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WEARABLE DEVICE REMOTE MONITORING TO PREVENT FRAILTY PROGRESSION IN ELDERLY: A PILOT STUDY

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Abstract

Background: Frailty is a multifactorial condition including physical, psychological, cognitive, economic, and social aspects, leading to a serious deterioration in the quality of life. With the increasing ageing population worldwide, there is an urgent need for efficient healthcare service to support well-being and better quality of life in elderly adults. Wearable sensors that monitor vital signs such as such heart rate variability, a proxy of orthostatic hypotension, respiration rate, and blood oxygen saturation offer a non-invasive, comfortable, and low-cost method for patients to measure health parameters and for health professionals to access real-time data for timely interventions.

Aim: This PhD project aimed to standardize a study protocol for developing a useful model to enhance local care in small population isolates, by remotely monitoring the health status of pre-frail individuals over 65 years. The intent was to support a healthy ageing and provide a foundation for future investigation with larger populations.

Method: Subjects aged 65 years and older were randomly recruited from the general population of the Molise region. The frail status of individuals was assessed using the *AGILE* questionnaire and all the individuals categorized as "*Light*" frail were invited to participate to the project. Baseline visits have been performed on a final study sample of 30 (number decided by the protocol) "*Light*" participants and included other frailty scales to confirm pre-frail status. Additional information on lifestyles, anthropometric measurements, adherence to the Mediterranean Diet, clinical history of chronic diseases and pharmacological treatments, self-perception of health, was collected. Biochemical markers for cardiovascular diseases were tested using fresh serum samples.

The use of *O2 Ring* wearable device which is equipped with a photoplethysmogram (PPG) sensor, will make possible the evaluation of, among others vital signs, heart rate variability, which are recognised as key health indicators.

Results: In a cohort of 78 older adults, the prevalence of "*Light*" frail individuals was 70.5% (mean score 2, mean age 70.2 ± 4.1 years), and "*Moderate*" frail individuals were 28.2% (mean score 4.9, mean age 70.1 ± 4.8 years). Only one individual was categorized as "*Severe*" frail (score 8, age 75.8 years). Among the 55 "*Light*" frail individuals, 30 were selected to participate to the project (mean age 71,5 ± 4,6 years, 73.3% men). All individuals had hypertension (mean systolic BP 148.0 ± 19.6 mmHg, mean diastolic BP 79.0 ± 7.7 mmHg), but only 56.7% were on treatment. More than 60% had good social support. Even if the 73.3% of population had a "*Medium-high*" adherence to the Mediterranean Diet, however, there is a different nutritional status among genders (68.2% of men had normal nutritional status, 75% of women were at risk of malnutrition).

No cognitive impairment was found. Pre-frail women had worse physical functioning and health perception compared to men, along with higher BMI. Physical activity levels were similar between genders. Pre-frail men had a healthier lipid profile, and women had poorer bone health.

Conclusion: Findings from this project are in line with previous data from epidemiological studies which investigated frailty in larger older populations worldwide. This pilot study put the basis for the for developing a useful model to enhance local care in small population isolates, by remotely monitoring the health status of pre-frail individuals over 65 years. Remote monitoring with the *O2 Ring* could provide further insights into the use of PPG sensors, in wearable devices, for both the management and the prevention of frailty, promoting healthy aging.

Chapter 1: Introduction

1.1 Frailty in elderly people: definition and characteristics

The term frailty appeared for the first time about 50 years ago in geriatric and gerontology literature, to describe older individuals with chronic diseases, debilitated, disabled, with limited physical mobility or functionally dependent [1,2]. Moreover, this concept was used to define older person at risk of mortality or other adverse outcomes [3].

Among the end of 1980's and the beginning of the 1990's, numerous studies have been investigated about frailty. In that period, frailty was mainly defined as a condition of older individuals having multiple comorbidities, that limited their daily living activities and that needed assistance from others [4-7]. Otherwise, frailty was reported as synonymous of disability [2,8,9], comorbidity [8] or advanced old age [10]. However, it is essential to distinguish frailty from these terms, because they are often used interchangeably to identify the physically vulnerable subset of older adults requiring enhanced care.

