. Thus, the management of frailty should be an important clinical priority for all health professionals, not just those caring for older people [6]. Frailty is identifiable in middle-aged as well as older adults and is associated with mortality independently of the extent of multimorbidity as well as age, sex, sociodemographic, and lifestyle factors [6].

Frailty reflects biological and phenotypic rather than chronological age [24,25]. Implicit in the frailty phenotype is the progression from pre-frailty to frailty [3]; however, this progression could be reversible in some patients [24,25]. Frailty predicts future disability but might be modifiable, particularly at an early stage [24,25], suggesting that identification of frailty and pre-frailty in middle age (those younger than 65 years) might have implications for prognosis, optimising care, and planning interventions [6].

2.2 Social vulnerability

According to the current knowledge, frailty appears to be strongly associated with social vulnerability [6], the accumulation of numerous, varied social problems with a bidirectional relationship on adverse health outcomes [26,27]. While evidence suggests this bidirectional relationship, the body of evidence showing that social vulnerability is associated with worsening frailty is more developed, as shown in a recent systematic review of studies assessing longitudinal changes both in frailty and social vulnerability in patients aged above 18 years (Figure 3) [26].

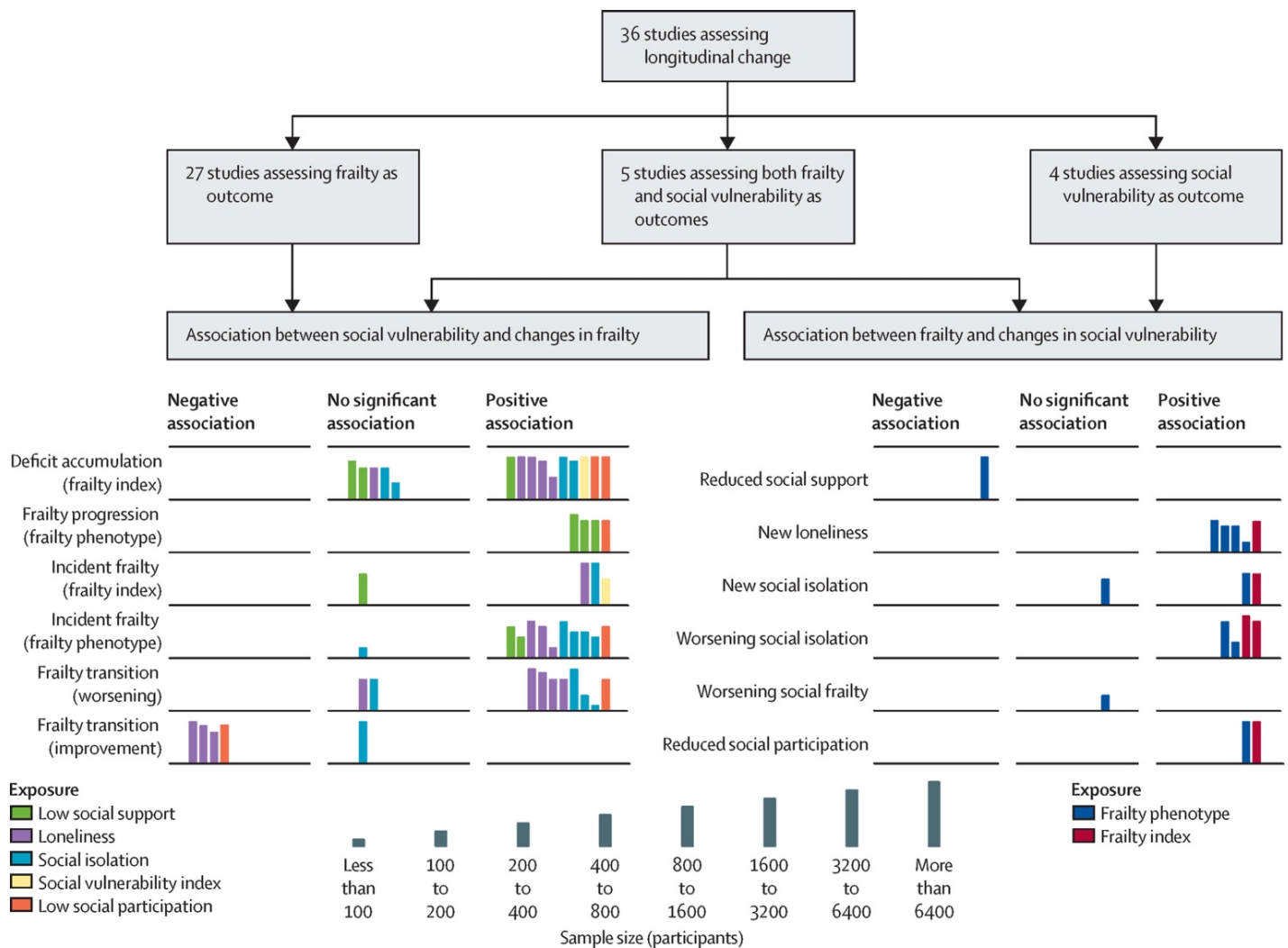


Fig. 3 – Harvest plot of longitudinal relationships between frailty and social vulnerability, adapted from [26]. Each bar represents a study. The height of the bar indicates the sample size. The position of the bar on the matrix shows the direction of association.

In another recent report covering 62 countries worldwide, it is highlighted that individuals with a socially vulnerable status are all at increased risk for frailty [1]. These findings are consistent with other cross-sectional [28,29] and longitudinal studies [30]; in particular, data from the English Longitudinal Study of Ageing, suggested that the 14-year trajectories of the frailty index are associated with social isolation [30]. Moreover, the association between frailty and social isolation has also been demonstrated among relatively younger people in an observational analysis conducted using the UK Biobank Resource (participant's mean age: 56.5 years) [31].

2.3 Alcohol use disorders: a model of “accelerated” frailty

Habitual alcohol consumption is one of the most common modifiable lifestyle factors that could lead in time to social vulnerability [32]. To date, the association between alcohol consumption and incident frailty remains controversial [32]. However, there are only a few studies that address this association, mainly evaluating the Fried’s phenotype rather than the FI, thus with a potential underestimation of the prevalence of frailty in people with alcohol use disorder (AUD).

Moreover, AUD is an underdiagnosed condition in most countries [33], and AUD-related stigma contributes to worsening it. In Italy, a recent report by the National Observatory on Alcohol shows that out of 710,000 estimated harmful users of alcohol in need of treatment, only 72,000 are followed by the alcohol services of the National Health System [34]. Thus, 90% of alcohol addicts in Italy cannot access treatment because it is not requested either by the addicted person or by a health professional in charge of identifying the problem [34]. People with AUD can feel isolated and rejected because they come to believe that the negative attitudes and false beliefs about AUD apply to them [35]. Stigma may consciously or unconsciously create biases even within experienced healthcare providers, and this can compromise the care path and lead to the worsening of social vulnerability [36].

Lastly, several studies provide biological evidence for accelerated aging in young patients with AUD [37,38]. Thus, the accumulation of deficits related to chronic alcohol-related diseases leads in time to an accelerated state of diminished physiological reserve that, in addition to the social vulnerability, could lead to an early onset of frailty in people with AUD.

2.4 Frailty related to the burden of care

Frailty places a burden not only on affected individuals but also on their families. Many older adults live in the community and need high levels of assistance for all activities of daily living. Such assistance is mainly provided by formal or informal caregivers [39].

Caregiving, as a chronic stressor, triggers a multifaceted stress response among caregivers, encompassing psychosocial aspects (such as depression and social isolation), behavioral patterns (like sedentary lifestyle and unhealthy dietary habits), and physiological changes (e.g., increased inflammation and metabolic abnormalities) [39]. These responses gradually deplete an individual’s physiological and psychological resources, eroding their physical and psychological resilience [40]. This results in caregivers falling into a vulnerable state due to significant health declines, manifesting as multidimensional frailty symptoms [39].

Consequently, for caregivers, the long-term responsibility of caregiving may further diminish resilience through chronic stress responses, thereby increasing the risk of frailty (Figure 4) [40].

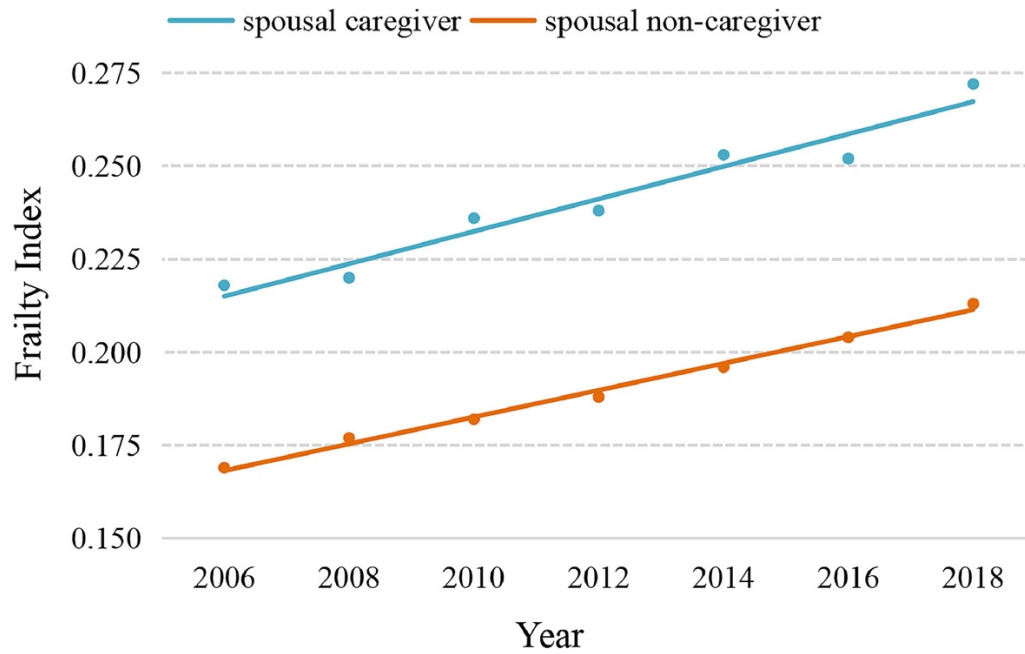


Fig. 4 – Predicted values of the frailty index grouped according to whether or not being a spousal caregiver, adapted from [40].

3. NEGLECTED FEATURES

3.1 Minor trauma and alcohol: the elephant in the room

Traumas are among the clinical conditions most frequently associated with AUD [41]. Excessive alcohol consumption appears to be among the major causes worldwide of fatal trauma [41,42]. In addition to acute deaths caused by unintentional injuries, motor vehicle crashes and falls, as well as the contributions of alcohol to intentional death, alcohol consumption is a leading contributing cause to minor trauma [41]. These are often underestimated clinical conditions, in particular at the Emergency Department (ED), mainly due to the burden of physicians but also to the underlying AUD-related stigma. This underestimation often leads to a significant delay in the recognition of AUD, often diagnosed after the onset of chronic alcohol-related conditions and the worsening of social vulnerability. Giving due weight to minor trauma could be one of the keys to early identifying people with AUD and sooner approaching them for specialized care.

3.2 Sleep disorders

Sleep/wake cycle is a physiological function that exhibits a circadian variation, and it is one of the most important lifestyle processes of a human being. Thus sleep duration and quality are crucial determinants of human's health [43]. The main sleep disorders are insomnia, i.e., difficulty initiating and maintaining sleep or waking up before the necessary sleep time; restless legs syndrome, i.e., involuntary movement of lower limbs during rest with relief during activities; obstructive sleep apnea, i.e., obstruction of the airways in the oropharyngeal region for circa 20 seconds during sleep; excessive daytime sleepiness, i.e., exaggerated need for sleep during the day with no improvement in sleepiness; and sleep fragmentation, i.e., frequent brief or long awakenings [44].

Sleep disorders lead in time to functional decline, decreased muscle strength, decreased growth hormone levels, low physical activity, anxiety, and even falls [43]. Since these are also involved in the pathogenesis of frailty, it was postulated that sleep disturbances could be associated with frailty [45,46]. Various potential mechanisms that may underlie the relationship between sleep disorders and frailty risk are outlined in Figure 5.

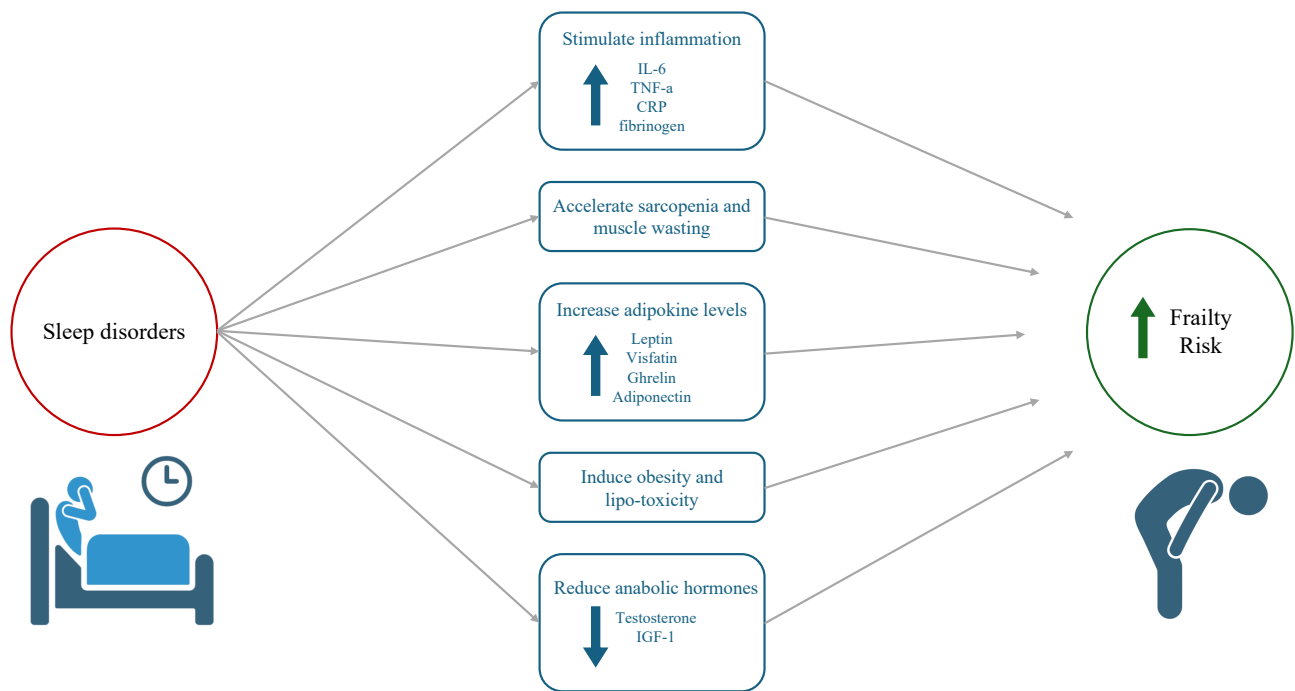


Fig. 5 – An overview of various possible mechanisms involved in the relationship between sleep disorders and frailty risk, adapted from [47]. Abbreviations: IL: Interleukine-6; TNF-a: tumour necrosis factor alfa; CRP: c-reactive protein; IGF-1: insulin grow factor 1

Previous studies have evaluated the associations between sleep disorders and frailty [43,47,48]. However, findings are inconsistent, and many of these studies are based on self-reported sleep assessments and cross-sectional designs.

Sleep quality and quantity could be assessed by evaluating different outcome measures, i.e., sleep duration (SD), sleep efficiency (SE), sleep latency (SL), and sleep fragmentation (SF). These outcome measures could be evaluated by using subjective and objective tools. Among the subjective tools, the Pittsburgh Sleep Quality Index (PSQI) [49] and the Epworth Sleepiness Scale (ESS) [50] are the most frequently used. The PSQI is a rating scale developed to provide a reliable and standardized measure of sleep quality. This scale consists of 19 items that must be evaluated by the subject himself and another 5 to which the bed or room partner must respond only serve as further information. The 19 items are grouped into 7 composite items that represent the subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of hypnotic drugs, and daytime disturbances. A score higher than 5 is considered indicative of the presence of sleep disorders [49]. The ESS is a self-administered questionnaire consisting of eight items that explore the tendency to sleep propensity in real-life scenarios over the past months. Each item can be scored from 0–3 points,

making the total score range from 0 to 24. The suggested score range for individuals without sleep issues is 0–10 [50].

Objective measurement of sleep quality and quantity could be evaluated using wearable sensor systems, which will be further discussed in detail.

4. NEW WAYS TO ADDRESS THEM

4.1 Needs for novel and tailored predictive models

Predictive modeling is an efficient method to identify people who could benefit from interventions to prevent adverse outcomes [51]. Predictive modeling involves the use of mathematical and computational methods to forecast future events or outcomes [51]. These methods encompass various techniques, such as regression analyses, decision trees, random forests, neural networks, and support vector machines. Equation-based models belong to a specific category of models that utilize mathematical equations to describe the relationship between variables [51].

To date, support vector machines were the most used techniques for predictive models of frailty, with the electronic frailty index (eFI) as the most predicted frailty score [52]. However, there is poor evidence focusing on other aspects of frailty, e.g., the social vulnerability.

4.2 Digital biomarkers and wearable sensor system

Biomarkers are defined as a set of characteristics that are objectively measured and used as indicators of normal biological processes, pathogenic processes or biological responses that appear due to exposure or therapeutic interventions [53]. The digitalisation of our world impacts daily living and healthcare, broadening the spectrum of the possible sources and methods used to measure biomarkers and introducing a novel dimension of measurable characteristics [53]. This allows digital devices used daily, such as smartphones, wearable devices, sensors, and smart home devices, to provide a new category of biomarkers, called 'digital biomarkers' [53].

Digital biomarkers are defined as objective, quantifiable, quantitative, physiological, and behavioural data collected to explain, influence and/or predict health-related outcomes, and measured by means of digital devices such as portables, wearables, implantables, or digestibles [54].

The measurement of digital biomarkers is characterized by its non-invasive nature and suitability for real-life evaluation. In particular, technological advancements over the past decade have resulted in the availability of wearable devices that can provide both assistance and monitoring to individuals in accordance with the "4P medical model," which stipulates that medicine should be preventive, predictive, personalized, and participative [55–57]. Wearable

devices can track movement and gather information about people's lifestyles and habits, such as their mobility levels [55] or real-world walking speed [58], using miniature motion sensors like accelerometers or gyroscopes. Accelerometers measure linear acceleration in real-time and can detect movement in up to 3 planes, i.e., vertical, anteroposterior and medio-lateral. Pedometers measure the number of steps taken and correlate well with uni-axial accelerometers [59]. Gyroscopes measure changes in orientation such as rotational or angular velocity, acceleration, or displacement [60].

The association between physical activity and frailty is well documented [61,62]. Traditionally, measurement of mobility and physical activity in studies accounting for frailty has relied on the use of self-reported questionnaires, surveys or diaries, or direct observation of physical performance tests, each with inherent difficulties and limitations [63]. Wearable sensors provide the opportunity for objective measurement of mobility and physical activity, and therefore their use in studies on frailty has risen in the last years [61,64–70].

However, wearable sensors should be employed to monitor the health status and well-being also of caregivers of people with chronic diseases, tracking the toll imposed by the burden of care and potentially allowing for early identification of burnout, frailty and other adverse health consequences.

4.3 (in search of) new associations to understand frailty

Understanding frailty and its associated factors is crucial for developing effective health promotion and disease prevention strategies. For example, it has recently been hypothesised that detrimental ageing-related alterations may also involve the gastrointestinal tract, leading to an altered inflammatory response [71,72], impaired intestinal permeability [73], and gut microbiota alterations [74]. These mechanisms may trigger the frailty syndrome (Figure 6) [72].

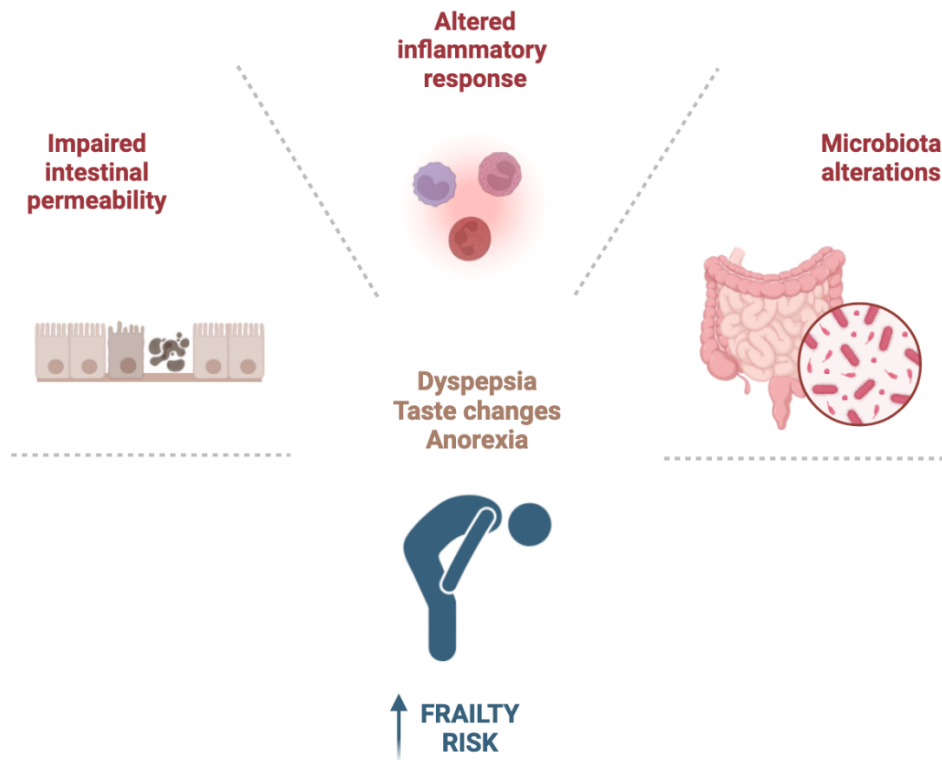


Fig. 6 – An overview of age-related gastrointestinal alterations that may lead to the worsening of frailty.