Although strictly connected, recent data have showed that these are different clinical entities, and as a consequence each of these has to be managed in a specific manner. Indeed, frailty is distinct from, but overlapping with, both comorbidity and disability. Disability is defined as difficulty or dependency in carrying out activities essential to independent living, including essential roles, tasks needed for self-care and living independently in a home, and desired activities important to one's quality of life. Physical disability is mostly diagnosed by self-report of difficulty in specific tasks, but objective, performance-based tests of function also exist. It is recommended by several organizations that clinicians screen for disability in self-care tasks (Activities of Daily Living, ADL) and tasks of household management (Instrumental Activities of Daily Living, IADL) on an annual basis in persons aged older than 70 years. Instead, comorbidity is the simultaneous occurrence of two or more medically diagnosed diseases in the same individual [11-13.]

During the past decades, the frailty status has gained international attention as the population of older have risen globally. This resulted in a rapid increase of different concepts and definition for this condition [1,2,14-19].

Altogether these several characterizations of frailty can broadly be grouped into two different conceptual models or frameworks:

1. The biomedical paradigm according to which frailty is defined as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes [9,15,16,20,21];
2. The bio-psyco-social paradigm according to which frailty represents: ‘‘A dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes [22].

Afterall, in a recent consensus statement, six major international scientific societies (International Association of Gerontology and Geriatrics; Society on Sarcopenia, Cachexia, and Wasting Diseases; International Academy of Nutrition and Aging; European Geriatric Medicine Society; American Medical Directors Association; American Federation for Aging Research) endorsed the definition of frailty as “a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death” [23].

Despite numerous contemporary theories and models, the causes of frailty are not yet fully understood. Otherwise, numerous physio-pathological characteristics have been recognized to help in the screening/ identification of frail individuals.

In 2001, Fried et al. proposed for the first time, the operational definition “*Phenotype of frailty*”, also useful to define an intervention protocol, tested in the Cardiovascular Health Study [1].

A “*Phenotype of frailty*” is identified by the presence of three or more of the following components:

a. *Shrinking*: weight loss, unintentional, of ≥10 pounds in prior year or, at follow-up, of ≥ 5% of body weight in prior year (by direct measurement of weight).
b. *Weakness:* grip strength in the lowest 20% at baseline, adjusted for gender and body mass index (BMI).
c. *Poor endurance and energy*: as indicated by self-report of exhaustion. Self-reported exhaustion, identified by two questions from the Center for Epidemiologic Studies Depression Scale (CES-D), is associated with stage of exercise reached in graded exercise testing, as an indicator of VO_2 max, and is predictive of cardiovascular disease.
d. *Slowness*: the slowest 20% of the population was defined at baseline, based on time to walk 15 feet, adjusting for gender and standing height.

e. *Low physical activity level*: a weighted score of kilocalories expended per week was calculated at baseline, based on each participant's report. The lowest quintile of physical activity was identified for each gender.

Many of these factors are related, and can be unified, theoretically, into a cycle of frailty associated with declining energetics and reserve (**Figure 1**). The core elements of this cycle are those commonly identified as clinical signs and symptoms of frailty. When these components are present, they identify the syndrome [1].

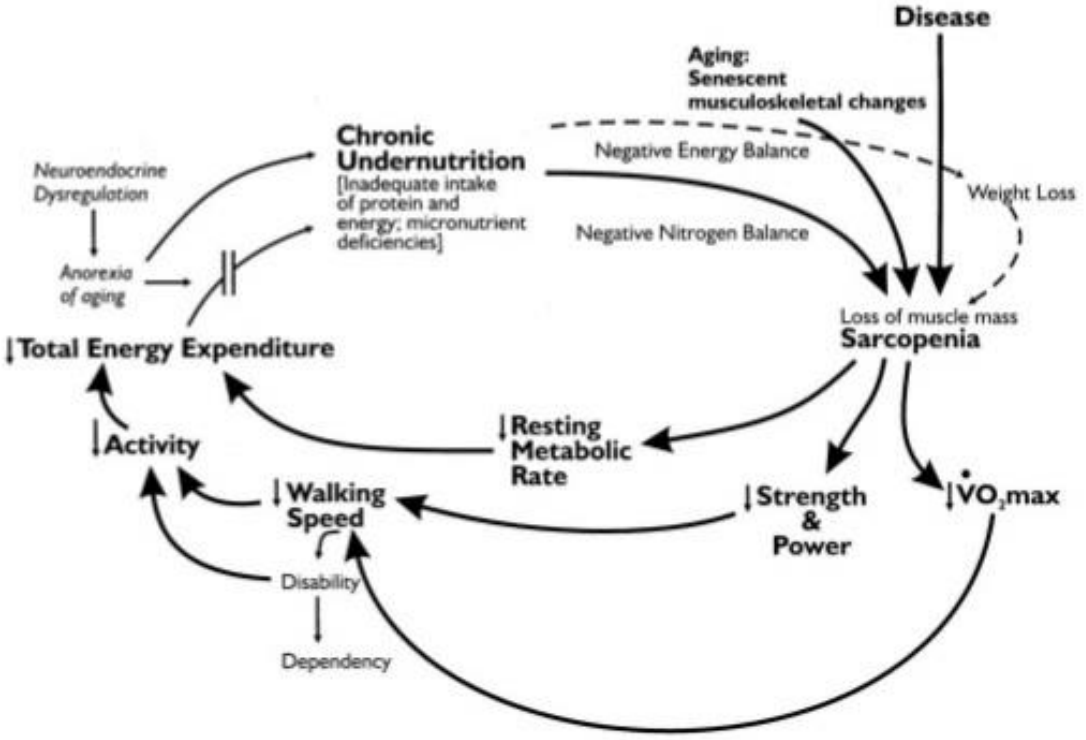


Figure 1 – Cycle of frailty hypothesized by Fried et al. Chroinc undernutrion due to an inadequate intake of protein and energy, weight loss and aging determines a condition of sarcopenia which results in a diminished strength, power, resting metablocic rate and walking of speed. All these factors could contribute to a frail phenotype [1].

Following this, also in 2001, Rockwood and Mitnitski proposed their "*Accumulated Deficits Model*" of frailty, based on the concept that frailty is resulting from the cumulative effects of multiple health deficits in different physiological systems rather than being defined by a single factor [24-26]

It is widely recognized that, as cells age, they develop deficits as a result of the accumulation of unrepaired cellular and molecular damage. Consequently, older adults collect deficits that are eventually manifested as frailty, disease, or disability. In the progression from molecular damage to

cellular damage and from cellular damage to tissues and then to organs, almost all adult-onset illnesses become more common with age. Even though all illnesses become more common as people age, most older adults remain healthy and do not need or receive the specialized care of geriatricians.

In this context, is important to select the right health-related deficits and in an adequate number, in order to assess frailty condition in older adults. Therefore, a method has been proposed, that can be derived from health databases by proposing criteria for deficits and procedures for counting deficits: the *Frailty Index of Accumulative Deficits (FI-CD)* [27].

The "*Frailty Index of Accumulative Deficits (FI-CD)*" is underpinned by biological causative theory [26,28] and involves:

1. **Selection of Deficits:** A wide range of health-related deficits are selected for assessment. These deficits can include chronic diseases, symptoms, physical impairments, cognitive deficits, laboratory abnormalities, and more. Essentially, any factor that reflects the health status of an individual can be considered a deficit. The exact list of health deficits for inclusion in the FI-CD does not specifically matter. Otherwise, they should be reflective of a range of

   physiological systems; and be associated with health and not age per se [29];
2. **Scoring:** Each deficit is scored based on its presence or absence. For example, if a person has hypertension, it may be scored as "1" if present and "0" if absent. Similarly, if they have difficulty walking, it may be scored as "1" if present and "0" if absent. The scoring system can vary, but the general principle is to assign a value to each deficit;
3. **Calculation of Frailty Index:** *The Frailty Index* is calculated by dividing the total number of deficits present by the total number of deficits measured. This results in a score ranging from 0 to 1, with higher scores indicating greater frailty. For instance, if there are 20 deficits measured and a person has 10 of them, their Frailty Index would be 10/20 = 0.5;
4. **Interpretation:** *The Frailty Index* provides a continuous measure of frailty, allowing for a more nuanced assessment compared to categorical classifications. It can help predict adverse outcomes such as disability, hospitalization, institutionalization, and mortality. Generally, higher Frailty Index scores indicate greater frailty and higher risk of adverse outcomes.