Thus, gastrointestinal symptoms such as anorexia, taste changes, and dyspepsia, need to be further investigated in relation to the development of frailty [72]. These symptoms can be evaluated through appropriate scales or questionnaires such as the Gastrointestinal Symptom Rating Scale (GSRS) [75]. GSRS is a disease-specific instrument of 15 items combined into five symptom clusters, i.e., reflux, abdominal pain, indigestion, diarrhoea, and constipation. The GSRS has a seven-point graded scale where 1 represents the absence of symptoms and 7 represents very troublesome symptoms [75].

4.4 Understanding the longitudinal trajectories of frailty

Frailty is dynamic, with both possible worsening and improving transitions [76]. This dynamic nature has been demonstrated in different cohorts worldwide [77–80]. However, more evidence is needed. To better characterize such dynamism, it is crucial to recognize and better describe the specific factors, modifiable and non-modifiable, that might influence the transitions across different frailty stages. Moreover, it will be of interest to provide an estimation of the probability of transition between different frailty stages and the usual permanence time in each status according to the identified specific factors.

Frailty trajectories may help identifying homogeneous groups of people with similar needs, and assist clinicians and health care systems in personalizing clinical interventions and preventive strategies.

SECTION II

5. RESEARCH AIMS

5.1. Overall aim

The overall aim of this thesis is to evaluate frailty from other perspectives in search of new strategies to prevent and slow its progression.

The scientific works included in this doctoral thesis mainly focused on patients other than older adults with high comorbidities to highlight the needs of these “neglected” individuals and subsequently try to intercept them earlier in their trajectory towards disability and death (Figure 7). To this aim these works investigate new ways to address them.

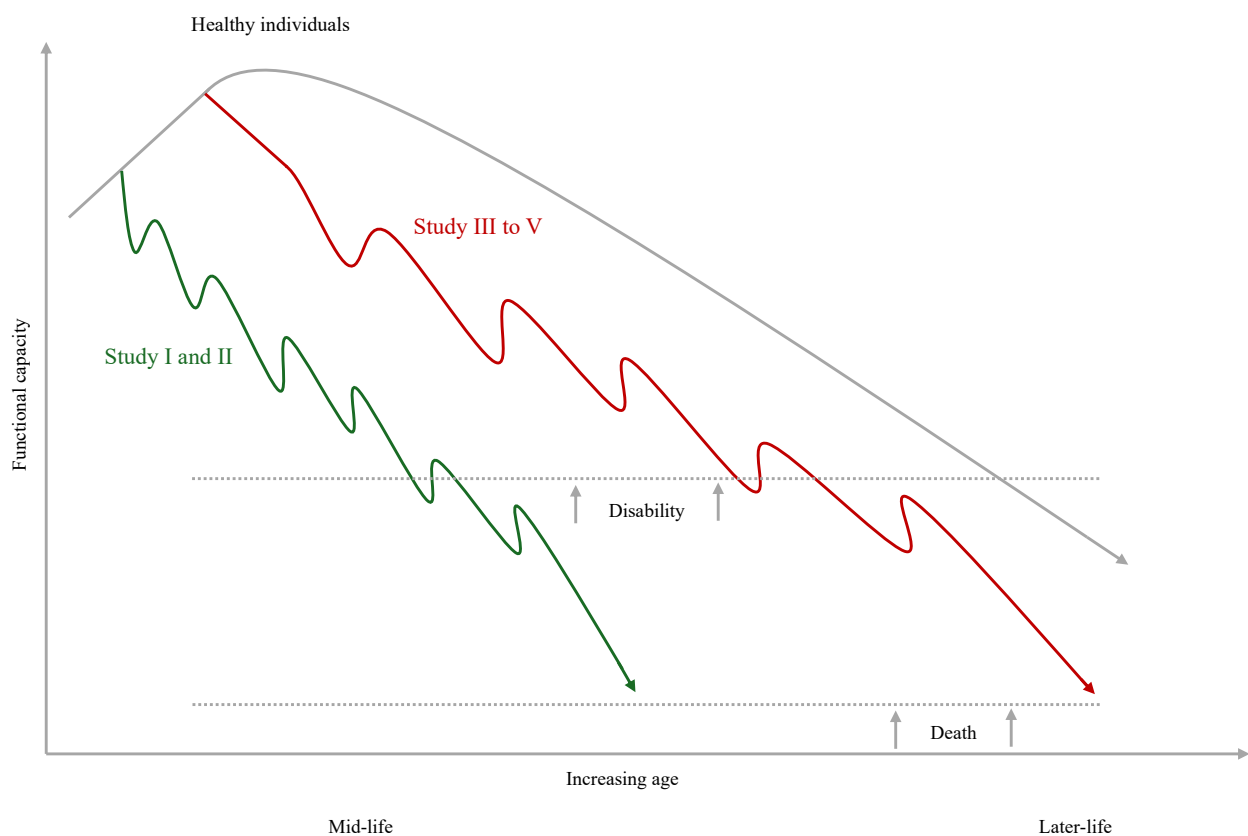


Fig. 7 – Usual frailty trajectories of the type of individuals evaluated in the five studies

5.2. Specific aims

The overall aim of this thesis is addressed through the following individual studies:

Study I: to assess long-term mortality and its association with chronic alcohol-related diseases in frail young patients admitted to the emergency department from 2005 to 2017 with acute alcoholic intoxication, focusing on the evaluation of minor trauma and social vulnerability;

Study II: to develop and internally validate a multivariable logistic regression model for the prediction of the probability of 1-year readmission to the emergency department in patients with acute alcohol intoxication.

Study III: to provide the first systematic map of the published evidence on the use of wearable sensors in caregivers of people with dementia, mainly focusing on sleep and physical activity evaluation;

Study IV: to obtain exploratory results on associations between sleep symptoms and gastrointestinal symptoms in pre-frail and frail hospitalized middle-aged and healthy older adults with low comorbidities and without cognitive impairment;

Study V: to explore the association between different multimorbidity patterns and physical performance tests by examining their longitudinal trajectories over 15 years in a community-based cohort of older adults.

	Study I - Study II	Study III	Study IV	Study V
Study population	Individuals with alcohol use disorder	Caregivers of people with dementia	Middle-aged and healthy older inpatients	Community-dwelling individuals aged >60
Neglected features	Minor trauma	Sleep disorders	Sleep disorders	Patterns of multimorbidity
New ways	Novel predictive models	Wearable sensor systems	Associations with unrelated symptoms	Physical performance trajectories

Fig. 8 – Graphical overview of the five studies included in the doctoral thesis

SECTION III

6. STUDY I

6.1 Specific aim

Early recognition of AUD is crucial because chronic alcohol abuse leads to long-term disease, e.g., liver cirrhosis, cardiovascular disease, and neurological disease. In Italy, the ED plays a central role in identifying patients with AUD, who often come there because of acute alcoholic intoxication (AAI) [34,81–83].

There are presently no data on long-term mortality in patients with AAI admitted to the ED and all the available studies of short-term mortality of AAI performed in the ED have focused on acute consequences of alcohol abuse, e.g., major trauma [84].

The aim of the present retrospective cohort study was therefore to assess long-term mortality and its association with chronic alcohol-related diseases in patients with AAI admitted to the ED of a large metropolitan hospital.

6.2 Materials and methods

6.2.1 Study design and setting

The present retrospective cohort study enrolled consecutive patients admitted for AAI to the ED of the Sant'Orsola- Malpighi Hospital (Bologna, Italy) from January 1, 2005, to December 31, 2017. The study was approved by the Ethical Committee of the Emilia-Romagna Region (CE-AVEC, number of approval 302/2020/Oss/AOUBo). Written informed consent was waived in view of the retrospective nature of the study.

6.2.2 Participants

Patients with AAI were eligible for the present study. We operationally defined AAI as at least one of the following diagnoses as coded by the International Classification of Diseases version 9 or 10 (ICD-9 and ICD-10) depending on the study period: (1) alcohol abuse; (2) alcohol dependence syndrome; (3) toxic effect of alcohol; (4) accidental poisoning by and exposure to alcohol; (5) intentional self-poisoning by and exposure to alcohol; (6) alcohol poisoning; (7)

evidence of alcohol involvement determined by blood alcohol level. The only exclusion criterion was age < 18 years.

6.2.3 Variables and data sources

The outcome variable was mortality rate. The last ascertainment of living status was made on 08 May 2020 using the ED electronic registry system, which is linked to the registry offices of the municipality where the patients were living at the time of death or at the end of the study.

The prespecified predictors of mortality, obtained from the ED electronic registry system using ICD-9 or ICD-10 codes depending on the study period, were: (1) age at first (“baseline”) admission (years); (2) male sex (0 = no; 1 = yes); (3) AUD (0 = no; 1 = yes); (4) substance use disorder (SUD) (0 = no; 1 = yes); (5) more than 1 admission to ED for trauma (0 = no; 1 = yes); (6) mental and behavioral disorders (0 = no; 1 = yes); (7) neurological disorders including non-cardiac syncope, vertigo, dizziness, and tremors (0 = no; 1 = yes); (8) cirrhosis (0 = no; 1 = yes); (9) cardiovascular disease (0=no; 1=yes).

6.2.4 Statistical analysis

Continuous variables are reported as median (50th percentile) and interquartile range (IQR, 25th and 75th percentiles) and discrete variables as the number and proportion of subjects with the characteristic of interest. Death rates were calculated per 1000 person years (PY). In addition to the overall death rate, we calculated the death rate associated with AUD, SUD, and their combination. A prespecified multivariable Cox regression model was used to evaluate the association between survival time and potential predictors. Survival time was calculated as the difference between the present and the previous admission or death or censoring, employing multiple records per patient [85]. Such format allowed to easily code for time-varying covariates. The time-fixed covariates of the Cox regression model were sex (discrete: 1 = male; 0 = female) and baseline age (continuous, years) divided by 5, to represent an increment of 5 years. The time-varying covariates of the Cox model were AUD (discrete, 0 = no; 1 = yes), SUD (discrete, 0 = no; 1 = yes), more than 1 admission to ED for trauma (discrete, 0 = no; 1 = yes), mental and behavioral disorders (discrete, 0 = no; 1 = yes), neurological disorders (discrete, 0 = no; 1 = yes), liver cirrhosis (discrete, 0 = no; 1 = yes), and cardiovascular disease (discrete, 0 = no; 1 = yes). Fractional polynomials were used to test whether the relationship

between continuous age and survival time was linear given the other discrete covariates [86]. The relationship was found to be linear and modeled as such. The 95% confidence intervals of the model coefficients and of the corresponding hazard ratios were calculated using the bootstrap on 1000 random samples with replacement [87]. The proportional hazards assumption made by the Cox model was ascertained using Schoenfeld residuals [88]. The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were used to assess model fit [89]. Standardized mortality ratios (SMR) were calculated every five years of age using reference data from Northern Italy for the years 2011–2017 (<http://dati.istat.it/Index.aspx>). Confidence intervals for rates and SMR were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. Statistical analysis was performed using Stata 17.0 (Stata Corporation, College Station, TX, USA).

6.3 Results

6.3.1 Participants

During the 13 years of the study, 883,683 emergency admissions were performed at the ED of the Sant’Orsola-Malpighi Hospital. Among these, 6415 (0.7%) were admissions for AAI that involved 3304 single patients. 133 of these 3304 patients died between 17 Sep 2007 and 08 May 2020.

6.3.2 Baseline measurements

The baseline measurements of the patients are given in Table 1.

Table 1 – Demographic and clinical characteristics at the first (“baseline”) admission of 3304 patients admitted to the Emergency Department for acute alcoholic intoxication between January 1, 2005, and December 31, 2017.

	<i>N</i> = 3304
Italian citizen	2068 (62.6%)
Male sex	2195 (66.4%)
Age (years)	30 (22; 43)

Aged < 18 years	172 (5.2%)
Homeless	262 (7.9%)
Alcohol use disorder	357 (10.8%)
Substance use disorder	175 (5.3%)
More than 1 admission to ED for trauma	425 (12.9%)
Mental and behavioural disorders	477 (14.4%)
Neurological disorders	257 (7.8%)
Dementia	12 (0.4%)
Cirrhosis	63 (1.9%)
Cardiovascular disease	138 (4.2%)

63% of the patients were Italian citizens and 66% were males. The median (IQR) age was 30 (22; 43) years and 5% of the patients were aged < 18 years. 8% of patients were homeless; 11% had already received a diagnosis of AUD and 5% one of SUD; 13% had previously had more than 1 admission to ED for trauma; 14% had mental and behavioral disorders and 8% neurological disorders, while dementia was uncommon (0.4%); cirrhosis was present in 2% and cardiovascular disease in 4% of the patients.

6.3.3 Measurements at the last available admission

Table 2 compares the characteristics at the last available admission of the 133 patients who died during the followup with those of the 3171 patients who were alive at the end of the follow-up.

Table 2 – Demographic and clinical characteristics at the last available admission of 3304 patients admitted to the Emergency Department for acute alcoholic intoxication between January 1, 2005, and December 31, 2017, stratified by living status as determined on May 8, 2020.

	Alive	Dead
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	<i>N</i> = 3171	<i>N</i> = 133
Italian citizen	1950 (61.5%)	118 (88.7%)
Male sex	2089 (65.9%)	106 (79.7%)
Age (years)	29 (22; 43)	61 (50; 73)
Aged < 18 years	172 (5.4%)	0 (0.0%)
Homeless	273 (8.6%)	24 (18.0%)
Alcohol use disorder	461 (14.5%)	83 (62.4%)
Substance use disorder	190 (6.0%)	26 (19.5%)
More than 1 admission to ED for trauma	557 (17.6%)	75 (56.4%)
Mental and behavioural disorders	518 (16.3%)	47 (35.3%)
Neurological disorders	267 (8.4%)	44 (33.1%)
Dementia	10 (0.3%)	8 (6.0%)
Cirrhosis	69 (2.2%)	29 (21.8%)
Cardiovascular disease	119 (3.8%)	41 (30.8%)

The patients who died were mostly Italian citizens (89%) and males (80%) and had a median age much higher than that of those who were still alive (61 vs. 29 years). AUD (62 vs. 14%), SUD (19 vs. 6%), more than 1 admission to ED for trauma (56 vs. 18%), mental and behavioral disorders (35 vs. 16%), neurological disorders (33 vs. 8%), cirrhosis (22 vs. 2%) and cardiovascular disease (31 vs. 4%) were also commoner among the patients who died.

6.3.4 Follow-up

The median number of admissions per patient was 1, but it was extremely skewed, ranging from 1 to 200. The median follow-up time was 9.3 years (range: 3 days to 15.3 years) and the time on risk was 30,053 PY with a death rate corresponding to 4.42 (95% CI 3.74 to 5.26) per 1000 PY (*n* = 133 deaths).

6.3.5 Death rate associated with AUD, SUD, and their combination

Table 3 reports the death rate in patients with AUD, SUD, and their combination.

Table 3 – Death rate in patients with AUD, SUD, and their combination.

		Death	PY	Rate (95%CI)
AUD-	—	50	25.25	1.98 (1.51 to 2.65)
AUD+	—	83	4.80	17.30 (14.04 to 21.52)
SUD-	—	107	28.14	3.80 (3.16 to 4.62)
SUD+	—	26	1.91	13.58 (9.36 to 20.37)
AUD-	SUD-	42	24.20	1.74 (1.29 to 2.38)
AUD-	SUD+	8	1.05	7.60 (3.88 to 16.87)
AUD+	SUD-	65	3.94	16.51 (13.05 to 21.16)
AUD+	SUD+	18	0.86	20.89 (13.35 to 34.22)

Death rate is calculated as death/person-time (per 1000). Abbreviations: AUD = alcoholic use disorder;

SUD = substance use disorder; PY = person-years.

The death rate was higher in patients with AUD (17.30 per 1000 PY) than in those without AUD (1.98 per 1000 PY), and in patients with SUD (13.58 per 1000 PY) than in those without SUD (3.80 per 1000 PY). Lastly, there was a clearly higher death rate among AUD+ SUD+ (20.89) compared to AUD- SUD-patients (1.74).

6.3.6 Multivariable prediction of time-to-death

Model 1 of Table 4 is the prespecified Cox regression model used to investigate the relationship between time-to-death and its potential predictors.

Table 4 – Multivariable Cox regression of time-to-death.

	Model 1	Model 2	Model 3
Male	1.64*	1.61*	1.68*
	[1.05 to 2.56]	[1.01 to 2.57]	[1.07 to 2.64]

Baseline age / 5 (years)	1.48 ^{***} [1.39 to 1.58]	1.49 ^{***} [1.39 to 1.58]	1.48 ^{***} [1.40 to 1.58]
Alcohol use disorder	2.13 ^{***} [1.36 to 3.34]	2.62 ^{***} [1.72 to 4.00]	—
Substance use disorder	3.69 ^{***} [2.13 to 6.41]	4.22 ^{***} [2.47 to 7.21]	4.00 ^{***} [2.25 to 7.11]
More than 1 admission to ED for trauma	2.02 ^{**} [1.31 to 3.12]	—	2.46 ^{***} [1.66 to 3.64]
Mental and behavioural disorders	0.96 [0.62 to 1.47]	0.98 [0.64 to 1.51]	1.10 [0.71 to 1.72]
Neurological disorders	1.46 [0.98 to 2.20]	1.49 [0.98 to 2.28]	1.62 [*] [1.06 to 2.46]
Liver cirrhosis	2.54 ^{***} [1.58 to 4.08]	2.73 ^{***} [1.71 to 4.37]	3.07 ^{***} [1.87 to 5.05]
Cardiovascular disease	1.50 [0.94 to 2.40]	1.62 [*] [1.03 to 2.55]	1.55 [0.96 to 2.50]
<i>AIC</i>	1645	1657	1657
<i>BIC</i>	1706	1711	1711

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Values are hazard ratios with 95% bootstrapped confidence intervals in brackets (see statistical analysis for details). Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

The multivariable predictors of time-to-death identified by Model 1 were male sex (HR = 1.64), baseline age (HR = 1.48 for an increase of 5 years), AUD (HR = 2.13), SUD (HR = 3.69), more than 1 admission to ED for trauma (HR = 2.02), and liver cirrhosis (HR = 2.54).

Because AUD and more than 1 admission for trauma were strongly associated (Spearman's rho = 0.52, $p < 0.0001$) suggesting multicollinearity [10], we fitted a second multivariable model without the more than 1 admission for trauma predictor (Model 2), and a third multivariable model without the AUD predictor (Model 3). Although there was some loss of gain in model

fit for Models 3 and 2 as compared to Model 1 as detected by both AIC and BIC, the point estimate of the HR and the lower 95% CI of the AUD predictor increased from Model 1 to Model 2 and the same was true for the more than one hospitalization for trauma predictor from Model 1 to Model 3. Because this may be a sign of multicollinearity, we preferred to employ Model 2, including AUD alone, for further analysis.

It should be noted that the removal of the more than 1 admission to ED for trauma predictor from Model 1 allowed cardiovascular disease to be statistically significant in Model 2 and neurological disorders to be statistically significant in Model 3. This is not clinically relevant, at least in the present cohort, because of the imprecision of the estimate of the corresponding HR as shown by the wide 95% CI. Incidentally, the same is true for male gender in all models.

Figure 9 plots the failure function of death estimated by Model 2 of Table 4 for AUD and SUD with all other variables set to their mean value, showing that SUD adds to AUD as the probability of death is concerned, confirming, and extending the findings obtained at univariable and bivariable analysis.