The "*Frailty Index of Accumulative Deficits (FI-CD)*" has been widely used in research and clinical practice to assess frailty and guide interventions aimed at improving the health and well-being of older adults. It provides a comprehensive way to evaluate an individual's health status across multiple domains, taking into account the complexity of frailty [24-26].

Later in 2005, Rockwood and colleagues performed a population-based prospective cohort study conducted in Canada to examine the health and aging of older adults: the Canadian Study on Health and Ageing (CSHA). Its first stage began in 1991 more than 10000 people aged 65 years and older, recruited. The *CSHA* collected data through comprehensive evaluations, including medical examinations, cognitive and functional assessments, and interviews with participants and their caregivers. It involved a nationally representative sample of older community-dwelling adults, as well as those residing in long-term care facilities. Findings from this study provided valuable insights, among the others, on frailty among older populations, as well as the factors related to healthy aging. Of note, thanks to this study, Authors identified 70 items including signs, symptoms and abnormal test who can be used to characterize frailty (**Figure 2**). In addition, CSHA contributed to the construction of a useful assessment for frailty identification in older individuals: "*The Clinical Frailty Scale"* [30].

Appendix 1: List of variables used by the Canadian Study of Health and Aging to construct the 70-item CSHA Frailty Index

- Changes in everyday activities
- Head and neck problems
- Poor muscle tone in neck
- Bradykinesia, facial
- Problems getting dressed
- Problems with bathing
- Problems carrying out personal grooming
- Urinary incontinence
- Toileting problems
- Bulk difficulties
- Rectal problems
- Gastrointestinal problems
- Problems cooking
- Sucking problems
- Problems going out alone
- Impaired mobility
- Musculoskeletal problems
- Bradykinesia of the limbs
- Poor muscle tone in limbs
- Poor limb coordination
- Poor coordination, trunk
- Poor standing posture
- Irregular gait pattern
- Falls
- Mood problems
- Feeling sad, blue, depressed
- History of depressed mood
- Tiredness all the time
- Depression (clinical impression)
- Sleep changes
- Restlessness
- Memory changes
- Short-term memory impairment
- Long-term memory impairment
- Changes in general mental functioning
- Onset of cognitive symptoms
- Clouding or delirium
- Paranoid features
- History relevant to cognitive impairment or loss
- Family history relevant to cognitive impairment or loss
- Impaired vibration
- Tremor at rest
- Postural tremor
- Intention tremor
- History of Parkinson's disease
- Family history of degenerative disease
- Seizures, partial complex
- Seizures, generalized
- Syncope or blackouts
- Headache
- Cerebrovascular problems
- History of stroke
- History of diabetes mellitus
- Arterial hypertension
- Peripheral pulses
- Cardiac problems
- Myocardial infarction
- Arrhythmia
- Congestive heart failure
- Lung problems
- Respiratory problems
- History of thyroid disease
- Thyroid problems
- Skin problems
- Malignant disease
- Breast problems
- Abdominal problems
- Presence of snout reflex
- Presence of the palmomental reflex
- Other medical history

Figure 2 – List of variables used by the Canadian Study on Health and Ageing to construct the 70-item frailty index [30].

Regardless of what definition of frailty is used, to be applied practically, frailty first needs to be operationally defined. A breakthrough in frailty measurement have been developed in the last years, both considered alone or grouped together to form scores, to predict adverse outcomes.

Nowadays, a plethora of frailty measurements are in existence. Overall, frailty measurements were used for frailty classification and prognosis across a broad range of medical patients, including: geriatric, oncology, surgical, orthopedic, cardiovascular and renal patients.

All the functional tests, questionnaires and indexes proposed to categorize frailty can be related to two main approaches:

1. The "*Frailty phenotype*" instrument as described by Fried et al, where frailty is categorized as: non-frail (0 criteria present), pre-frail (1–2 criteria present), and frail (≥3 criteria present). This method was validated as consistent with a medical syndrome, linked to distinct biology;
2. The "*Frailty Index*", also known as accumulated deficit models of frailty as described by Rockwood and Mitnitski, which considered not only the physical components of frailty, but also the psychosocial aspects of frailty [25].

However, identifying which frailty measurement is most suitable for clinical and/or research application is currently a topic of heated debate.

In a recent systematic review performed by Dent et al., Authors aimed to determine which measurement could accurately identify frailty; which could reliably predict patient outcomes and response to potential therapies; and which were based on biological theory [27].

The *"Frailty index derived from comprehensive geriatric assessment (FI-CGA)"* is a variation of the Frailty Index that includes information obtained from a Comprehensive Geriatric Assessment (CGA). A CGA is a multidimensional, interdisciplinary diagnostic process used to determine the medical, functional, and psychosocial capabilities and limitations of older adults. This is the global standard clinical assessment for older people, and comprises medical, nutritional, functional and psychological evaluations. The *FI-CGA* based on the traditional *Frailty Index* by incorporating specific components of the CGA into the assessment of frailty [28,31,32]. The *FI-CGA* was initially developed as a ten-domain index, with 14 CGA components included [31,32] It was later expanded out by Rockwood and colleagues to include 52 CGA components [28].

These components typically embrace:

1. **Medical History and Comorbidities:** Information about chronic medical conditions, past medical history, and current medications is gathered to assess the individual's overall health status;

2. **Physical Function:** Assessment of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) to evaluate functional independence and mobility;
3. **Cognitive Function:** Evaluation of cognitive status, including screening for dementia and assessing memory, attention, and executive function;
4. **Nutritional Status:** Assessment of nutritional intake, weight loss, and signs of malnutrition or dehydration;
5. **Psychosocial Factors:** Evaluation of social support, mood, emotional well-being, and any psychosocial stressors impacting the individual's health and quality of life;
6. **Medication Review:** Assessment of medication appropriateness, adherence, and potential adverse effects or interactions;
7. **Sensory Impairments**: Screening for visual or hearing impairments that may impact the individual's functional abilities and quality of life;

Nowadays, many clinical studies have adopted a *FI-CGA* for frailty assessment. Indeed, it has been found to predict patient response in multiple fields, including: oncology, orthopedics, immunology, urology, and cardiology [27]. Each component assessed in the *CGA*, indeed contributes to the overall *Frailty Index* score, providing a comprehensive evaluation of the individual's frailty status.
The *FI-CGA* offers a more detailed and holistic assessment of frailty by integrating clinical information obtained through a standardized geriatric assessment process. Moreover, it helps identify specific areas of vulnerability and guides the development of targeted interventions to optimize the health and well-being of older adults.

The "*Edmonton Frailty Scale (EFS)*" is a valid and reliable clinical tool developed by Dr. Darryl Rolfson and his colleagues at the University of Alberta in Edmonton, Canada. The *EFS* evaluates multiple domains of frailty, providing a comprehensive picture of an individual's frailty status [33].
The *EFS* domains comprises:

1. **Cognition**: Assessing cognitive impairment or dementia;
2. **Functional Independence**: Evaluating the ability to perform activities of daily living (ADLs) independently;
3. **General health status:** Assessing how many admissions to hospital occurred in the last year;
4. **Self-reported health:** Assessing self-perception of health status;
5. **Social Support:** Evaluating the availability of social support and the extent of social engagement;
6. **Nutritional Status:** Assessing nutritional intake and risk of malnutrition;
7. **Medication use/polypharmacy:** Evaluating the number of medications and potential adverse effects;

8. **Mood**: Assessing mood and emotional well-being;
9. **Continence:** Evaluating urinary and bowel continence;
10. **Functional Performance**: Assessing mobility and physical function;

Each item is scored on a scale from 0 to 1 or from 0 to 2, with higher scores indicating greater frailty. Component scores from each item are then summed to calculate the total *EFS* score, which ranges from 0 to 17. A higher *EFS* score indicates a higher level of frailty. The following cut-off are used to classify frailty severity: not frail (0–5); apparently vulnerable (6–7); mildly frail (8–9); moderately frail (10–11) and severely frailty (12–17) [33].