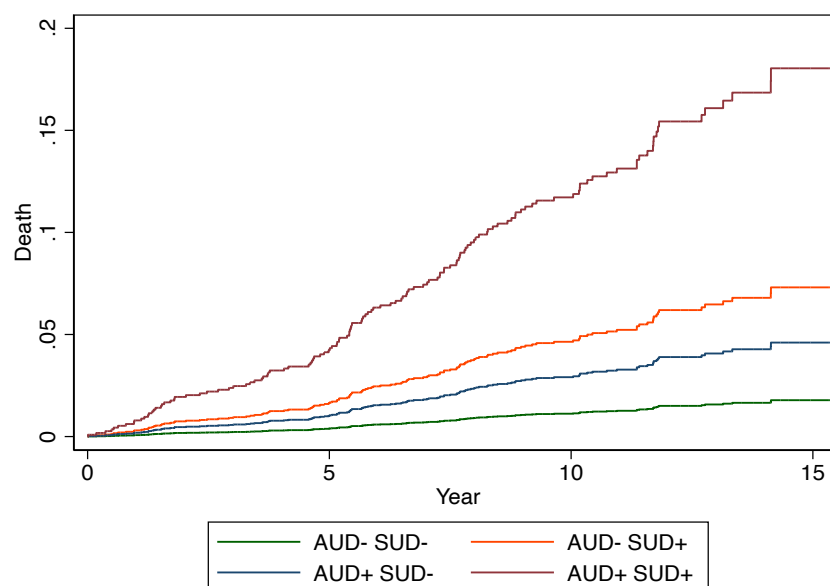


Fig. 9 – Failure function of death estimated by Model 2 of Table 4 for AUD and SUD with all other variables set to their mean value.

6.3.7 Standardized mortality ratios

Table 5 gives the SMR for the study cohort. A clear excess of observed vs. expected deaths can be detected from 40 to 65 years and for the (75–80] years age band.

Table 5 – Standardized mortality ratios. Abbreviations: PY = person years; Obs. = observed; Exp. = expected; SMR = standardized mortality ratio; 95%CI = 95% confidence interval.

Age band (years)	PY	Obs. Deaths	Exp. Deaths	SMR (95%CI)
(15 – 20]	765	0	0.15	—
(20 – 25]	3685	0	1.11	—
(25 – 30]	5161	2	1.55	1.29 (0.32 to 5.17)
(30 – 35]	4392	0	1.32	—
(35 – 40]	3421	4	1.71	2.34 (0.88 to 6.23)
(40 – 45]	2871	8	2.30	3.48 (1.74 to 6.97)
(45 – 50]	2560	9	3.64	2.47 (1.29 to 4.75)
(50 – 55]	2114	12	4.86	2.47 (1.40 to 4.35)
(55 – 60]	1571	17	5.97	2.85 (1.77 to 4.58)
(60 – 65]	1193	17	7.99	2.13 (1.32 to 3.42)
(65 – 70]	832	10	9.15	1.09 (0.59 to 2.03)
(70 – 75]	572	11	10.76	1.02 (0.57 to 1.85)
(75 – 80]	334	18	11.16	1.61 (1.02 to 2.56)
(80 – 85]	250	10	15.25	0.66 (0.35 to 1.22)
(85 – 90]	187	11	22.30	0.49 (0.27 to 0.89)
> 90	105	4	23.24	0.17 (0.06 to 0.46)
Total	30053	133	122.44	1.09 (0.92 to 1.29)

There were no deaths among patients aged ≤ 25 years, whose characteristics are given in Table 6.

Table 6 – Demographic and clinical characteristics at the first (“baseline”) admission of 3304 patients admitted to the Emergency Department for acute alcoholic intoxication between January 1, 2005, and December 31, 2017, stratified by age.

	> 25 years	≤ 25 years
	N=2099	N=1205
Hour at admission	10 (3; 20)	3 (2; 5)
Italian citizen	1,233 (58.7%)	835 (69.3%)
Male sex	1,496 (71.3%)	699 (58.0%)
Age (years)	39 (31; 50)	21 (19; 23)
Homeless	239 (11.4%)	23 (1.9%)
Alcohol use disorder	335 (16.0%)	23 (1.9%)
Substance use disorder	145 (6.9%)	30 (2.5%)
More than 1 admission for trauma	358 (17.1%)	67 (5.6%)
Mental and behavioural disorders	414 (19.7%)	64 (5.3%)
Neurological disorders	221 (10.5%)	35 (2.9%)
Dementia	12 (0.6%)	0 (0.0%)
Cirrhosis	63 (3.0%)	0 (0.0%)
Cardiovascular disease	130 (6.2%)	8 (0.7%)

This ancillary analysis was performed because binge drinking represents the first cause of death in subjects ≤ 25 years [34,90,91]. Patients aged ≤ 25 years were mostly Italian citizens (69% vs. 58%) with a lower frequency of homeless patients (2% vs. 11%) as compared to those aged > 25 years. The median (IQR) hour of the ED admission of the younger patients was 3:00 (2:00; 5:00) while that of the older patients was 10:00 (03:00; 20:00). Interestingly, 2% of the younger patients had already received a diagnosis of AUD and 2% one of SUD. Figure 10 plots the proportion of patients aged ≤ 25 years admitted to the ED during the study period. In line with

the available literature [34,90,91], the figure shows an increase in the proportion of patients aged ≤ 25 years starting from 2010.

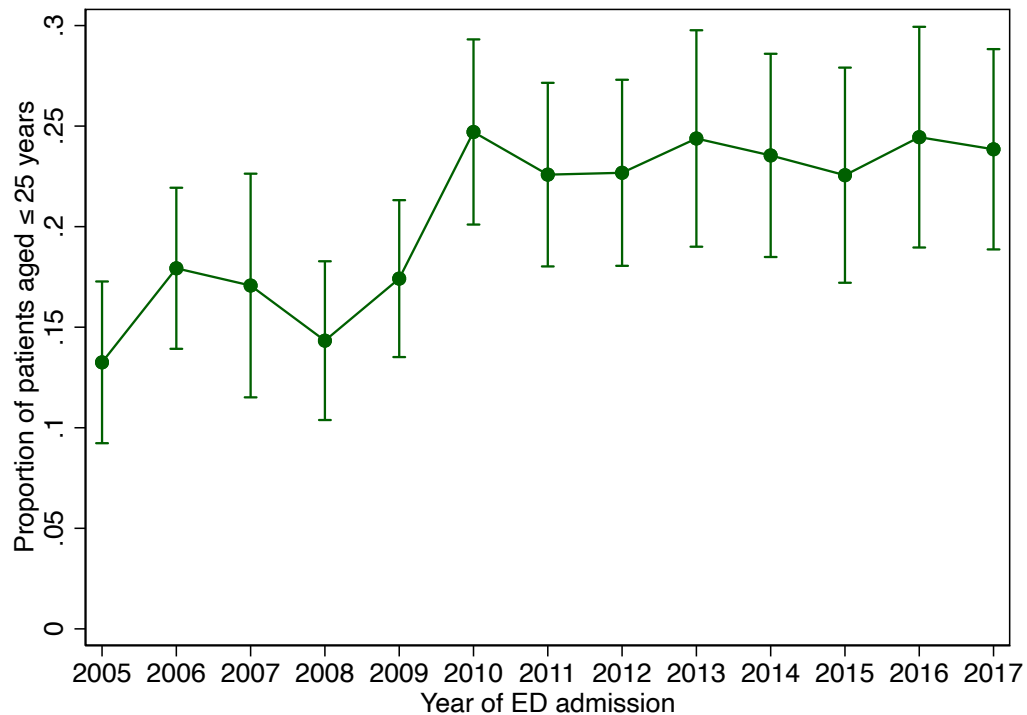


Fig. 10 – Proportion of patients aged ≤ 25 years admitted to the emergency department during the study period. Values are marginal proportions and cluster 95% confidence intervals estimated by using logistic regression with year of hospitalization as discrete predictor.

6.4 Discussion

The present retrospective cohort study was aimed at assessing long-term mortality and its association with chronic alcohol-related diseases in patients with AAI admitted to the ED. Our estimate of the frequency of admissions for AAI over the study period (0.7%) is in line with national data ($\leq 1\%$) [34]. We quantified the mortality rate in 4.42 (95%CI 3.74–5.26) per 1000 PY and identified AUD, SUD, and liver cirrhosis as strong and independent predictors of time-to-death. Importantly, there was a clear excess of deaths, as detected by the standardized mortality ratio (SMR), for the age bands from (40–45] to (60–65] years and in the age band (75–80] years.

The main strength of the present study is that it is the first one to investigate long-term mortality and its association with chronic alcohol-related diseases in patients with AAI. We performed such study in the ED because in Italy and most countries it is the first interface between the National Health System and persons with undiagnosed AUD. Another strength is the sample size, consisting of 3304 patients for a total of 6415 admissions performed during 13 consecutive years. A third strength is the fact that the median (IQR) age at the baseline admission was only 30 (22; 43) making it less likely at the population level that death occurs because of chronic disease related to alcohol consumption.

The present study has several limitations. We obtained mortality data from the registry offices of the municipality where the patients were living at the time of death or at the end of the study. It is thus possible that some deaths might have gone undetected among homeless patients. Nonetheless, 18% of the deaths which were recorded by the registry offices occurred in homeless patients. Another limitation is that it is likely that there is a proportion of cases where the ICD coding system was inappropriately used, leading to misclassification of AAI and of the predictors of interest. Having not performed an internal cross-validation of the ICD coding in this cohort, we cannot tell how much large such proportion is. Moreover, as the predictors are concerned, although it would be very useful to stratify them by etiology, e.g., viral vs. alcoholic liver cirrhosis, this cannot be reliably done from the ED database, as it is generally true for death certificates. Another limitation is that this is a single-center study performed in a hospital which is not a hub center for major trauma. Thus, we may have missed major traumas related to acute alcohol abuse even if the corresponding deaths if any were available in the ED system. Moreover, the aim of the present study was to evaluate the association between mortality and chronic alcohol-related diseases.

AAI is often an underestimated cause of access to the ED which can hide serious underlying chronic diseases [92]. It is well known that chronic diseases such as liver cirrhosis, AUD, and SUD carry a mortality rate higher than that of the general population [93–95]. Mild AAI requires a short stay in the ED and only supportive therapy and does not lead to serious complications [81]. In most cases, however, AAI underlies AUD, and recognizing this association may lead to immediate care and prevention of chronic alcohol-related diseases [96]. Our study shows for the first time that the mortality rate of a large population accessing the ED for AAI is associated not only with the acute effects of alcohol but also with chronic alcohol-related diseases. This suggests that the ED is a crucial place not only for treating the acute effects of AAI but also to identify patients with AUD and send them to the alcohol services of

the National Health System. The most interesting finding of the present study is how SUD adds to AUD as the mortality rate is concerned. This fact is expected from the available literature [97,98], but this is the first time that this relationship is reported for long-term mortality and for patients with AAI seen at the ED and has important clinical and organizational implications. Interestingly, while there were no deaths among the patients aged ≤ 25 years, 2% of them had already received a diagnosis of AUD and 2% one of SUD, which is not negligible. In conclusion, mortality is higher in AAI than in the general population and chronic alcohol-related diseases are strongly associated with it.

7. STUDY II

7.1 Specific aim

The notion that the ED could serve as a hub for the identification of patients with alcohol-related disorders to direct them to specific alcohol treatment centers is widely supported [33,83]. In fact, patients with AUD could be identified using questionnaires such as the 10-item alcohol use disorder identification test (AUDIT) or its condensed version, the 3-item AUDIT-C. However, these tools are underutilized in the ED due to time pressure and other factors [33,83]. Many studies have therefore been conducted with the aim of identifying readily available predictors of hospital readmission for AAI. However, these studies usually lasted for 30 days, and few studies have evaluated potential predictors of the probability of 1-year readmission [99]. The present study aimed therefore to develop and internally validate a multivariable prediction model for estimating the probability of 1-year readmission to the ED for AAI.

7.2 Materials and methods

7.2.1 Source of data

The development and internal validation of the multivariable model for the prediction of the probability of 1-year readmission to the ED was performed using the previously described retrospective cohort of AAI patients who accessed the ED of the Sant'Orsola-Malpighi Hospital from January 1, 2005, to December 31, 2017.

7.2.2 Participants

Patients with AAI who were admitted to the ED of the Sant'Orsola-Malpighi Hospital between January 1, 2005, and December 31, 2017, were eligible for the present study. AAI was defined as at least one of the following diagnoses: 1) alcohol abuse; 2) alcohol dependence; 3) alcohol toxicity; 4) accidental alcohol poisoning; 5) intentional alcohol poisoning; 6) alcohol poisoning (general); 7) alcohol intoxication, as measured by the blood alcohol level. Based on the study period, these diagnoses were made using the ICD codes version 9 or 10. The only criterion for exclusion was age < 18 years.

7.2.3 Outcome and Predictors

The binary outcome was readmission to the ED of the Sant'Orsola-Malpighi Hospital for AAI within 365 days from the first admission (0 = no; 1 = yes). We compiled the following list of potential predictors before performing any modeling: 1) age of the patient at baseline admission (continuous, years); 2) male sex (binary, 0 = no; 1 = yes); 3) AUD (binary, 0 = no; 1 = yes); 4) SUD (binary, 0 = no; 1 = yes); 5) at least one previous admission for trauma (binary, 0 = no; 1 = yes); 6) mental or behavioral disorder (binary, 0 = no; 1 = yes); 7) homelessness (binary, 0 = no; 1 = yes).

The age of the patient was determined by subtracting the date of admission to the ED from the patient's birthdate, which was found either through the electronic registry of the ED or by asking the patients directly after they had recovered from AAI. Because we expected that the logit of age would not be linear, the functional form of age was pre-specified as having two terms that would be later defined using multivariable fractional polynomials (MFP) with bootstrap evaluation of stability [100,101]. Sex was defined as biological sex. Based on the study period, the ED electronic registry provided a previous diagnosis of AUD and SUD based on ICD-9 or ICD-10 codes. Additionally, the ED electronic registry was used to evaluate the presence of at least one previous admission for trauma and to obtain a previous diagnosis of a mental or behavioral disorder.

7.2.4 Sample size

This is a retrospective cohort study performed on an available dataset of 3304 patients with AAI. Before performing any modeling, we selected a list of potential predictors (see section 2.4), determined their functional form (see section 7.2.3), and calculated the 1-year readmission rate (15.7%; 518/3304). We used the number of predictors (9 because age was prespecified as being coded by 2 predictors; see section 7.2.3) and the 1-year readmission rate to evaluate the minimum sample size needed to minimize overfitting and allow a precise estimation of model parameters [102–104]. In detail, we calculated that 2451 subjects were needed to detect a Cox-Snell R^2 of 0.1078, corresponding to a C-statistic of 0.70, which we deemed as the minimal acceptable optimism-corrected discrimination while ensuring: 1) a shrinkage of predictor effects < 5%; 2) a difference of 5% in the model apparent and adjusted Nagelkerke R^2 and; 3) an estimation within 5% of the average outcome risk in the population [102–104]. The available

sample size of 3304 subjects was thus more than enough to develop a model with the desired discrimination and calibration features.

7.2.5 Statistical analysis

Most continuous variables were not Gaussian-distributed, and all are reported as median (50th percentile) and interquartile interval (25th and 75th percentiles). Discrete variables are reported as the number and percentage of subjects with the characteristic of interest.

We started modeling by defining a benchmark multivariable logistic regression model (LRM) using 1-year readmission for AAI as the binary outcome, age as a continuous predictor, and sex, AUD, SUD, at least one previous admission for trauma, mental or behavioral disease, and homelessness as binary predictors. The hypothesis that AUD and possibly SUD were likely predictors of the probability of 1-year readmission prompted us to compare the calibration and discrimination of the benchmark model with those of simpler prespecified models not including AUD or SUD among predictors. The underlying model development strategy is detailed in Table 4. To this aim, the benchmark LRM was gradually simplified to get the most parsimonious LRM with a similar fit, discrimination, and calibration. Overall fit was evaluated using the scaled Brier score, i.e., the Brier score scaled by its maximum score (Briermax) according to the equation $(1 - \text{Brier score}) / \text{Briermax}$, with a higher score representing greater accuracy. Discrimination, i.e., the ability to separate subjects with disease from those without disease, was evaluated using Harrell's C-statistic which, for the case of logistic regression, equals the area under receiver-operating characteristic curve [105].

Calibration, i.e., the agreement between observed and predicted risk, was assessed by evaluating: 1) "mean calibration" or "calibration-in-the-large", by comparing the observed event rate with the average predicted risk; 2) "weak calibration", by performing a logistic analysis testing whether the calibration slope is 1; and, 3) "moderate calibration", by using a "calibration plot" to test whether the predicted risks correspond to the observed event rates. Such a graph plots the predicted (expected) outcome probabilities (x-axis) against the observed outcome frequencies (y-axis). As suggested by the TRIPOD guidelines, we performed the calibration using tenths of the predicted risk and superimposed a line obtained by locally weighted scatterplot smoothing. A well-calibrated model shows predictions lying or around the 45-degree line of the calibration plot [105].

All models were internally validated by calculating the scaled Brier score, C-statistic, calibration in the large, calibration slope, and drawing a calibration plot with 95% confidence interval on 1000 bootstrap samples [105,106,106].

The linearity of the logit of age in all models was evaluated using MFP with bootstrap evaluation of stability [101]. Collinearity among predictors was assessed by evaluating the condition matrix [107] and by using Spearman's rho [108]. Unlike our previous study (4), we did not use a previous episode of AAI as a predictor in the present study because it was expected to be collinear with AUD.

Statistical analysis was performed using Stata 18.0 (Stata Corporation, College Station, TX, US) using the mfpboot, bsvalidation and pmsampsize user-written commands.

7.3 Results

7.3.1 Distribution of potential predictors

The baseline distribution of the potential predictors of the probability of 1-year readmission for AAI is shown in Table 7.

Table 7 – Baseline distribution of potential predictors of the probability of 1-year readmission for acute alcohol intoxication.

	<i>N</i> = 3304
Male sex	2195 (66.4%)
Age (years)	30 (22; 43)
Homeless	262 (7.9%)
Alcohol use disorder	357 (10.8%)
Substance use disorder	175 (5.3%)
At least one previous admission for trauma	425 (12.9%)
Mental or behavioral disease	477 (14.4%)

Continuous variables are reported as median (50th percentile) and interquartile interval (IQI, 25th and 75th percentiles). Discrete variables are reported as the number and proportion of subjects with the characteristic of interest.

7.3.2 Readmission for AAI at 1 year

The readmission rate at 1 year was 15.7% (95%CI 14.4% to 16.9%, 518/3304). The readmission rate increased with increasing decade of age up to the 4th decade to decrease

thereafter (6%, 95%CI 5% to 7% for age $\leq$ 2nd decade; 23%, 95%CI 20% to 26% for age < 3rd decade; 35%, 95%CI 31% to 39% for age < 4th decade; 27%, 95%CI 21% to 32% for age < 5th decade; 15%, 95%CI 10% to 21% for age $\geq$ 6th decade; 13%, 95%CI 6% to 19% for age $\geq$ 70 years) and was higher in men (17.9%, 95%CI 16.3 to 19.5%) than in women (11.4%, 95%CI 9.5 to 13.2%). The readmission rate was also higher in homeless (54.6%, 95%CI 48.6 to 60.6%) patients than in those with a fixed residence (12.3%, 95%CI 11.2 to 13.5%), in patients with (44.4%, 95%CI 39.3 to 49.6%) than in those without AUD (12.2%, 95%CI 11.0 to 13.4%), in patients with (36.0%, 95%CI 28.9 to 43.1%) than in those without SUD (14.5%, 95%CI 13.3 to 15.8%), in patients with (32.0%, 95%CI 27.6% to 36.4%) than in those without (13.3%, 95%CI 12.0 to 14.5%) one previous admission for trauma, and in patients with (32.2%, 95%CI 28.0% to 36.4%) than in those without (12.9%, 95%CI 11.6% to 14.1%) mental or behavioral disease.

7.3.3 Determination of the functional form of age

As readily detected by using a locally weighted scatterplot smoother, the logit of age was not linear for all models. To determine the functional form of age, for which we had prespecified two terms, we used MFP with bootstrap evaluation of stability. To this aim, every model reported in Table 8 was run on 1000 bootstrap samples without replacement. Age was selected in all models with an FP functional form.

Table 8 – Multivariable modeling strategy for the prediction of the probability of 1-year readmission for acute alcohol intoxication.

	M1	M2	M3	M4	M5	M6
Male sex (binary)	✓	✓	✓	✓	✓	✓
Age (continuous)	✓	✓	✓	✓	✓	✓
Alcohol use disorder (binary)	✓	✓	—	—	—	—
Substance use disorder (binary)	✓	—	—	—	—	—
At least one previous admission for trauma (binary)	✓	✓	✓	—	—	—
Mental or behavioral disease (binary)	✓	✓	✓	✓	—	—
Homeless (binary)	✓	✓	✓	✓	✓	—

M1 is the prespecified benchmark model. M4 to M6 are prespecified simplified models aimed at evaluating the hypothesis that the unavailability of SUD and AUD status can be circumvented by knowledge of other readily available predictors.

Legend: ✓ = predictor included in the model; — = predictor not included in the model.

7.3.4 Development and internal validation of the multivariable model

Table 9 presents the internally validated LRMs and their metrics of overall fit, calibration, and discrimination. Internal validation, i.e., correction for optimism, was performed on 1000 bootstrap samples without replacement.

Table 9 – Comparison of multivariable models for the prediction of the probability of 1-year readmission for acute alcohol intoxication.

	M1	M2	M3	M4	M5	M6
Male sex	0.25* [0.01 to 0.49]	0.25* [0.01 to 0.49]	0.27* [0.04 to 0.51]	0.30* [0.07 to 0.54]	0.15 [-0.08 to 0.38]	0.31** [0.08 to 0.53]
Age (years)	0.92*** [0.72 to 1.11]	0.94*** [0.74 to 1.13]	0.94*** [0.75 to 1.14]	0.96*** [0.77 to 1.16]	1.02*** [0.83 to 1.21]	1.15*** [0.96 to 1.34]
Age (years)*ln[age (years)]	-0.19*** [-0.23 to -0.15]	-0.19*** [-0.24 to -0.15]	-0.19*** [-0.24 to -0.15]	-0.20*** [-0.24 to -0.16]	-0.21*** [-0.25 to -0.17]	-0.24*** [-0.28 to -0.20]
Alcohol use disorder	0.90*** [0.62 to 1.18]	0.95*** [0.67 to 1.22]	—	—	—	—
Substance use disorder	0.46* [0.09 to 0.84]	—	—	—	—	—
≥ 1 access for trauma	0.49*** [0.23 to 0.76]	0.50*** [0.24 to 0.77]	0.58*** [0.33 to 0.84]	—	—	0.78*** [0.54 to 1.03]
Mental or behavioral disorder	0.62*** [0.36 to 0.88]	0.67*** [0.41 to 0.92]	0.86*** [0.62 to 1.11]	0.96*** [0.72 to 1.21]	—	—
Homeless	1.55*** [1.26 to 1.84]	1.57*** [1.28 to 1.85]	1.66*** [1.38 to 1.94]	1.69*** [1.41 to 1.97]	1.63*** [1.35 to 1.90]	—
Intercept	-10.54*** [-10.65 to -10.44]	-10.66*** [-10.76 to -10.55]	-10.85*** [-10.95 to -10.74]	-10.99*** [-11.09 to -10.88]	-11.30*** [-11.41 to -11.20]	-12.38*** [-12.48 to -12.28]
Brier-scaled (%)	18.4	18.5	17.0	16.7	14.8	10.7
C-statistic	0.813 [0.794 to 0.835]	0.811 [0.792 to 0.832]	0.799 [0.778 to 0.821]	0.793 [0.773 to 0.815]	0.775 [0.754 to 0.797]	0.753 [0.731 to 0.775]

E:O ratio	0.999 [0.936 to 1.064]	0.999 [0.936 to 1.064]	0.999 [0.936 to 1.070]	0.999 [0.930 to 1.070]	0.999 [0.930 to 1.070]	1.000 [0.930 to 1.064]
CITL	0.000 [-0.102 to 0.100]	0.000 [-0.100 to 0.100]	0.000 [-0.099 to 0.099]	0.000 [-0.100 to 0.099]	0.000 [-0.098 to 0.097]	-0.001 [- 0.088 to 0.094]
Calibration slope	0.979 [0.894 to 1.077]	0.982 [0.896 to 1.081]	0.985 [0.893 to 1.088]	0.988 [0.892 to 1.093]	0.988 [0.890 to 1.106]	0.988 [0.873 to 1.125]

* p<0.05, ** p<0.01, *** p<0.001

The values are logistic regression coefficients (from male sex to intercept) or performance metrics (from Brier-scaled to calibration slope) with a 95% confidence interval in brackets. The values were adjusted for optimism by bootstrapping 1000 samples without replacement.

Abbreviations: ln = natural logarithm; E:O ratio = expected vs. observed ratio; CITL = calibration in the large.

Figure 11 depicts the corresponding calibration plots.

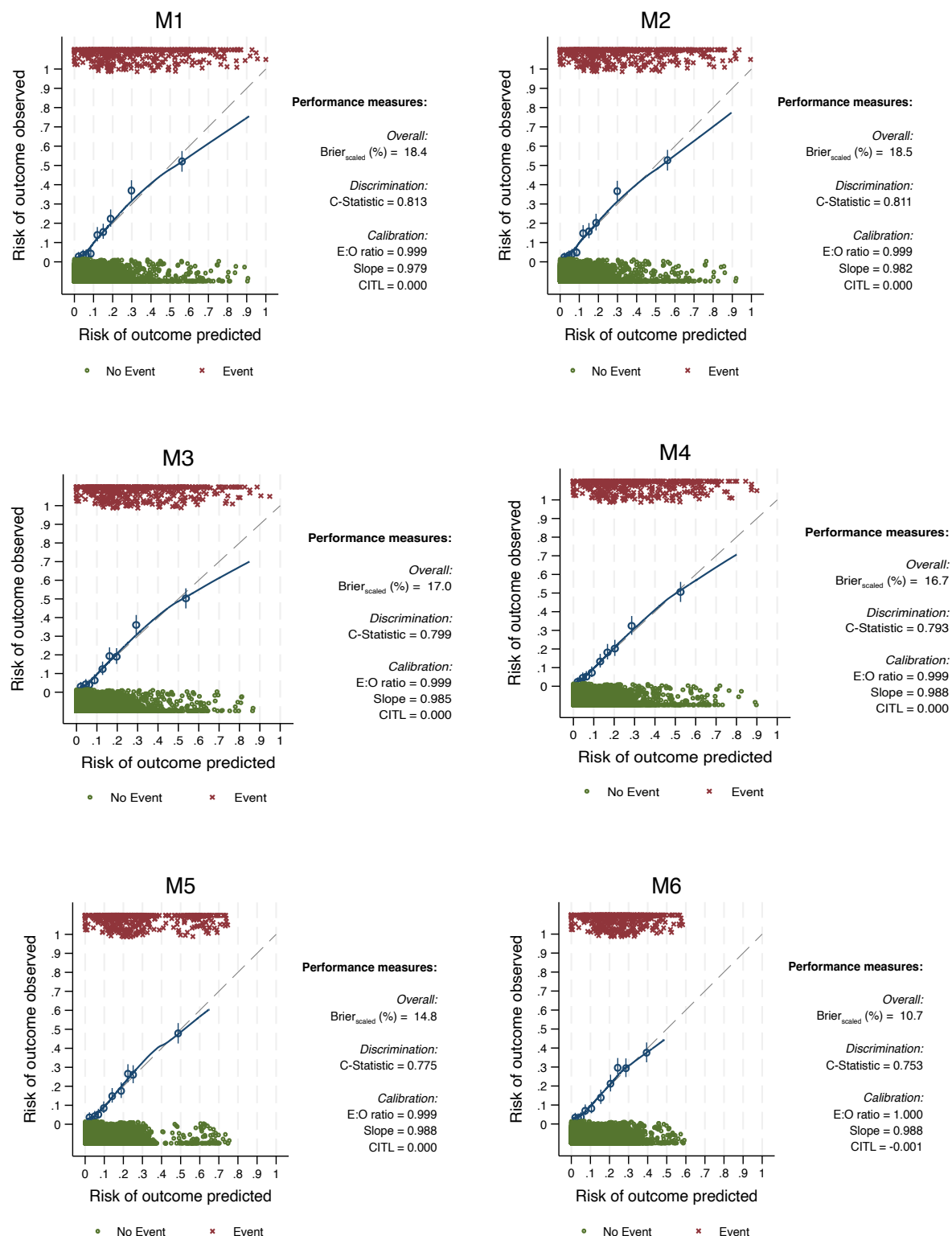


Fig. 11 – Calibration plots of the multivariable logistic regression model the for the prediction of the probability of 1-year readmission for acute alcohol intoxication.

The performance of all models greatly exceeded our expectations. The benchmark model M1 and the reduced model M2, which excluded SUD from the predictors, were virtually identical as detected by discrimination, calibration, and model fit statistics. Interestingly, removing AUD from model M2 to get model M3, which is based on more easily available predictors, made the prediction only slightly worse, with a scaled Brier score changing from 18.5 to 17%. For models M4 to M6, which were devised with the aim of evaluating the separate contribution of the more readily available predictors, the loss of performance versus model M2 was more evident, with a scaled Brier score changing from 18.5% to 16.7% and 14.8% respectively. Lastly, the probability of 1-year readmission was not accurately predicted by age and sex alone (Model M6, scaled Brier score 10.7%).

7.3 Discussion

The aim of the present study was to develop and internally validate a multivariable model for the prediction of the probability of 1-year readmission to ED for AAI.

The prespecified benchmark model (Model M1 of Table 9), which included sex, age, AUD, SUD, at least one previous admission for trauma, mental or behavioral disease, and homelessness, demonstrated both good discrimination and calibration according to current standards. It is useful to remember that calibration is central for a diagnostic model to be properly employed in clinical practice and that it plays a more important role than discrimination. Importantly, a simplified model excluding AUD and SUD from the predictors (Model M3 of Table 9), performed only slightly worse and is certainly acceptable for practical usage. Model M3, which we developed based on the results of a previous study performed on a much lower number of events and patients, is the one that we suggest to externally validate for clinical application. The corresponding equation is reported in Table 10 with a worked-out example.

Table 10 – Prediction equation (Model M3 of Table 9)

A. Calculate the linear predictor model (LP)	$LP = 0.27 * \text{male} + 0.94 * \text{age_term1} - 0.19 * \text{age_term2} + 0.58 * \text{trauma} + 0.86 * \text{mental} + 1.66 * \text{homeless} - 10.85$
	where
	male = 1 if male sex, 0 otherwise;

	age_term_1 = age(years); age_term_2 = age(years)*ln(age(years)) where ln = natural logarithm; trauma = 1 if previous access for trauma, 0 otherwise; mental = 1 if mental or behavioral disorder, 0 otherwise; homeless = 1 if homeless, 0 otherwise.
B. Calculate the probability of 1-year readmission from the linear predictor	Probability = $e^{LP} / 1 + e^{LP}$ where e is the base of natural logarithms The probability ranges from 0 to 1. If you wish to have it on a percentage scale, multiply it by 100.
C. Example	What is the probability of 1-year readmission for acute alcoholic intoxication for an homeless man aged 38 years without previous access for trauma and without mental disease? male = 1; age_term_1 = 38; age_term_2 = 38*ln(38) = 138; homeless = 1; trauma = 0; mental = 0. $LP = 0.27*1 + 0.94*38 - 0.19*138 + 0.58*0 + 0.86*0 + 1.66*1 - 10.85 = 0.58$ Probability = $e^{0.58} / 1 + e^{0.58} = 0.64$
D. Note	You can get the equations for the other models of Table 9 by using the above procedure.

This study has several limitations. A limitation is that this study was performed at a single ED and evaluated the probability of 1-year readmission for AAI at the same ED. We had in fact not the possibility of checking whether other admissions for AAI were performed at EDs other than ours. More importantly, we wanted to be sure that AAI was operationally defined according to the criteria listed under Section 2.2. This, however, implies that we might be underestimating the true probability of AAI. Another limitation, already discussed in study I, is that there may be instances where the ICD codes were improperly applied, leading to an incorrect

classification of the outcome and some predictors. Given that we have not performed an internal validation of the ICD coding system in this cohort, the proportion of such misclassification remains unknown. Another limitation is that a patient may have had an AUD or SUD when they were admitted to the ED, but this was not yet known or recorded in the ED electronic registry. It is therefore possible that Models M1, M2 and M3 (Table 9) might be actually built on an underestimated prevalence of AUD or SUD. Another limitation is that, although our internal validation was done according to current standards and gave satisfactory results (Table 9), we did not perform an external validation. An external validation of any diagnostic or prognostic model is however essential because it is the first step to determine its clinical utility. Our case-mix of patients together with how healthcare is provided under the Italian National Health System is likely to prevent the generalizability of our prediction model to other countries. However, we expect that it will work in similar contexts. Importantly, the external validation of our model is not expected to be onerous because it uses commonly collected data to make the prediction.

The model that we propose for external validation uses sex, age, at least one previous admission for trauma, mental or behavioral disease, and homelessness as predictors. In the present study, sex and age were independent predictors of AAI. We were not surprised to find at least one previous admission for trauma among the predictors of AAI because of the substantial evidence base linking trauma recidivism to alcohol abuse, as discussed in the overall introduction. The same holds true for the strong linkage between alcohol consumption and psychological and behavioral disorders [81]. Lastly, there is ample literature showing that homelessness is a risk factor for alcohol abuse.

In conclusion, a multivariable prediction model could be used to estimate the probability of 1-year readmission to ED for AAI based on sex, age, at least one previous admission for trauma, mental or behavioral disease, and homelessness. This model should be externally validated to prove its clinical usefulness. More than the model equation, which may require recalibration, evidence that readily available predictors such as at least one previous admission for trauma, mental or behavioral disease, or homelessness are independent predictors of the probability of a 1-year readmission should be looked at more closely. Provided that our model is proven to be useful by external validation, it should be evaluated in a randomized controlled trial to see if the calculation of the probability of readmission for AAI at 1-year has practical consequences for AAI patients, such as a sooner approach to specialized care.

8. STUDY III

8.1 Specific aim

Evidence on the use of wearable sensors is available in people with dementia, centered on sleep quality analysis, behavioral and psychological disorders, and physical activity [109–112]. Even though it is known that the health and well-being outcomes of people with dementia are connected with those of their caregivers, the evidence of wearable sensor use specifically in the caregivers of people with dementia has received less attention [112,113]. Therefore, this scoping review aims to provide a systematic map of the published evidence regarding the use of wearable sensors in caregivers of people with dementia.

The review was designed to answer the following questions:

- What is the available evidence regarding the use of wearable sensors by caregivers of people with dementia?
- Which sensor technologies (e.g., inertial measurement units, photoplethysmography), sensor locations (e.g., wrist, belt), sensed variables (e.g., acceleration, heart rate), and sensor regulatory features (e.g., medical device category) have been included in published reports on caregivers of people with dementia?
- What is the feasibility, usability, and acceptability of wearable sensors as assessed by caregivers of people with dementia?
- How does information on caregivers of people with dementia, measured with wearable sensors, affect caregiver quality of life, anxiety, depression, burden of care, stress, or any other outcomes related to caregiver health and well-being?
- What evidence is available about how information obtained with wearable sensors on caregivers of people with dementia impacts their care receivers?

8.2 Materials and methods

The study protocol for this review was developed according to the PRISMA-ScR guidelines [114]. Although designed for systematic reviews, the PRISMA-P guidelines were also applied

to this scoping review [115]. The study protocol was deposited on the Open Science Foundation website (<https://doi.org/10.17605/OSF.IO/M72E4>).

In April 2024, systematic electronic searches were conducted in the following databases:

- MEDLINE and PubMed Central (PMC), searched through PubMed;
- SCOPUS;
- Web of Science, searched through Clarivate Analytics;
- PsycInfo, searched through EBSCOHost;
- IEEE.

The selection of search terms and the construction of search queries were accomplished through collaborative efforts between members of the working group and an experienced librarian. The review included papers focusing on the use of wearable sensors by caregivers of people with dementia. Wearable sensors are devices that measure the physical signals of the human body for a given amount of time [116]. Both formal and informal caregivers and all stages and types of dementia were considered. We checked papers written in English, German, French, and Italian. Conference abstracts, conference proceedings (except those published in the IEEE database), non-peer-reviewed articles, dissertations, theses, books, research protocols, letters, and editorials were not considered relevant to our aim. After removing duplicates, each paper was screened independently by two reviewers using Rayyan software [117]. The papers judged to meet the screening inclusion criteria by at least one reviewer were evaluated by two independent reviewers based on their full text. The selection of the papers to be included in the review was made by consensus between the two reviewers involved in the selection process and after discussion with the entire research team.

8.3 Results

8.3.1 Search results

The study selection process is summarized in Figure 12.

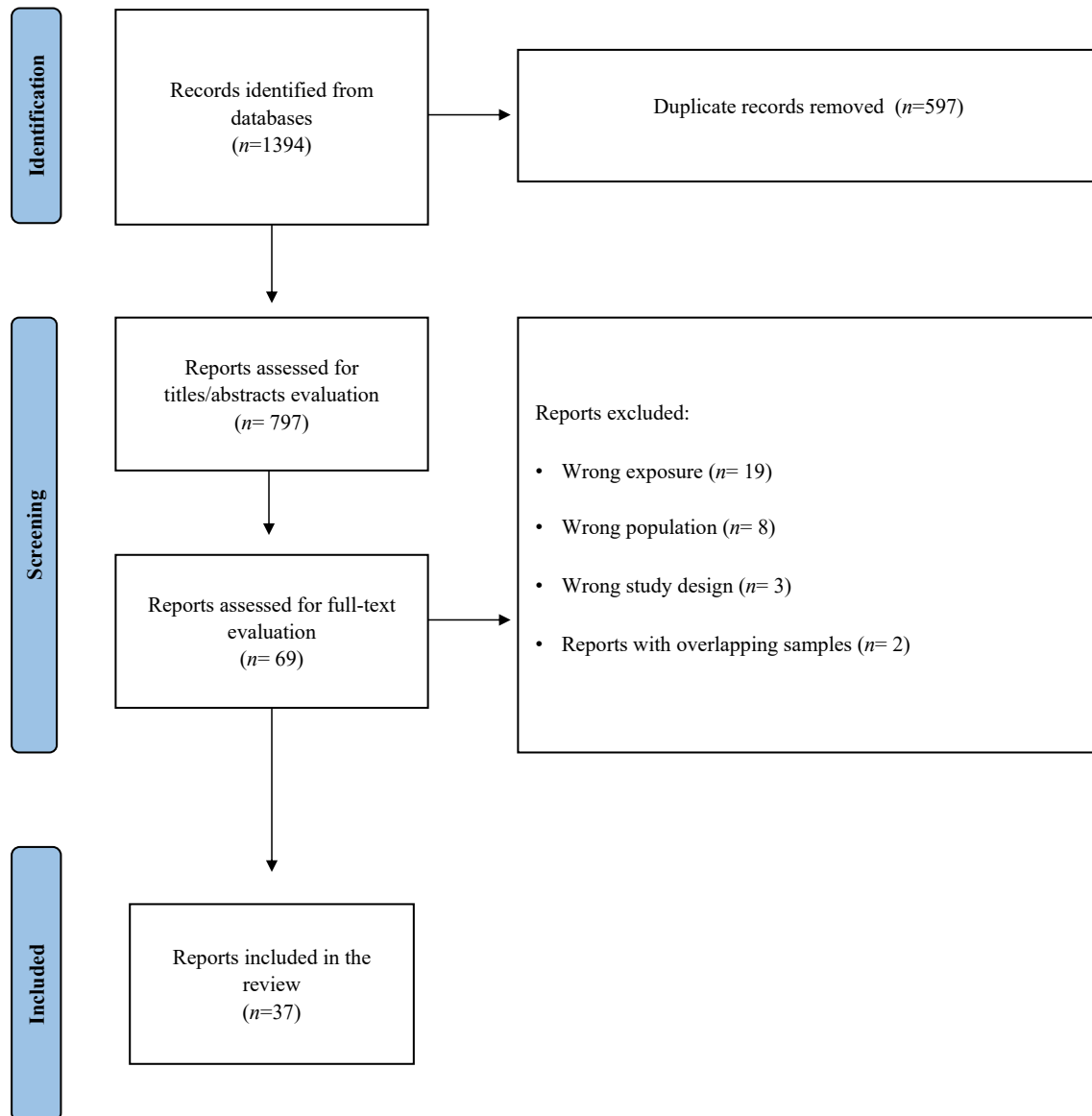


Fig. 12 – PRISMA flow diagram of the study selection process

We identified 1394 papers from the online databases; we short-listed 69 papers after screening and selected 37 papers after full-text evaluation.

8.3.2 Characteristics of the included studies

The characteristics of the studies selected for inclusion are described in Table 11.

Table 11 – Main characteristics of the selected studies on wearable sensors for caregivers of people with dementia.