To summarize, "*The EFS"* is designed to be administered by healthcare professionals, such as physicians, nurses, or other trained personnel, in various clinical settings, including hospitals, outpatient clinics, and long-term care facilities. It provides a standardized and reliable method for assessing frailty, guiding clinical decision-making, and identifying appropriate interventions to improve the health and quality of life of older adults [34-36].

The *"Fatigue, Resistance, Ambulation, Illness, Loss of Weight (FRAIL) Index"* has been proposed by the International Association of Nutrition and Ageing (IANA), and is composed of five components:

1. **Fatigue** (self-report);
2. **Resistance**;
3. **Ambulation** (slow walking speed),
4. **Illness**;
5. **Loss of weight** (5% or more in the past year).

Fatigue was measured by asking respondents how much time during the past 4 weeks they felt tired with responses of "all of the time "or "most of the time" scored 1 point. Resistance was assessed by asking participants if they had any difficulty walking up 10 steps alone without resting and without aids, and Ambulation by asking if they had any difficulty walking several hundred yards alone and without aids; "yes" responses were each scored as 1 point. Illness was scored 1 for respondents who reported 5 or more illnesses out of 11 total illnesses. Loss of weight was scored 1 for respondents with a weight decline of 5% or greater within the past 12 months based on self-report.

"FRAIL" scale scores range from 0–5 (i.e., 1 point for each component; 0=best to 5=worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status [37].

"FRAIL" is considered to be clinically advantageous due to its simple nature and ability to be obtained from data already included in a patient CGA [37]. It has been found to be predictive of mortality in specific populations [38,39]. Further validation studies of "*FRAIL*" are needed for both hospitalized and community dwelling older people.

"*The Clinical Frailty Scale (CFS)"* is a well validated frailty measurement that originated from Dalhousie University in Canada.

The CFS categorizes individuals into one of seven levels of frailty based on their functional status and degree of independence. The scale ranges from 1 (very fit) to 7 (severely frail):

1. **Very Fit:** Individuals who are robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age;
2. **Well:** Individuals Without active disease, but less fit than people in category 1;
3. **Well, with treated co-morbid disease:** Individuals with disease symptoms but that are well controlled compared with those in category 4;
4. **Apparently vulnerable:** Although are not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms;
5. **Mildly Frail:** Individuals with limited dependence on others for instrumental activities of daily living;
6. **Moderately Frail:** Individuals who need help with bot instrumental and non-instrumental activities of daily living;
7. **Severely Frail:** Individuals who are completely dependent on others for the activities of daily living, or terminally ill.

Each point on its scale corresponds with a written description of frailty, complemented by a visual chart to assist with the classification of frailty. A score ≥ 5 is considered to be frail CGAs [30].

The *CFS* can be extracted from data from medical charts, and therefore can also be derived from CGAs. It has been validated as an adverse outcome predictor in hospitalized older people [40,41].

The *"Tilburg Frailty Indicator (TFI)"* is a self-administered questionnaire developed by researchers at Tilburg University in the Netherlands during 2010 [42,43].

The "TFI" contains 15 simple self-reported items encompassing:

1. **Physical components:** (health, weight loss, difficulty in walking, balance, hearing, vision, gripping and tiredness);
2. **Psychological factors:** (memory, feeling down, anxiety and coping);
3. **Social elements:** (living alone, social isolation,social support).