Authors	Study design	Caregivers				Care-receiver		
		<i>N</i>	Mean Age (SD)	% female	Type of caregiver	Mean Age (SD)	% female	Type of dementia
Pollak & Stokes, 1997	CS	25	67.3 (10.2)	24	I	80.7 (7.9)	52	AD VD UD
Akkerman & Ostwald, 2004	RCT	5	–	–	I	–	–	AD
Ancoli-Israel et al., 2005	RCT	63	GLM: 67.7 (15.9) DPZ: 69.4 (11.4)	52 53	I	76.5 (7.7) 77.8 (6.2)	68 56	AD
McCurry et al., 2005	RCT	36	IG: 62.8 (15.3) CG: 63.7 (16.7)	76 68	I	77.8 (8.1) 77.6 (6.7)	41 47	AD
Lee et al., 2007	PCS	39	67.4	67	I	76.5	33	AD UD
McCurry et al., 2008	CS	44	64.6 (15.2)	67	I	78.8 (7.2)	50	AD
Rowe et al., 2008	CS	31	70.7 (7.8)	74	I	–	–	–
Beaudreau et al., 2008	CS	60	64.8 (12.5)	100	I	81.2 (7.2)	–	–
Merrilees et al., 2009	CR	1	53	100	I	58	0	FTD
Simpson & Carter, 2010	Non-RCT	10	63 (14.85)	50	I	–	–	–
Higgins et al., 2010	MCS	1	73	100	I	80	0	VD
Rowe et al., 2010	RCT	49	IG: 61.52 (13.53) CG: 62.81 (10.50)	74 88	I	80 (8.58)	53	AD LBD UD

Marquez et al., 2012	CS	24	68.6 (9.1)	75	I	–	–	AD UD
Merrilees et al., 2013	CS	22	bvFTD: 59.9 (9.1) svFTD: 63 (10.8)	64	I	bvFTD: 61.5 (5.9) svFTD: 66.2 (8.9)	36	FTD
Schwartz et al., 2013	CS	126	74.16 (7.98)	71	I	–	–	AD
Merrilees et al., 2014	CS	22	bvFTD: 59.9 (9.1) svFTD: 63 (10.8)	64	I	bvFTD: 61.5 (5.9) svFTD: 66.2 (8.9)	36	FTD
von Känel et al., 2014	LS	126	74.16 (7.98)	71	I	–	–	AD
D'Aoust et al., 2015	CS	53	63.15 (12)	81	I	–	–	–
Sakurai et al., 2015	CS	20	60	80	I	–	–	–
Figueiro et al., 2015)	CS	34	71.8 (12.3)	79	I	80.8 (7.9)	26	AD
McCrae et al., 2016)	CS	55	62.8 (12.21)	78	I	–	–	–
Fowler et al., 2016	RCT	28	IG: 60 (12.77) CG: 67 (12.2)	27 69	I	85 (9.71) 78 (8.64)	–	–
Smagula et al., 2017	CS	57	74 (7.4)	77	I	–	–	AD UD
Peng et al., 2019	CS	43	65.40 (9.84)	93	I	77.40 (9.02)	30	AD VD UD
Gibson & Gander, 2019	CS	15	72	87	I	80	–	AD VD LBD UD
Sadeghi et al., 2019	CS	8	–	75	I	–	–	–
Kajiwarra et al., 2019	CS	9	65 (8.9)	44	I	83.1 (11.5)	67	AD LBD UD

Lai Kwan et al., 2019	CS	3	–	67	I	–	100	–
Sakurai & Kohno, 2020	CS	10	65.05 (9.7)	60	I	83.2 (11.8)	40	–
Chang et al., 2020	CS	43	65.40 (9.84)	93	I	–	–	–
Carpenter et al., 2020	CS	14	59.4 (6.9)	100	I	–	–	AD
Song et al., 2022	CS	122	74.31 (8)	70	I	–	–	AD
Chen et al., 2022	CS	22	65.4 (8.9)	32	I	61.7 (14.2)	68	AD UD
Smagula et al., 2023	CS	56	71 (6.7)	68	–	–	–	–
de Dios-Rodríguez et al., 2023	RCT	176*	IG: 59 (–) CG: 69 (–)	76 67	I	81.5 (–) 82 (–)	69 59	–
Farina et al., 2024	CS	26	76.4 (5.9)	73	I	79.8 (5.8)	38	–
Song et al., 2024	RCT	30	67 (10.9)	93	I	82.9 (9.4)	37	AD VD LBD UD

Abbreviations: I: informal caregivers; AD: Alzheimer's disease; VD: vascular dementia; FTD: frontotemporal dementia; bv: behavioral variant; sv: semantic variant; LBD: Lewy body dementia; UD: dementia of unknown cause; RCT: randomized controlled trial; CS: cross-sectional study; L: longitudinal study; PCS: prospective case series; MCS: methodological case study; CR: case report; IG: intervention group; CG: control group; GLM: galantamine; DPZ: donepezil; SD: standard deviation.

– not specified

* study in which the numbers of caregivers (176) and care-receivers (140) were different

Except for the work of Pollak & Stokes [118], published in 1997, the included studies were published between 2004 and 2024 and had different study designs. All studies involved informal caregivers, except for one study where the type of caregivers was not specified [119], with a predominantly female population. Care-receivers in most studies (19/37) were individuals with Alzheimer's disease or dementia of unknown cause.

8.3.3 Caregiver outcome measures

The most evaluated caregiver outcomes were sleep quality and quantity (28/37), followed by physical activity (12/37). Metrics of autonomic nervous system (ANS) activity, i.e., heart rate variability and electrodermal activity, were the focus of 5 studies. Eight studies focused on sleep combined with either physical activity evaluation (5/37) or ANS metrics (3/37). The results are summarized in Figure 13.

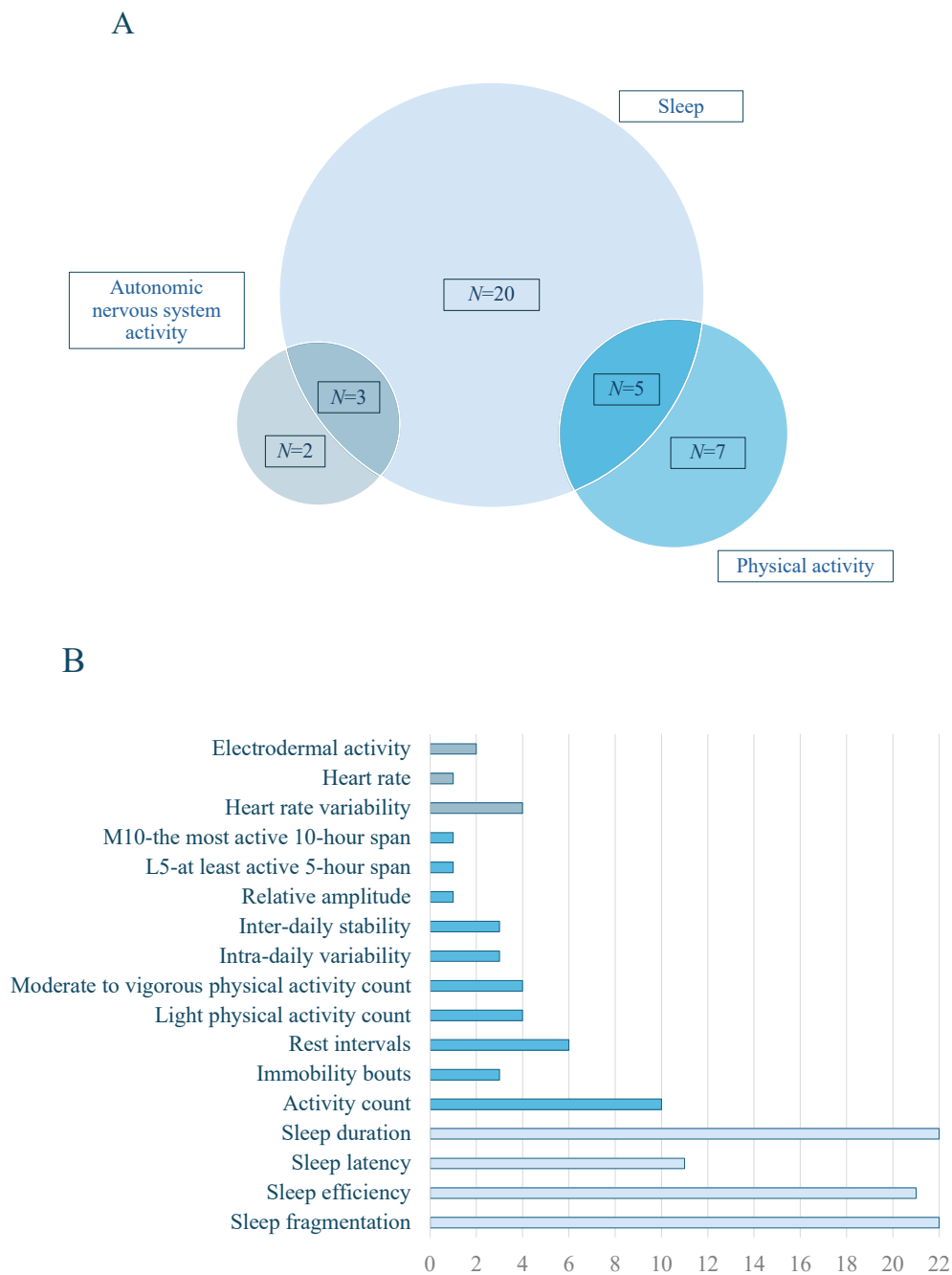


Fig. 13 – Objective outcomes (A) and variables (B) measured with wearable sensors in caregivers of people with dementia in the selected studies.

8.3.4 Sleep quality and quantity

Sleep quality and quantity were evaluated based on different outcome measures, such as sleep duration (22 studies), sleep efficiency (21 studies), sleep latency (11 studies), and sleep fragmentation (22 studies). These studies had variable aims, such as comparing people with dementia with their caregivers (4 studies), comparing caregivers with a non-caregiver control group (3 studies), and evaluating the effectiveness of interventions (8 studies).

The results of the studies that compared caregivers with non-caregivers were controversial. Rowe et al. found that caregivers had longer sleep latency, lower sleep duration and efficiency, and greater night-to-night sleep variability than non-caregivers [120]. In contrast, no significant differences were observed between caregivers and non-caregivers in other studies [121,122]. However, according to self-reported questionnaires on sleep quality and quantity, caregivers presented significantly worse sleep than non-caregivers [121,122].

The results of the studies assessing people with dementia and their caregivers highlighted poor sleep quality of both members of the caregiving dyad [123–126]. It is noteworthy to mention the finding of McCurry 2008 et al., wherein the adverse sleep outcome measures in one member of the caregiving dyad were not directly correlated with the evidence of sleep disruption in the other member [127].

Eight studies examined the efficacy of various interventions to enhance the sleep quality of caregivers. According to Akkerman & Ostwald, a cognitive-behavioral intervention for caregivers improved sleep duration and fragmentation [128]. Figueiro et al. showed that lighting improved caregivers' sleep duration and efficiency in winter compared to summer [129]. McCurry et al. found that a comprehensive sleep education program significantly improved sleep duration and fragmentation of caregivers [123]. No other intervention enhanced the sleep outcome measures in the other selected studies.

Two studies assessed the impact of respite care, which is temporary institutional care provided to people with dementia to alleviate the burden of their usual caregivers, on the sleep quality of caregivers [130,131]. Lee et al. conducted a sleep analysis before, during, and after two weeks of institutional respite care, evaluating sleep differences between caregivers who shared or did not share the bedroom with the care receiver. The sleep analysis revealed that non-sharer caregivers demonstrated the greatest improvement in sleep duration during respite, while sharer caregivers did not increase sleep duration [130]. In a study by Sakurai & Kohno, there was no

significant improvement in sleep outcome measures after one night of "short-stay services" respite care [131].

8.3.5 Physical activity

The caregivers' physical activity and rest-activity rhythm were evaluated in 12 studies based on different outcome measures, including activity counts, duration of the rest interval, number and duration of immobility bouts, intra-day variability, and inter-day stability of the rest-activity rhythm. The main objectives were to compare either people with dementia with caregivers or caregivers with non-caregivers and to evaluate the effectiveness of different interventions.

Similar rest-activity patterns [118] and similar levels of physical activity [132] were reported between caregivers and non-caregivers. According to Marquez et al., caregivers and non-caregivers only differed in the duration of light-intensity activity in the early morning, with caregivers appearing to be less active [132].

The included studies showed that caregivers were more active than people with dementia and that there was a positive association of physical activity within the dyad [118,133–135].

Two studies investigated the effectiveness of different interventions to improve physical activity and the rest-activity rhythm of caregivers but found no significant results [129,136].

Lastly, Merrilees et al. conducted a two-year monitoring of a caregiver, revealing a progressive decrease in activity counts, an increase in the duration of the rest interval, an increase in the number and duration of inactivity bouts, and a decrease in inter-day stability [133].

8.3.6 Autonomic nervous system activity

Five studies focused on evaluating the autonomic nervous system in caregivers, assessing heart rate, heart rate variability, electrodermal activity, and skin temperature.

Kajiwara et al. showed a significant increase in heart rate after vs. before caregiving [137]. Lai Kwan et al. evaluated an intelligent assistive technology for significant-moment detection (i.e., moments of significant interpersonal connection) based on heart rate variability, electrodermal activity, and skin temperature, in contrast to conventional subjective reports [138]. The intelligent assistive technology identified distinct and personal characteristics of physiological

reactivity in each participant, demonstrating that personalized algorithms can identify meaningful moments experienced by both dyad members with good agreement with subjective reports [138].

According to the research conducted by Sakurai et al., caregivers demonstrated a significantly higher level of sympathetic nervous system activity during sleep in comparison to non-caregivers despite the absence of any objective distinctions in the sleep measures [131]. However, this conclusion was based on higher values of the LF/HF index of heart rate variability, a disputed indirect index of cardiac sympathetic activity [139]. In a subsequent study by the same author, the LF/HF index was found to be significantly lower in caregivers on respite days than on caregiving days, but only during the first half of the sleep period [121].

8.3.7 Subjective outcome measures

A total of 15 studies assessed the potential correlation between objective measurements obtained through wearable sensors and subjective outcome measures related to the health and well-being of caregivers and people with dementia, including depression, anxiety, quality of life, and burden of care (Table 12).

Table 12 – Outcomes measured in the 15 studies assessed the potential correlation between objective measurements obtained through wearable sensors and subjective outcome measures related to the health and well-being of caregivers and people with dementia.

Authors	Study objectives	Caregiver		People with dementia	
		Objective outcomes measured with Wearable sensors		Subjective outcomes	
		Outcomes	Variables	Outcomes	Tools
McCurry et al. (2005)	Evaluating whether a sleep education program could improve sleep in people with dementia and their caregivers.	Sleep	SF, SE, SD –	–	Cognitive functioning. MMSE Depression CSDD

McCurry et al. (2008)	Measuring the day-to-day variation in sleep characteristics and the concordance between nighttime sleep of people with dementia and their family caregivers.	Sleep	SF, SE, SD	Depression Health status Other	CES-D SF-36 DMSS	Cognitive functioning Depression	MMSE CSDD
Beaudreau et al. (2008)	Measuring whether distress and disease burden were associated with objective measures of sleep disturbance in caregivers.	Sleep	SF, SE, SL, SD	Depression Health status	BDI 1 item from MOS short-form general health survey	Cognitive functioning Nighttime behavior	MMSE 1 item from RMBPC
Merrilees et al. (2013)	Measuring daytime activity in people with dementia and their caregivers.	PA	AC, IB	–	–	Apathy	NPI
von Känel et al. (2014)	Measuring the relationship between positive affect and sleep in caregivers.	Sleep	SF, SE, SD	Affect	PANAS BPSD		RMBPC
D'Aoust et al. (2015)	In caregiver of people with dementia, measuring a set of factors that are modifiable and associated with high levels of depression in other population and determining whether these factors are predictive of depression after controlling for non-modifiable, demographic, and clinical factors.	Sleep	SF, SE, SL, SD	Depression Burden Affect	CES-D ZBI PANAS	–	–

Sakurai et al. (2015)	Measuring autonomic nervous system activity and quality of sleep in caregivers and non-caregivers.	Sleep ANS	SF, SE, SL, SD HRV	Stress	Visual analog BPSD scale	DBDS
McCrae et al. (2016)	Measuring sleep and affect association in caregivers	Sleep	SF	Affect	PANAS –	–
Smagula et al. (2017)	Measuring the associations of sleep with non-sleep depression symptom severity among strained caregivers who were currently without clinical depression.	Sleep	SF SD	Depression	HRSD –	–
Peng et al. (2019)	Measuring factors associated with caregivers' sleep.	Sleep	SF, SE, SL, SD	Sleep Depression Burden Health status	SHI CES-D CBI CIRS Sleep	SDI
Kajiwara et al. (2019)	Measuring the relationship between caregiver burden and caregiver pulse rate.	ANS	HR	Burden	ZBI –	–
Chang et al. (2020)	Measuring factors associated with fatigue among caregivers of people with dementia.	Sleep	SF, SE, SL, SD	Fatigue	VAS-F–	–
Song et al. (2022)	Measuring the discrepancy between self-reported and objective SD, considering the role of caregiving status (caregivers vs non-caregivers).	Sleep	SD	Depression Affect	CES-D PANAS –	–

Chen et al. (2022)	Measuring how linkage in couples' daily somatic activity (e.g., synchronized movement measured from wrist sensors) was associated with relationship quality and mental health in caregivers and people with dementia.	PA	AC, RI	Anxiety Depression Relationship quality	BAI CES-D – MAT	–
Smagula et al. (2023)	Measuring how levels of PA throughout the day differed in caregivers with and without depression symptoms and testing whether such differences predicted changes in symptoms 6 months later.	Sleep PA	SF AC, RI	Depression	PHQ-9 CES-D	–

Abbreviations: PA: physical activity; AC: activity counts; IB: immobility bouts; RI: rest interval; SF: sleep fragmentation; SE: sleep efficiency; SL: sleep latency; SD: sleep duration; LPA: light physical activity counts; MVPA: moderate to vigorous physical activity counts; HRV: heart rate variability; HR: heart rate; EDA: electrodermal activity; IS: inter-day stability; IV: inter-day variability; ANS: autonomic nervous system; BPSD: Behaviour and Psychological Symptoms of Dementia scale; NPI: Neuropsychiatric Inventory; BAI: Beck Anxiety Inventory; CES-D: Center for Epidemiological Studies Depression scale; HRSD: Hamilton Rating Scale for Depression MMSE: Mini Mental State Examination RMBPC: Revised Memory and Behavior Problem Checklist; CIRS: Cumulative Illness Rating Scale; PANAS: Positive and Negative Affect Schedule; ESS: Epworth Sleepiness Scale; VAS-F: Visual Analog Scale for Fatigue; PSQI: Pittsburgh Sleep Quality Index; CSDD: Cornell Scale for Depression in Dementia; SF-36: SF-36 Health Survey; DMSS: Dementia Management Strategies Scale; BDI: Beck Depression Inventory; MAT: Marital Adjustment Test; MOS: Medical Outcomes Study; CBI: Caregiver Burden Inventory; SDI: Sleep Disorder Inventory; SHI: Sleep Hygiene Index.
– not defined

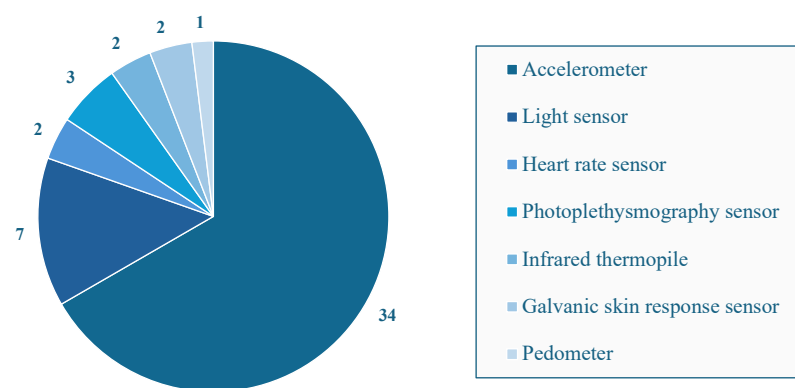
Depressive symptoms among caregivers were associated with lower SE [140,141], greater SF [119,142], and longer SL [141]. In contrast, no significant correlation was found between objective sleep measures and depression in the study by D'Aoust et al. Moreover, longer SL was associated with a more significant burden of care and fatigue perceived by caregivers [141,143], and lower SE was associated with a more significant burden of care and poorer self-rated health status [141,143]. No significant correlation was reported between caregivers' objective sleep measures and positive or negative affect measures. Lastly, Chen et al. related caregivers' anxiety with the physical activity of the dyad, reporting that a lower in-phase physical activity linkage between caregivers and non-caregivers was associated with greater caregiver anxiety.

8.3.8 Feasibility and acceptability of wearable sensors

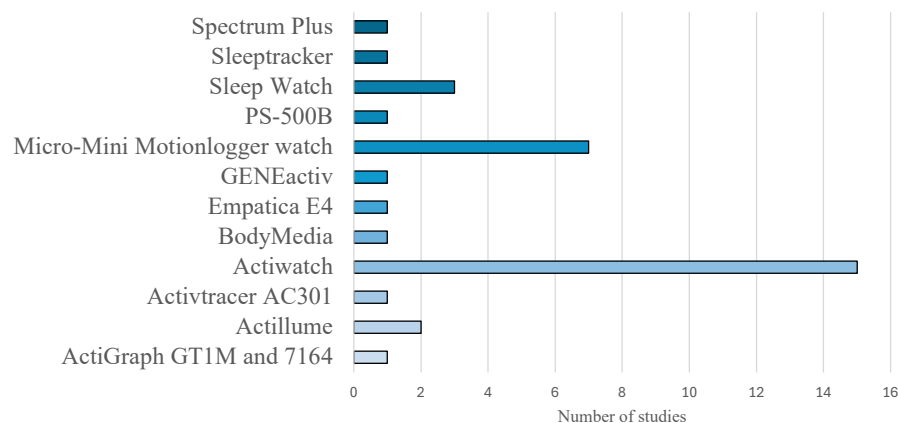
Only two studies have provided information regarding the acceptability of wearable sensors, and they have yielded a satisfactory acceptance rate among caregivers [125,144]. It is worth mentioning that these studies are quite old, and that the form factor and usability of wearable sensors largely increased since then.

Figure 14 shows information on the wearable sensors used in the selected studies, i.e., the type of sensors, the actigraphy devices used, the sensor placement locations, and the length of the recordings.

A



B



C

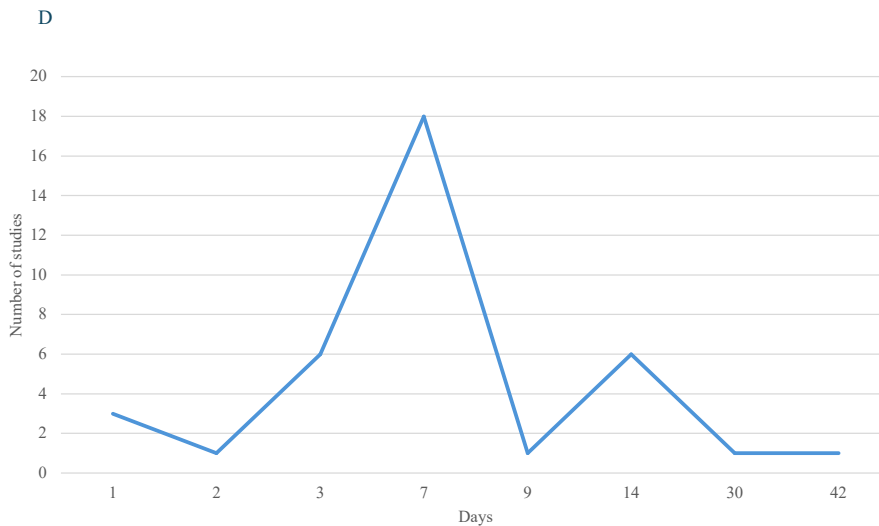
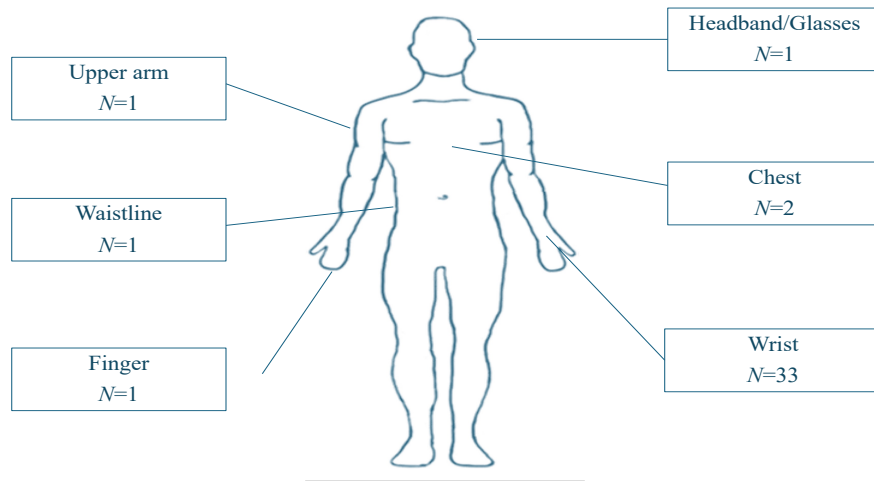


Fig. 14– Information on the wearable sensors used in the selected studies on caregivers of people with dementia, i.e. the type of sensors (A), the actigraphy devices used in the studies (B), the sensor placement locations (C), and the length of the recordings (D).

In Table 13 are summarized the information on the wearable sensors used in the selected studies. A single device was used in 34 studies, with the wrist being the most common sensor placement location (33 studies), in particular at the non-dominant wrist (16 studies). Caregivers were monitored for one or more weeks in 27 studies, particularly for one week in 18 studies, 9 days in one study, two weeks in 6 studies, and more than two weeks in two studies. Among the most used actigraphy devices, the Actiwatch (Philips Respironics, Murrysville, PA, USA) was

selected in 15 studies, while the Micro-Mini Motionlogger watch (Ambulatory Monitoring Inc., Ardsley, NY, USA) was selected in 7 studies.

Table 13 – Information on the wearable sensors used in the selected studies.

Authors	Year	Type of sensors	Device*	Site	Duration of the recording
Pollak & Stokes	1997	Accelerometer	Micro-Mini Motionlogger (Ambulatory Monitoring Inc., Ardsley, NY, USA)	Wrist (non-dominant)	9 days
Akkerman & Ostwald	2004	–	–	Wrist (–)	48 hours
Ancoli-Israel et al.	2005	Accelerometer	Actiwatch (Mini Mitter Co, Inc; Bend, OR, USA)	Wrist (–)	7 days [#]
McCurry et al.	2005	Accelerometer	Actillum (Ambulatory Monitoring, Inc., Ardsley, NY, USA)	Wrist (–)	7 days [#]
Lee et al.	2007	Accelerometer	Actiwatch (Mini Mitter Co, Inc; Bend, OR, USA)	Wrist (–)	6 weeks
McCurry et al.	2008	Accelerometer	Actillum (Ambulatory Monitoring, Inc., Ardsley, NY, USA)	Wrist (–)	7 days
Rowe et al.	2008	Accelerometer	Actiwatch (Mini Mitter Co, Inc; Bend, OR, USA)	Wrist (non-dominant)	7 days
Beaudreau et al.	2008	Accelerometer	Micro-Mini Motionlogger (Ambulatory Monitoring Inc., Ardsley, NY, USA)	Wrist (non-dominant)	72 hours
Merrilees et al.	2009	Accelerometer	Actiwatch (Mini Mitter Co, Inc; Bend, OR, USA)	Wrist (non-dominant)	14 days [#]

Simpson & Carter	2010	Accelerometer	Micro-Mini Motionlogger (Ambulatory Monitoring Inc., Ardsley, NY, USA)	Wrist (dominant)	72 hours [#]
Higgins et al.	2010	- Accelerometer - Light sensor	- Sleepwatch-L (Ambulatory Monitoring Inc., Ardsley, NY, USA) - Daysimeter (–)	- Wrist (–) - Attached to a headband or glasses	7 days
Rowe et al.	2010	- Accelerometer - Light sensor	ActiWatch L (Philips Respironics, Murrysville, PA, USA)	Wrist (–)	7 days
Marquez et al.	2012	Accelerometer	ActiGraph GT1M and 7164 (Actigraph, Pensacola, FL, USA),	Waistline	7 days
Merrilees et al.	2013	Accelerometer	ActiWatch (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	7 days
Schwartz et al.	2013	Accelerometer	ActiWatch L (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	72 hours
Merrilees et al.	2014	Accelerometer	Sleep Watch (Ambulatory Monitoring, Inc., Ardsley, NY, USA)	Wrist (non-dominant)	72 hours
von Känel et al.	2014	Accelerometer	ActiWatch (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	14 days
D'Aoust et al.	2015	- Accelerometer - Light sensor	ActiWatch L (Philips Respironics, Murrysville, PA, USA)	Wrist (–)	7 days
Sakurai et al.	2015	- Accelerometer - Heart rate monitor	- Micro Motionlogger watch (Ambulatory Monitoring, Inc., Ardsley, NY, USA) - Activtracer AC301 (GMS Inc., Tokyo, Japan)	- Wrist (non-dominant) –	24 hours
Figueiro et al.	2015	- Accelerometer - Light sensor	- Motionlogger watch (Ambulatory Monitoring, Inc., Ardsley, NY, USA) - Daysimeter (–)	- Wrist (–) - Worn as a pendant at chest length	7 days

McCrae et al.	2016	• Accelerometer • Light sensor	ActiWatch L (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	7 days
Fowler et al.	2016	Accelerometer	Sleeptracker (Innovative Sleep Solutions, Atlanta, GA, USA)	Wrist (-)	14 days [#]
Smagula et al.	2017	Accelerometer	ActiWatch 2 (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	14 days
Peng et al.	2019	Accelerometer	ActiWatch 2 (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	7 days
Gibson & Gander	2019	• Accelerometer • Light sensor	ActiWatch 2 (Philips Respironics, Murrysville, PA, USA)	Wrist (non-dominant)	7 days
Sadeghi et al.	2019	• PPG sensor • Accelerometer • Infrared Thermopile • GSR sensor	Empatica E4 (Empatica inc., Cambridge, MA, USA)	Wrist (-)	14 days (nighttime)
Kajiware et al.	2019	• PPG sensor, • Accelerometer	PS-500B (Seiko Epson Co. Ltd., Nagano, Japan)	Wrist (-)	72 hours
Lai Kwan et al.	2019	• PPG sensor • Infrared Thermopile • GSR sensor	eVu-TPS (Thought Tech Ltd, Montreal, Canada)	Finger	45 minutes [#]
Sakurai & Kohno	2020	• Accelerometer • Heart rate sensor	Micro Motionlogger watch (Ambulatory Monitoring, Inc., Ardsley, NY, USA) WHS-1 (Union Tool Co., Tokyo, Japan)	Wrist (-) Chest	12 hours (nighttime)
Chang et al.	2020	Accelerometer	ActiWatch 2 (Philips Respironics, Murrysville, PA, USA)	Wrist (-)	7 days

Carpenter et al.	2020	Accelerometer	BodyMedia (Sensewear, Pittsburgh, PA, USA)	Upper Arm	7 days
Song et al.	2022	Accelerometer	Sleep Watch (Ambulatory Monitoring, Inc., Ardsley, NY, USA)	Wrist (non- dominant)	72 hours
Chen et al.	2022	• Accelerometer • Light sensor	ActiWatch 2 (Philips Respironics, Murrysville, PA, USA)	Wrist (non- dominant)	7 days
Smagula et al.	2023	Accelerometer	Spectrum Plus (Philips Respironics, Murrysville, PA, USA)	Wrist (non- dominant)	14 days
de Dios-Rodríguez et al.	2023	Pedometer	HJ-321 (Omron Healthcare Inc., Lake Forest, IL, USA)	–	7 days
Farina et al.	2024	Accelerometer	GENEactiv (Activinsights Ltd., Cambridgeshire, UK)	Wrist (–)	30 days
Song et al.	2024	Accelerometer	Micro Motionlogger watch (Ambulatory Monitoring, Inc., Ardsley, NY, USA)	Wrist (–)	7 days

Abbreviations: PPG: Photoplethysmography; GSR: Galvanic skin response.

* some devices are multiple sensor systems; here are only the types of sensors used in the selected study.

studies in which multiple separate sessions of recording have been repeated over time according to the different study protocols.

– not defined

8.5 Discussion

The application of wearable sensors to caregivers of people with dementia has never been directly assessed with a critical review of the published literature. Only two reviews in the scientific literature marginally address this topic [112,113]. Gao et al. published a systematic review with a meta-analysis of the sleep quantity and quality of caregivers of people with dementia [112]. However, most included studies assessed sleep using subjective measures, such as self-reported questionnaires, with only 9 studies focusing on outcomes derived from wearable sensors. More recently, Mattos et al. evaluated the relationship between care burden

and sleep quantity and quality in caregivers of people with dementia with a scoping review, but only 4 of the included studies evaluated outcomes measured with wearable sensors [113].

This scoping review provides the first comprehensive map of the published evidence on the use of wearable sensors in caregivers of people with dementia. We identified and selected 37 reports, which largely exceeds the number of reports on wearable sensors discussed in previous reviews that marginally addressed this topic. Sleep measures were the most frequently evaluated outcomes (28/37). Eight reports assessed the effectiveness of different interventions targeting both caregivers and care receivers and found no improvement in caregivers' sleep; 3 compared the sleep of caregivers of people with dementia with controls, with conflicting results; 5 focused on depressive symptoms; and 4 associated these symptoms with shorter sleep duration and greater sleep fragmentation and sleep latency. Physical activity was evaluated in 12 reports, again with conflicting results. A single device was used in 34 reports, and sensors were most commonly placed at the wrist (33/37). Most studies monitored caregivers for one or more weeks (27/37). No studies were conducted on formal caregivers.

For caregivers of people with dementia, the potential applications of wearable sensors remain incompletely explored, with significant gaps in our understanding due to limitations of the available evidence. It is still unclear whether information obtained with wearable sensors may help predict and prevent burnout and adverse health effects due to the care burden in caregivers of people with dementia and ameliorate the disease trajectory of their care-receivers.

More studies are needed with specific study designs (caregivers vs. non-caregivers and pre- vs. post-interventions) and including formal caregivers. Specific research on the potential of multi-wearable sensor systems, including > 1 sensor sites and ANS metrics, is warranted in caregivers of people with dementia. Finally, although the limited available evidence on the feasibility and acceptability of wearable sensors in this specific population is promising, it needs to be confirmed, and more diverse samples, including as a function of formal/informal caregiving, age, gender, and sensor location.

9. STUDY IV

9.1 Specific aim

Although there have been reports suggesting connections between gastrointestinal symptoms and sleep disorders, there remains limited understanding of how these two factors are interrelated with frailty, particularly in older adults. Additionally, the influence of age and gender on these associations has not been extensively studied, leaving important gaps in our knowledge regarding how these variables interact and potentially contribute to the development of frailty over time.

The aim of this specific analysis of the ongoing FRaiLty study was to obtain exploratory results on the associations between sleep symptoms and gastrointestinal in pre-frail and frail hospitalized middle aged and healthy older adults with low comorbidities and cognitive impairment.

9.2 Materials and methods

9.2.1 Study design and setting

The ongoing prospective FRaiLty study enrolls adults acutely hospitalized at the Internal Medicine Hospital Units of the Ravenna District, Italy. The enrolment started in May 2023 and will last up to December 2026. The study was approved by the Ethical Committee of the Emilia-Romagna Region (CEROM, number of approval 3124/2022).

9.2.2 Participants to the FRaiLty study

Patients are considered eligible for the study if admitted to the Internal Medicine Unit within 48 hours the date of enrolment.

The exclusion criteria of this ongoing study are age < 18 years and history of moderate/severe cognitive impairment.

9.2.3 Variables and data sources

Patients are evaluated twice, at the admission (t0) and discharge (t1).

At t0 the following data are collected:

- demographic characteristics;
- psychological and social assessment (e.g. marital status, education, presence/absence of caregiver, loneliness and social connection);
- admission main diagnosis, coded in accordance with the ICD-10;
- history of cognitive impairment;
- drugs before admission, coded according to the first and second level of the Anatomical Therapeutic Chemical (ATC) classification;
- chronic diseases, sorted into 60 chronic disease categories in accordance with a clinically driven methodology [145];
- comorbidity rating, by using the CIRS and Barthel index;
- chronic organ failure prognostic scores, i.e. the Child-Pugh score for patients with cirrhosis, creatinine clearance for patients with renal failure, the New York Heart Association (NYHA) functional classification for patients with chronic heart failure, the Global Initiative for Obstructive Lung Disease (GOLD) classification for patients with Chronic obstructive pulmonary disease (COPD);
- nutritional assessment using the Malnutrition Universal Screening Tool (MUST) Weight assessment at admission
- dysphagia assessment using the EAT-10 questionnaire.
- frailty assessment according to Fried phenotype score and to the Frailty Index.
- muscle strength assessment at admission, using the hand-grip strength test (HGS).
- sleep disorders assessment using the PSQI and ESS.
- gastrointestinal symptoms assessment by using the GSRS.

At t1 the study provides the evaluation of intercurrent clinical events, as well as reassessment of weight and HGS at discharge.

Lastly, drugs are reassessed upon discharge, in order to obtain specific data on prescribing/deprescribing.

9.2.4 Statistical analysis

Baseline characteristics of participants were reported using numbers and percentages for categorical variables, and either mean and SD or median and IQR for continuous variables. To compare the characteristics by Fried frailty score (FFS), appropriate statistical tests such as the

Chi-square test for categorical variables and independent *t*-test for continuous variables were performed. The Spearman's rho was used to determine associations.

9.3 Results

To the purpose of this analysis, 83 in-patients with available data on GSRS, ESS and PSQI were evaluated. To avoid statistical noise, we excluded the patients with a FFS=0 (6/83). The remaining 77 patients were categorized as pre-frail (FFS=1-2) or frail (FFS=3-5) and evaluated.

The characteristics of the study population by Fried category are presented in Table 14.

Table 14 – Descriptive characteristics of the study population by Fried Frailty score

	Total	pre-Frail	Frail	p-value
	N=77	N=39	N=38	
Sex (female), <i>n</i> (%)	38 (49%)	16 (41%)	22 (58%)	0.14
Age (years), mean (SD)	71.7 (13.4)	70.8 (11.9)	72.7 (14.9)	0.54
Length of hospital stay (days), mean (SD)	8.6 (4.7)	7.4 (3.8)	9.8 (5.2)	0.023
CIRS, mean (SD)	7.8 (5.0)	6.7 (4.3)	8.9 (5.6)	0.061
MMSE, mean (SD)	27.8 (8.9)	27.6 (2.7)	28.0 (12.5)	0.85
GDS, mean (SD)	9.1 (6.3)	7.7 (6.5)	10.4 (5.8)	0.057
Impaired gait speed, <i>n</i> (%)	32 (42%)	10 (26%)	22 (58%)	0.004
Impaired grip strength (kg), <i>n</i> (%)	30 (39%)	10 (26%)	20 (53%)	0.015
Weight loss of at least 1 kg in the last 3 months, <i>n</i> (%)	31 (40%)	5 (13%)	26 (68%)	<0.001
Fatigue in the last three months, <i>n</i> (%)	61 (79%)	24 (62%)	37 (97%)	<0.001
Physical activity less than 2-3 times/month, <i>n</i> (%)	47 (61%)	14 (36%)	33 (87%)	<0.001
SARC-F, mean (SD)	3.3 (3.0)	1.9 (1.8)	4.7 (3.3)	<0.001
At least one fall in the last year	32 (42%)	14 (36%)	18 (47%)	0.31

SD: standard deviation; CIRS: cumulative illness rating scale; MMSE: mini mental state examination; GDS: geriatric depression scale;; SARC-F: sarcopenia finding tool.

The median values of GSRS, ESS, and PSQI according to the FFS are depicted in Figure 15.

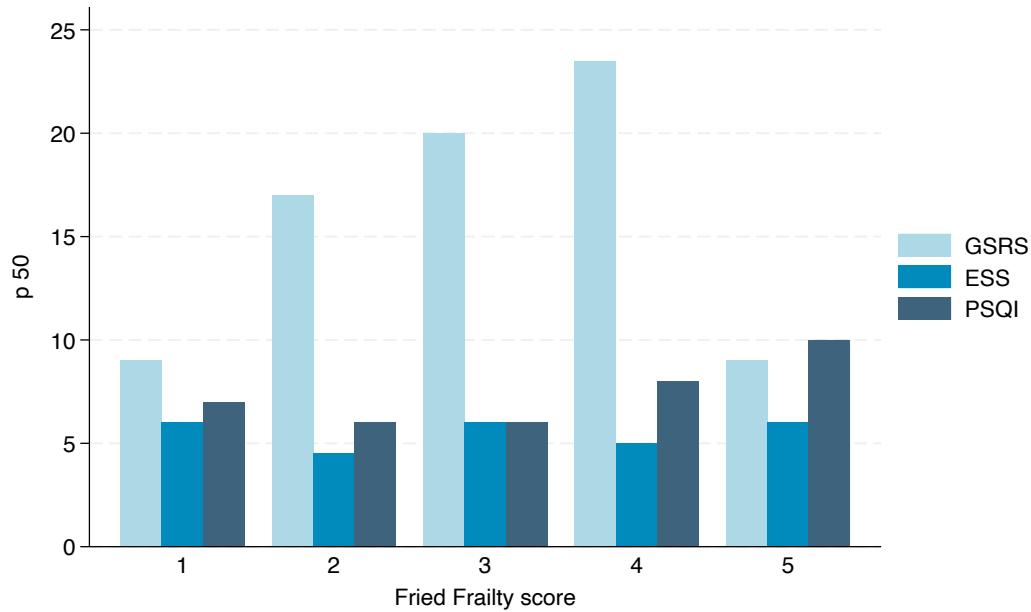


Fig. 15 – Median values of GSRS, ESS, and PSQI according to the FFS

The median values of the FFS in patients aged over and above 65 are depicted in Figure 16.

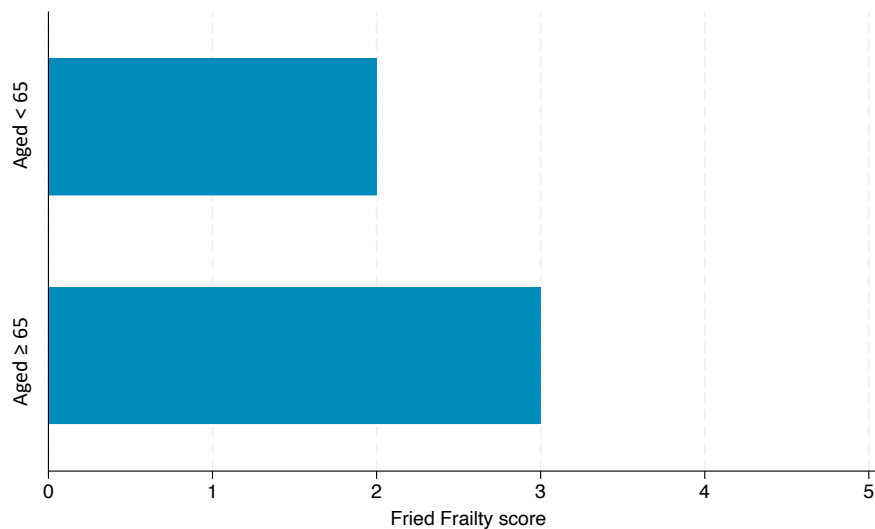


Fig. 16 – Median values of the Fried frailty score in middle-aged individuals vs older adults.

As concerns the specific aim of this preliminary analysis, i.e. the evaluation of any associations between gastrointestinal and sleep symptoms according to frailty, a significant positive correlations between FFS and PSQI ($\rho=0.244$; $p=0.034$), and between GSRS and either PSQI ($\rho=0.336$; $p=0.003$) or ESS ($\rho=0.323$; $p=0.004$) were found. Sub-group analyses were

conducted dividing patients according to FFS (pre-frail vs. frail), age (under vs. above the median age), and gender. The positive correlation between PSQI and FFS was confirmed in frail patients ($\rho=0.441$; $p=0.006$). Positive correlations between GSRS and PSQI were confirmed in pre-frail ($\rho=0.349$; $p=0.030$), younger ($\rho=0.353$; $p=0.029$), and female patients ($\rho=0.327$; $p=0.048$). Positive correlations between GSRS and ESS were confirmed in pre-frail ($\rho=0.389$; $p=0.014$), older ($\rho=0.417$; $p=0.009$), and male ($\rho=0.419$; $p=0.008$) patients.

9.4 Discussion

The aim of this specific analysis conducted on the ongoing FRaiLty study was to obtain exploratory results on the associations between frailty, sleep disorders, and gastrointestinal symptoms in hospitalized individuals. The study population consists of individuals with low burden of chronic diseases and with low degree of cognitive impairment. Nevertheless, the percentage of individuals that score zero to the FFS is very low (7%), with both pre-frail and frail status well represented in the sample. Interestingly, after dividing the sample in middle-aged and older adults, the median values of the FFS did not differ a lot between the two groups. This finding confirms the necessity to assess the “hidden” frailty also in middle-aged healthy individuals. Although the results did not reach the statistical significance, likely due to sample size, it is interesting that depressive symptoms and accidental falls occurred frequently in these healthy individuals. As concerns the relationship between gastrointestinal symptoms, sleep, and frailty, these preliminary results suggest different associations according to frailty degree, sex, and age among hospitalized older adults. However, these observations remain preliminary. As the FRaiLty study is still in progress and has not yet reached its full sample size, these initial trends must be interpreted with caution. More comprehensive data collection and detailed analyses are necessary to further investigate and potentially confirm these associations. A larger sample size will provide greater statistical power, ensuring that the relationships observed are robust and not due to chance.

10. STUDY V

10.1 Specific aim

The global population is rapidly aging, mainly due to the increasing life expectancy among older adults [146]. Although a longer life can be considered a valuable resource, the opportunities it offers depend significantly on how individuals age healthily. While physical function progressively declines with age [147], the heterogeneity in physical function trajectories can lead to widely varying patterns of aging, ranging from accelerated to successful aging [148,149]. Indeed, the World Health Organization (WHO) defined healthy aging as “the process of developing and maintaining the functional ability that enables wellbeing in older age” [146]. Functional ability, according to WHO, is primarily determined by the combination of both cognitive and physical functions [146], two broad and complex dimensions closely and bidirectionally related [19,150,151]. Indeed, cognitive impairment has been shown to predict decline in physical function [152] and, viceversa, decline in physical function has been shown to be a relevant markers of prodromal dementia [153]. Although, the exact mechanisms underlying this bidirectional relationship have not yet been fully described, they have been partially attributed to specific brain networks, such as the prefronto-parietal and cingulate areas, that are commonly affected by diseases that accompany aging [151]. Moreover, it has been shown that physical function is the most valued by older people when it comes to preservation of functional ability.

Objective measures of physical performance have widely shown higher sensitivity in detecting functional decline than the self-reported measures, e.g. the indexes for Activities of Daily Living (ADL). Several tests objectively assess physical performance, mainly involving the evaluation of two domains, i.e. mobility and strength [14]. Walking speed is a reliable measure of mobility, widely used not only in geriatric care settings, that has been associated with several clinical outcomes, e.g. hospitalizations, falls, and death [154,155]. The repeated chair stands test is considered a reliable tool to assess both mobility and strength limitation, as it can be also used as a proxy for strength of leg muscles [156,157]. Chair stands test has been identified as an independent predictor of survival in older adults [158].

Chronic diseases have shown to impact physical performance [159]. This is especially true in presence of multimorbidity, i.e. the co-occurrence of multiple chronic diseases within the same individual [18], whose prevalence is sharply increasing, mainly due to longer survival of

individuals with chronic conditions [160]. Yet, most of the previous evidence on how chronic diseases impact physical performance have focused on single diseases [159]. Multimorbidity can be defined in terms of chronic disease counts or clustering individuals by pattern of diseases, i.e. finding systematic associations amongst diseases based on expert criteria or statistical association [21]. This operational definition of multimorbidity is grounded on the principle that certain diseases share common risk factors and pathophysiological pathways, enabling the identification of groups of individuals who may benefit from targeted interventions, including strategies to prevent the decline of physical performance [145].

However, few studies have explored the long-term impact of multimorbidity patterns on physical performance [19,161]. Therefore, the aim of this project was to explore the association between different multimorbidity patterns and physical performance by examining their longitudinal trajectories over 15 years in a community-based cohort of older adults.

10.2 Materials and methods

10.2.1 Study population

Data were gathered from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), an ongoing prospective study that involves adults aged 60 years or older, residing in the Kungsholmen district of Stockholm, Sweden. SNAC-K was approved by the Regional Ethical Review Board in Stockholm, and all participants or next of kin (for cognitively impaired individuals) provided written informed consent. The baseline (2001-2004) of the study involved 3363 individuals from 11 age cohorts (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, 99+ years), who were followed up every 6 years (< 78 years old) or 3 years (≥ 78 years old) (Figure 17). The present study included data from the baseline wave to the fifth follow-up wave, spanning from 2001 to 2019. From the initial cohort, we excluded individuals with clinical diagnosis of dementia at baseline ($n = 241$), resulting in an analytical sample of 3112. At each study wave, SNAC-K participants underwent a comprehensive clinical and functional assessment carried out by trained physicians, nurses, and neuropsychologists. Consistent protocols were followed across all study waves to ensure data collection uniformity. In cases of inability to attend the visit site, home visits were arranged.

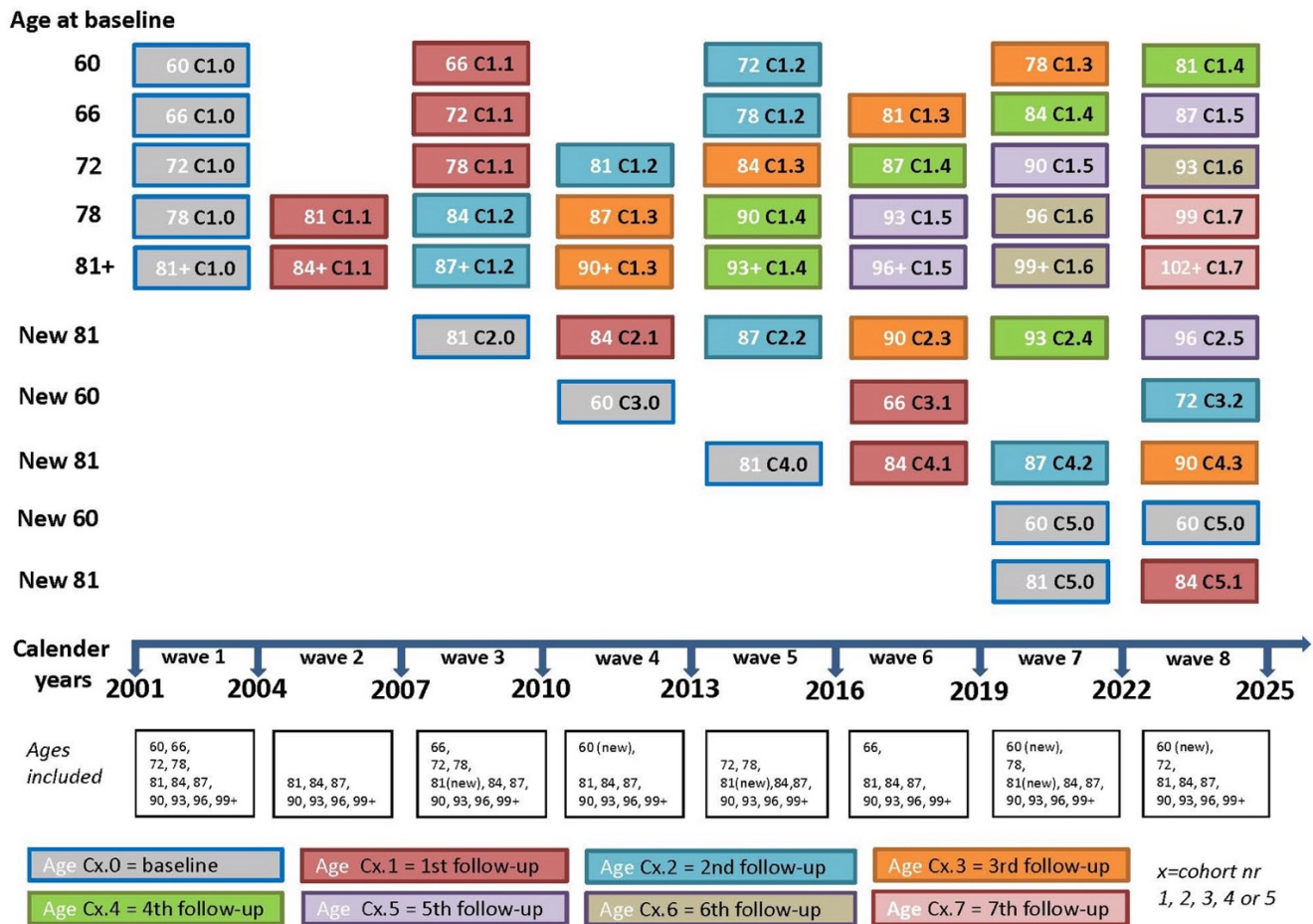


Fig. 17 – Study design and population age structure of the SNAC-K study. The number in the box represents the specific age cohort, while the color reflects the number of follow-up examination for each age cohort.

10.2.2 Assessment of physical performance

In SNAC-K, physical performance was objectively assessed through an extensive physical performance battery, which included the walking speed test [155], and the chair stand test [162]. The walking speed test was timed as participants walked 6 meters (m), or 2.4 m for those who considered themselves slow walkers. Participants missing the walking speed test were classified as slow walkers if they: 1) could not stand up or walk without assistance; 2) used a wheelchair; 3) could not move around without assistance; 4) or could not walk 100–200 meters without great difficulty. A value of 0 s was assigned to participants unable to perform the test due to physical limitations. For this study, impaired tests were defined as walking speed resulted ≤ 0.8 m/s, according to previously defined cutoffs [157].

The chair stand test assessed the time it took for the participant to stand up from a chair five times consecutively as quickly as possible [162]. The test was measured in seconds, with shorter time indicating greater lower limb muscle strength. A value of 52 s, the worst value recorded in our study population, was assigned to participants unable to perform the test due to physical limitations. For the present study, the cutoff to identify impairment in chair stand test was set at 15 s, based on previous research [157].

10.2.3 Multimorbidity assessment

Physicians collected information on diagnoses via physical examination, medical history, examination of medical charts, self-reported information, and/or proxy interviews. Clinical parameters, laboratory tests, drug information, and inpatient and outpatient care data were also used to identify specific conditions. All diagnoses were coded following the International Classification of Diseases 10th revision (ICD-10). For this study, 60 chronic disease categories based on clinically driven operationalization of 918 ICD-10 codes were used to derive data-driven multimorbidity patterns (see Statistical analyses for details) [20,163,164].

10.2.4 Vital status, loss to follow-up and other variables

Information about vital status was derived from death certificates provided by Statistics Sweden, the Swedish governmental statistics agency. Survival status was assessed throughout the follow-up period. Participants were considered lost to follow up if they or a proxy declined to participate, could not be contacted, had moved out of the study area, or canceled an assessment. Several personal, lifestyle, and anthropometric data were measured at baseline during the nurse interview, including age, sex, education (elementary school, high school, and university or above), smoking status (never, former, or current smoker), alcohol intake (no or occasional, light to moderate, and heavy), and body mass index (BMI). In SNAC-K drugs are coded in accordance with the Anatomical Therapeutic Chemical classification. The MMSE was used as a measure of global cognition at baseline.

10.2.5 Statistical analysis

Baseline characteristics of participants were reported using numbers and percentages for categorical variables, and either mean and standard deviation (SD) or median and interquartile

range (IQR) for continuous variables. To compare the baseline characteristics of each multimorbidity pattern, appropriate statistical tests such as the Chi-square test for categorical variables and ANOVA for continuous variables were performed.

The identification of groups of individuals with similar diseases patterns at baseline was carried out through latent class analysis (LCA). For this analysis, out of the previously mentioned 60 chronic disease categories, only those with a prevalence $>2\%$ in the study population were considered, to reduce statistical noise. The optimal number of latent classes was detected by comparing the Bayesian Information Criterion (BIC) and the adjusted BIC of different models, where the lowest values indicate the highest data fitness. The latent classes identified were named based on the observed/expected (O/E) ratios of diseases and by comparing the frequency of chronic conditions in each class with that in the study population. Disease exclusivity was computed as the ratio between the number of disease cases in a class and the total number of individuals with that disease in the population. A chronic disease with an exclusivity $\geq 25\%$ and an O/E ratio ≥ 2 was considered to characterize a given pattern. Linear mixed models with random intercept and random slope were used to assess the association between baseline multimorbidity patterns and changes in physical performance test over time. Follow-up time was used as a timescale. The multimorbidity patterns at baseline were the exposures, while the reference group was the group of individuals without multimorbidity for the main analysis, and individuals grouped in the Unspecific pattern for a secondary analysis. An interaction term between multimorbidity patterns and time (in years) was introduced to estimate the average annual decrease in physical function of a given pattern compared to the reference group. The physical performance test was employed as continuous variables and further z-scored to enable standardized comparisons. A combined measure of physical function was derived by the mean of z-scores and used as the main outcome. All the analysis were adjusted for baseline age, sex, and education. Inverse probability weights (IPW) were used to account for the effect of censoring due to death or drop-out through different multimorbidity patterns. IPW were derived by modeling the probability of death and drop-out given the individuals baseline characteristics, i.e. age, sex, education, MMSE, alcohol behavior, smoking habit, activities of daily living (ADL) index, chronic disease count, and follow-up time (computed as the time between the baseline evaluation date and either death or the end of follow-up, whichever came first). Stratified were conducted to investigate potential effect modifiers , i.e. age and sex. Sensitivity analyses were performed to assess the robustness of the findings after 1) excluding individuals with less than two measures of physical performance tests during follow-up (n=854), and 2) further adjusting for number of chronic diseases. Statistical analyses were

carried out with STATA 18.0 (Stata Corp., College Station, TX, USA), and R: A language and environment for statistical computing, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) by using the poLCA package for the LCA. In all analyses, a p-value <0.05 was considered statistically significant.

10.3 Results

10.3.1 Multimorbidity pattern characterization

The analytical sample comprised 3112 dementia-free individuals from Swedish National study on Aging and Care in Kungsholmen (SNAC-K), with mean age 73.5 ($\pm$ 10.7) and 63.3% female participants.

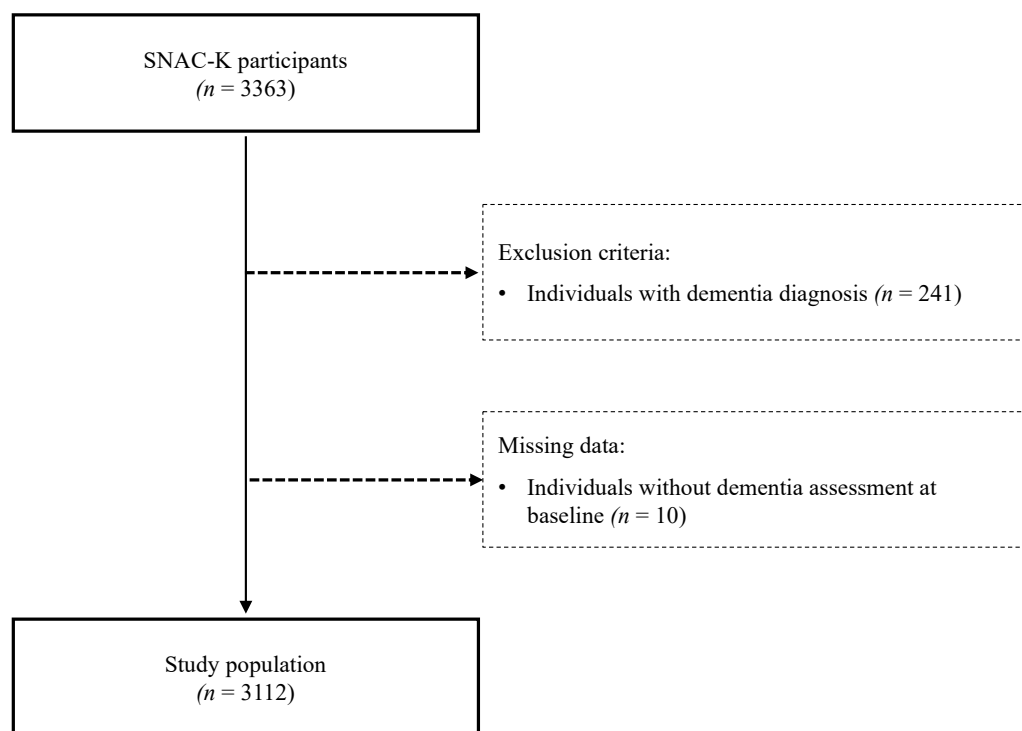


Fig. 18 – Study population definition flow-chart

After applying latent class analysis to classify participants according to their chronic diseases, four multimorbidity patterns were detected: 1) Psychiatric, respiratory, & musculoskeletal (n=482), 2) Anemia & sensory impairment (n=609), 3) Cardiometabolic & inflammatory (n=354), and 4) Unspecific (n= 1246), a pattern where nonspecific chronic conditions were

over-represented (Table 15). The remaining 421 participants had one or no chronic diseases, i.e., no multimorbidity.

Table 15. Characterizing diseases with prevalence over 20% within each multimorbidity pattern.

Multimorbidity pattern	Characterizing chronic diseases	Prevalence within the pattern (%)
Unspecific	-	-
Psychiatric, respiratory & MSK	Depression mood disease	36
	Colitis related disease	26
	Asthma	24
	Thyroid disease	24
Anemia & sensory impairment	Anemia	31
	Deafness hearing loss	27
	Cataract lens disease	21
	Glaucoma	20
Cardiometabolic & inflammatory	Heart failure	75
	Ischemic heart disease	55
	Atrial fibrillation	45
	Anemia	32
	Diabetes	23
	Cerebrovascular disease	21

Chronic diseases with observed/expected ratio ≥ 2 and exclusivity $>25\%$. MSK: musculoskeletal; COPD: chronic obstructive pulmonary disease

The baseline descriptive characteristics of the study population according to the specific disease pattern are presented in Table 16.

Table 16. Baseline descriptive characteristics of the study population by disease patterns (n=3112).

	Total	No MM	Unspecific	Psychiatric, respiratory & MSK	Anemia & sensory impairment	Cardiometab olic & inflammatory
	N=3,112	N=421 (13.5%)	N=1,246 (40%)	N=482 (15.4%)	N=609 (19.6%)	N=354 (11.4%)
Sex (female), <i>n</i> (%)	1,971 (63.3%)	224 (53.2%)	739 (59.3%)	370 (76.8%)	413 (67.8%)	225 (63.6%)
Age (years), mean (SD)	73.5 (10.7)	65.0 (6.7)	70.4 (8.7)	71.7 (9.5)	81.2 (9.4)	83.5 (8.9)
Education (university), <i>n</i> (%)	1,063 (34.3%)	218 (51.9%)	457 (36.7%)	162 (33.9%)	164 (27.1%)	62 (17.7%)
Alcohol consumption						
no or occasional, <i>n</i> (%)	1,069 (34.7%)	67 (16.0%)	333 (26.8%)	190 (40.0%)	282 (47.4%)	197 (56.6%)
light-to-moderate, <i>n</i> (%)	1,511 (49.1%)	280 (66.7%)	681 (54.9%)	190 (40.0%)	236 (39.7%)	124 (35.6%)
heavy drinking, <i>n</i> (%)	499 (16.2%)	73 (17.4%)	227 (18.3%)	95 (20.0%)	77 (12.9%)	27 (7.8%)
Smoking habit, <i>n</i> (%)	452 (14.7%)	74 (17.8%)	188 (15.2%)	95 (20.1%)	57 (9.5%)	38 (10.9%)
Malnutrition (BMI<18.5 kg/m ²), <i>n</i> (%)	81 (2.6%)	2 (0.5%)	14 (1.1%)	19 (3.9%)	30 (4.9%)	16 (4.5%)
No. of drugs, mean (SD)	3.9 (3.3)	1.3 (1.6)	2.8 (2.5)	5.2 (3.5)	4.5 (2.9)	7.7 (3.6)
No. of chronic diseases, mean (SD)	3.9 (2.4)	0.8 (0.4)	3.2 (1.2)	4.5 (1.9)	5.0 (1.8)	7.6 (2.3)
Hypertension, <i>n</i> (%)	2,170 (69.7%)	129 (30.6%)	1,075 (86.3%)	261 (54.1%)	467 (76.7%)	238 (67.2%)
Diabetes, <i>n</i> (%)	275 (8.8%)	4 (1.0%)	118 (9.5%)	16 (3.3%)	54 (8.9%)	83 (23.4%)
<i>PHYSICAL PERFORMANCE ASSESSMENT</i>						
Walking speed test (m/s)						
mean (SD)	1.0 (0.4)	1.3 (0.3)	1.1 (0.4)	1.0 (0.4)	0.8 (0.4)	0.6 (0.4)
impaired test, <i>n</i> (%)	789 (25.9%)	18 (4.3%)	154 (12.5%)	123 (26.0%)	272 (45.9%)	222 (66.1%)
Chair stands test (s)						
mean (SD)	21.7 (16.7)	12.4 (7.9)	16.9 (13.1)	23.3 (17.0)	29.3 (18.4)	34.7 (18.5)

impaired test, <i>n</i> (%)	1,288 (42.0%)	58 (13.9%)	386 (31.1%)	224 (47.4%)	375 (62.7%)	245 (72.1%)
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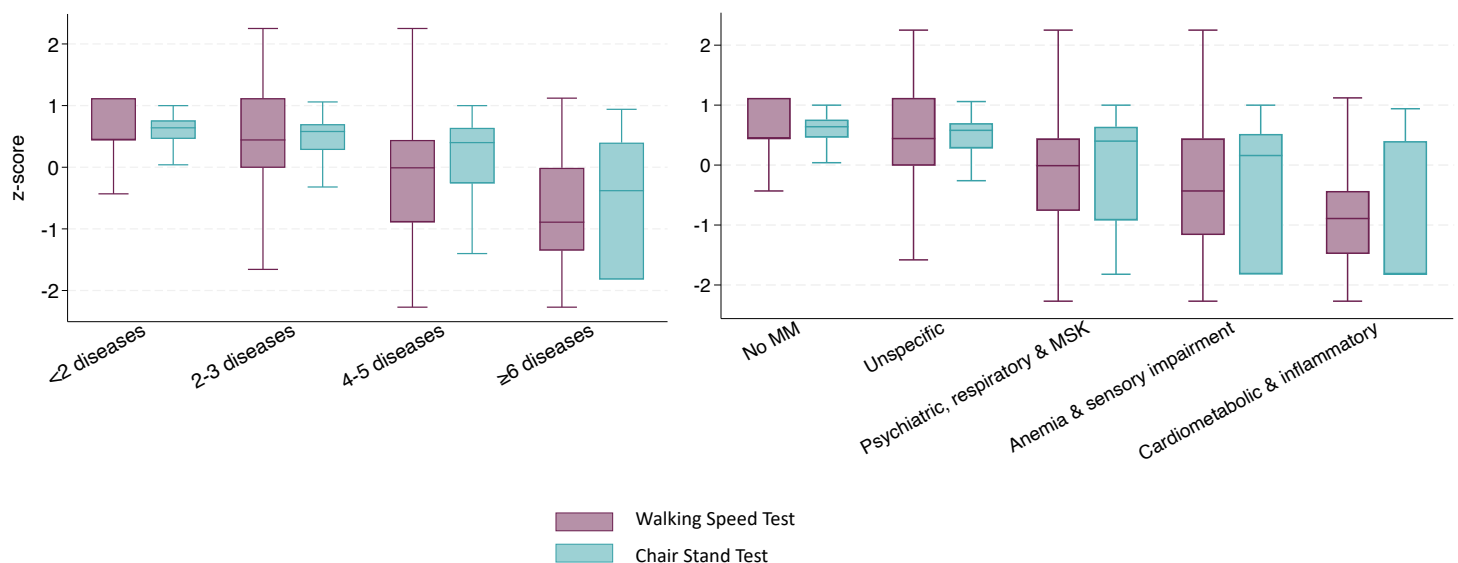
SD: standard deviation; MM: multimorbidity; MSK: musculoskeletal; BMI: body mass index.

Missing data: age (*n* = 8) education (*n* = 14), alcohol consumption (*n* = 33), smoking (*n* = 35), walking speed test (*n* = 63), chair stand test (*n* = 42).

All tests across disease patterns were statistically significant.

Among the ones with multimorbidity, individuals in the “Unspecific” pattern were more likely to be men, younger, and generally healthier than those in the other multimorbidity patterns. However, they exhibited high prevalence of cardiometabolic risk factors, i.e. the highest prevalence of hypertension (86.3%), and the second highest prevalence of diabetes (9.5%). Individuals in the “Cardiometabolic & inflammatory” pattern were more likely to be older, with lower education level, and with higher burden of diseases and drugs than those in the other multimorbidity patterns. With regards to physical performance, the prevalence of impaired walking speed test (66.1%), and chair stands test (72.1%), were sharply higher among individuals in the “Cardiometabolic & inflammatory” pattern, followed by those in the “Anemia & sensory impairment” one. Figure 19 depicts the distribution of physical performance operationalized as a standardized average between walking speed and chair stand measures at baseline according to number of chronic diseases and disease patterns. As the number of chronic disease or the complexity of multimorbidity pattern increased, baseline physical performance tended to decline.

Figure 19. Distribution of the walking speed test (z-score) and chair stand test (z-score) by chronic diseases count and multimorbidity patterns.

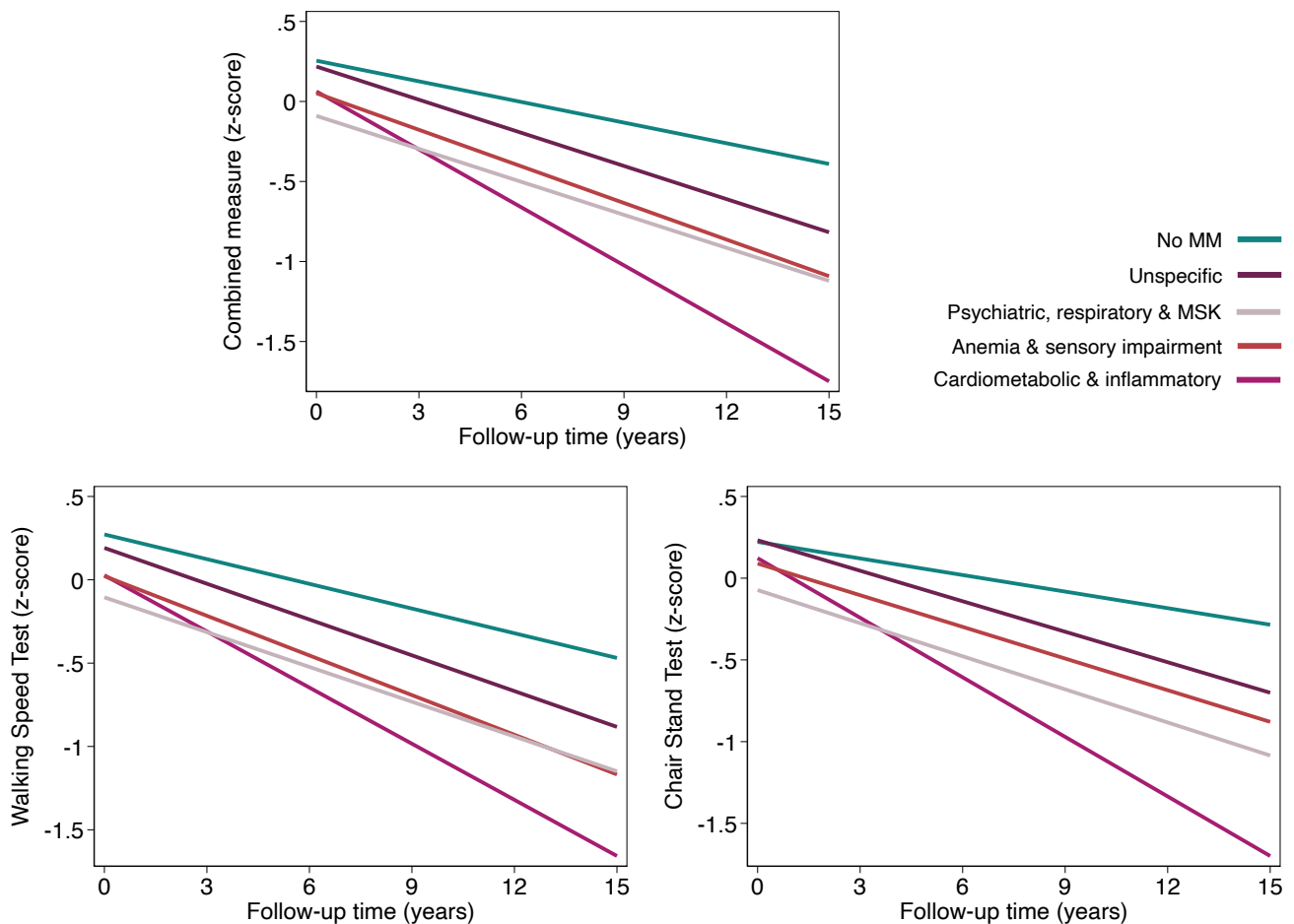


10.3.2 Multimorbidity and longitudinal trajectories of physical performance

Multimorbidity patterns were differently associated with accelerated decline in physical performance test compared with individuals without multimorbidity (Figure 20).

Figure 20. Trajectories of the combined physical function measure (z-score), walking speed test (z-score) and chair stand test (z-score) over 15 year by multimorbidity patterns ($n=3036$).

Trajectories derived from mixed-effect linear regression models adjusted for baseline age, sex and education. Reference group:



individuals without multimorbidity. MM: multimorbidity; MSK: musculoskeletal.

Table 17 reports the β coefficients reflecting the annual change in the combined physical function measure, along with changes in walking speed and chair stand analyzed separately, over the 15-year follow-up.

Table 17. Associations between chronic diseases count and multimorbidity patterns and annual change (β coefficients) in walking speed test (z-score), chair stand test (z-score) and combined physical function measure (z-score) over the 15-year follow-up ($n=3036$).

	Chronic diseases count			MM Patterns			
	2-3 ($n=1117$)	4-5 ($n=830$)	≥ 6 ($n=672$)	Unspecific ($n=1231$)	Psychiatric, respiratory & MSK ($n=470$)	Anemia & sensory impairment ($n=587$)	Cardiometabolic & inflammatory ($n=333$)
Combined measure (z-score)	-0.022 [-0.036,- 0.009]	-0.028 [-0.041,- 0.014]	-0.060 [-0.095,- 0.026]	-0.026 [-0.039,- 0.013]	-0.026 [-0.045,- 0.007]	-0.033 [-0.051,- 0.016]	-0.078 [-0.122,-0.034]
Walking speed test (z-score)	-0.020 [-0.032,- 0.008]	-0.023 [-0.036,- 0.009]	-0.049 [-0.084,- 0.013]	-0.022 [-0.034,- 0.011]	-0.020 [-0.037,- 0.003]	-0.030 [-0.047,- 0.013]	-0.063 [-0.109,-0.016]
Chair stand test (z-score)	-0.022 [-0.039,- 0.006]	-0.031 [-0.049,- 0.013]	-0.072 [-0.111,- 0.033]	-0.028 [-0.044,- 0.013]	-0.034 [-0.059,- 0.008]	-0.031 [-0.055,- 0.006]	-0.088 [-0.136,-0.039]

MM: multimorbidity; CI: confidence interval; MSK: musculoskeletal.

Models adjusted for age, sex, education. Reference group: individuals without multimorbidity ($n=415$)

95% confidence intervals in brackets;

All results were statistically significant.

Individuals in the Cardiometabolic & inflammatory pattern presented the fastest annual decline in all physical performance measures, with a steepest decline in chair stands test (β : -0.088, 95% CI: -0.136, -0.039) compared to those without multimorbidity after adjusting for age, sex, and education and including inverse probability weighting to account for attrition over the follow-up. Individuals in the Psychiatric, Respiratory, and Musculoskeletal pattern were those with the most marked difference from the reference group at baseline across all physical performance tests. However, their decline over time were less pronounced, in particular in walking speed test (β : -0.020, 95% CI: -0.037, -0.003). Conversely, individuals in the Unspecific pattern exhibited baseline physical performance measurements comparable to those

of individuals without multimorbidity, while their trajectories diverged significantly from the reference group over time, with the main difference registered in chair stands test (β : -0.028, 95% CI: -0.044, -0.013).

After dividing the study population by the number of chronic diseases rather than multimorbidity patterns, having at least six chronic diseases was associated with the most pronounced deterioration in both physical performance tests compared to the reference group, with the steepest decline observed in chair stands test (β : -0.072, 95% CI: -0.111, -0.033).

Specifically concerning the two investigated tests, the decline in physical performance across multimorbidity patterns was predicted differently for the walking speed and chair stands tests. Indeed, while no differences were observed between the two tests in the Anemia & Sensory Impairment pattern (walking speed: β : -0.030, 95% CI: -0.047, -0.013 vs. chair stands: β : -0.031, 95% CI: -0.055, -0.006), a relevant difference was instead observed in the Cardiometabolic & inflammatory pattern (walking speed: β : -0.063, 95% CI: -0.109, -0.016 vs. chair stands: β : -0.088, 95% CI: -0.136, -0.039).

When restricting the analysis to the individuals with multimorbidity, the annual rates of physical performance decline were attenuated across all patterns when compared to the Unspecific pattern, with only the cardiometabolic one retaining statistical significance.

In sensitivity analyses, results remained consistent also after adjusting for number of chronic diseases. Few significant associations emerged upon stratifying by age and sex.

Further, excluding individuals with less than two measures of physical performance tests during follow-up yielded results consistent with the main findings.

10.4 Discussion

In this population-based cohort of dementia-free older adults, long-term trajectories of physical performance varied according to specific patterns of chronic diseases. Longitudinal analyses revealed that individuals with higher number of chronic diseases and those clustered in the Cardiometabolic & inflammatory pattern, presented faster declines in physical performances. Notably, multimorbidity patterns remained independently associated with a steeper decline in physical performance after adjusting for the total disease count, suggesting that they provide more insight into predicting physical performance worsening than the mere count of diseases. Lastly, across multimorbidity patterns, declining in physical performance was differently predicted between the investigated tests, i.e. walking speed and chairs stand test.

Worldwide, an increasing number of studies are investigating clusters of multimorbidity across different populations and settings [21,23,145,165]. Consistent with prior studies [166,167], we found high variability in multimorbidity clustering at baseline, with approximately 54% of participants being classified into a well-defined cluster: 1) Psychiatric, respiratory & MSK, 2) Anemia & sensory impairment, and 3) Cardiometabolic & inflammatory. The remaining 46% of the participants were sorted into an unspecific pattern, where nonspecific chronic conditions were over-represented. These individuals present a lower burden of chronic diseases at baseline while exhibiting a higher prevalence of cardiometabolic risk factors.

To our knowledge, the longitudinal associations between data-driven multimorbidity patterns and physical performance have been investigated in only one previous study, conducted using data from the China Health and Retirement Longitudinal Study [161], which reported results generally consistent with our findings. Nonetheless, direct comparisons between the two studies are limited for several reasons. First, unlike Yao et al., we excluded individuals with a clinical diagnosis of dementia from our analytical sample. This exclusion was intended to ensure that the associations between multimorbidity patterns and physical performance were not affected by severe cognitive impairment. Second, In Yao et al., physical performance was assessed, in addition of walking speed, using the handgrip strength test. In contrast, our study focused on chair stands test, a more complex measure of physical performance that requires the interplay of muscle strength, balance, and movement coordination. Notably, the chair stands test is a core component of the widely used Short Physical Performance Battery (SPPB) for assessing physical performance [168]. Third, in SNAC-K the ascertainment of chronic conditions was performed by physicians, with chronic diseases coded in accordance with the International Classification of Diseases, 10th revision (ICD-10); for the present study 60 chronic disease categories based on clinically driven operationalization of 918 ICD-10 codes were used to derive data-driven multimorbidity patterns, by using a methodology previously developed and tested by our group 19. Lastly, our study encompassed a longer follow-up, with repeated measurements over a 15-year period.

As depicted in Figure 20, individuals clustered in the Cardiometabolic & Inflammatory pattern exhibited a faster annual decline in physical performance as measured by objective tests, followed by individuals in the Anemia & Sensory Impairment, Psychiatric, Respiratory & MSK, and Unspecific patterns. These findings highlight worse physical performance trajectories among individuals with more biologically complex multimorbidity patterns compared to those with simpler patterns. While the higher burden of chronic disease may account part of this difference, we hypothesized that it does not fully explain for the entire

phenomenon. Indeed, while more complex multimorbidity patterns tended to have higher number of diseases, additional adjustment for total disease count revealed that these patterns remained independently associated to faster functional decline. This suggest that sharing specific diseases, rather than having multiple comorbidities, has an independent detrimental effect on physical performance, potentially due to the activation of overlapping pathophysiological pathways, e.g. chronic systemic inflammation, metabolism alteration, endocrine dysfunction, nutritional depletion, and use of common medications [21,169,170].

In our sample, the decline in physical performance varied across multimorbidity patterns and was differently predicted by the tests investigated. Specifically, the chair stands test exhibited the steepest annual decline, particularly in individuals clustered in the Cardiometabolic & Inflammatory pattern, while the Anemia & Sensory Impairment pattern showed similar longitudinal trajectories for both physical performance tests. These differences may be related to the specific characteristics of each test, which could reflect physical functions from different perspectives. The chair stands test, for instance, has been previously considered a measure of physical performance particularly related to cardiovascular health [170–173], which could explain the more pronounced decline seen in individuals within the Cardiometabolic & Inflammatory pattern.

The findings of this study may have significant implications for prevention and clinical practice. First, given the evidence supporting the effectiveness of interventions in mitigating aging-related physical decline [174–178], identifying patterns of chronic diseases, highlighting specific needs, using specific objective measurements, and further personalizing interventions, may be more effective in preventing the progressive worsening of physical performance in people with multimorbidity.

Second, given that physical performance decline across all patterns over time, it should be mandatory to assess physical performance in all individuals with multimorbidity, even in those with lower clinical complexity. Indeed, given the dynamic progression of multimorbidity patterns over time, characterized by a transition from lower to higher complexity patterns [20], individuals grouped in the Unspecific pattern should be considered at risk for this transition, as they present the lower number of chronic diseases but the higher prevalence of cardiometabolic risk factors. Consequently, those individuals are likely to benefit most from preventive interventions and should receive targeted efforts to address potential declines in physical performance at an early stage [20].

The strengths of our study include a large study population, a 15-year follow-up period, the use of two distinct objective measures of physical performance, the application of inverse

probability weights to address attrition bias, the comprehensive clinical evaluation that allows for chronic disease assessment, the rigorous clinically driven methodology that were used to operationalize multimorbidity, and the definition of data-driven multimorbidity patterns.

However, several limitations of this study should be acknowledged and discussed. Firstly, participants in the SNAC-K study are relatively fit and healthy individuals, which may limit the generalizability of our findings to other populations of older adults. Secondly, it is reasonable to assume that the longitudinal trajectories of physical performance and patterns associated with higher attrition due to mortality and dropout may be underestimated. To mitigate this issue, we employed inverse probability weights.

Conversely, the inclusion of data from individuals with only one assessment of physical performance may have led to an overestimation of the associations, particularly for patterns with milder multimorbidity. However, limiting the analysis to individuals with at least two assessments of physical performance during follow-up confirmed the associations, thereby reinforcing the robustness of our findings.

In conclusion, our findings suggest that multimorbidity patterns are differently associated with accelerated decline in physical performance test compared. This study contributes to enhancing our understanding of how co-occurring diseases impact physical performance, with potential implications for preserving physical function among older adults.

SECTION IV

11. OVERALL CONCLUSIONS

Frailty is a dynamic and multidimensional condition, with physical, psychological, and social factors playing a part in its development. The ambition of this doctoral thesis was to explore this condition from other perspectives, providing novel instruments to approach it. This thesis broadens the debate on frailty syndrome towards types of patients who are often overlooked, but who frequently present adverse health outcomes. Traditionally, frailty has been studied predominantly in the context of older adults, but other groups of patients also demonstrate characteristics of frailty and therefore could benefit from more attention. These groups, though not necessarily older adults, may exhibit vulnerabilities due to chronic conditions, disabilities, or socio-environmental factors.

The decision to emphasize frailty as a common feature and valuable marker for identifying these patients early stems from the condition's inherently multidimensional nature. Frailty is not just a physical phenomenon; it emerges from a complex interplay between physical, psychological, and social factors. Each of these dimensions contributes in varying degrees to the overall frailty of an individual. For example, physical aspects may include mobility issues, nutritional deficits, or chronic diseases, while psychological dimensions could involve cognitive decline, depression, or anxiety. Additionally, social factors like isolation, lack of support networks, and socio-economic challenges further exacerbate the risk of frailty.

The interaction between these domains is marked by considerable complexity, making frailty difficult to diagnose and manage. This thesis contributes to a better understanding of this complexity by exploring new insights and providing promising instruments to address it. However, future research is needed to address our limitations, and further extend the knowledge of the field.

Understanding the intricate web of interrelationships that depicts frailty could be the key to improving outcomes for frail individuals, as carefully addressing them through innovative and tailored approaches to prevention and care could help foster their resilience and improve the ability to prevent functional decline up to death.

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