Each item is scored on a binary scale (0 = no, 1 = yes), indicating the presence or absence of the frailty-related characteristic. The scores for each item are then summed to calculate a total TFI score, which can range from 0 to 15. A score ≥ 5 is indicative of frailty [42]. The TFI has showed good validity and reliability for community-dwelling older people [42,44]. In addition, its physical components have been found to have good predictive ability of adverse outcomes, as opposed to its social components [43]. For this reason, the *"TFI"* is intended to be used more as a screening tool,

rather than as a diagnostic instrument. This review showed that there are multiple measurements used to identify frailty in older people. There is a wide range in the applicability of these frailty measurements: from short, fast and crude frailty screening instruments to the sophisticated, time-consuming measurements. Based on the findings of this review, it is evident that different frailty measurements are suited to different populations. Some are better for population-level frailty screening, whereas others are best suited for clinical screening, or for clinical assessment. This means that a universally validated approach to assess frailty is still lacking [27].

An important Frailty Instrument for primary investigation has been created in 2010 by Romero-Ortuno et al, through the Survey of Health, Aging and Retirement in Europe (SHARE): *"The SHARE-FI"*. This specific instrument, is a multidisciplinary and cross-national database collecting data on health, socio-economic status, social and family of individuals aged 50 years or older, projected to assess frailty among older adults. This is a validated and simple tool for frailty screening which includes a set of questions to capture various domains of frailty such as physical health, cognitive function, and psychosocial well-being. These questions cover a range of domains, including mobility, activities of daily living (ADLs), instrumental activities of daily living (IADLs), cognitive status, depressive symptoms, and social engagement. The responses to these questions are used to generate a frailty index, which provides a quantitative measure of frailty. This index is calculated by summing the scores assigned to each item or domain, with higher scores indicating greater frailty. The "*SHARE-FI"* thus provides a comprehensive assessment of frailty that can help identify older adults at risk of adverse health outcomes and inform interventions to improve their well-being and quality of life [45]. In this study, Authors created and validated a simple frailty screening instrument for primary care with a sufficient construct and predictive validity.

1.2 Frailty risk factors

To date it is widely recognized that frailty is a common, dynamic, multidimensional syndrome in older adults. The rapid expansion of the ageing population of the last decades, has brought a concomitant rise in the number of older adults with frailty [46,47].

Several recent studies indeed have identified for frailty many risks and protective factors including biological, lifestyle, environmental, and clinical elements. Moreover, frailty domains are related but largely independent of each other and that each domain incrementally increased risk estimates of various adverse health outcomes [48-50].

Altogether these factors involve:

- **Chronic Inflammation:** Chronic low-grade inflammation, often referred to as "inflammaging," is common in older adults and is associated with frailty. Elevated levels of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), may contribute to tissue damage, oxidative stress, and functional decline [51-54];
- **Endocrine Dysregulation:** Dysregulation of the endocrine system, including alterations in hormone levels such as testosterone, estrogen, insulin-like growth factor 1 (IGF-1), thyroid hormones, hormones related to the vitamin D axis, and adrenocorticoids of the hypothalamic–pituitary–adrenal axis (HPA) has been associated with one or more indicators in the frailty phenotype. Indeed, hormonal changes can affect muscle mass, bone density, metabolic function, and overall physiological resilience [55];
- **Mitochondrial Dysfunction:** Age-related decline in mitochondrial function, including impaired energy production and increased oxidative damage, may contribute to frailty. Mitochondrial dysfunction can compromise cellular metabolism and contribute to tissue dysfunction and frailty-related symptoms [56];
- **Genetic and epigenetic regulation**: Genetic predisposition may play a role in an individual's susceptibility to frailty. Variations in genes involved in in muscle function, inflammation, oxidative stress response, and other biological processes related to frailty can influence the development and progression of this condition [57]; Frailty has been also associated with epigenetically accelerated aging measured by the difference between predicted DNA methylation age and chronologic age [58];
- **Nutritional Deficits:** Malnutrition, poor dietary intake, and weight loss are risk factors for frailty. Inadequate nutrition can lead to muscle wasting, weakness, and decreased functional capacity [50,59-62];

- **Clinical Conditions**: The presence of chronic diseases, such as, diabetes, cardiovascular risk factors (hypertension, atherosclerosis, atrial fibrillation, heart failure and vascular diseases), depression or neurological conditions (age-related changes in nervous system that contribute to mobility, balance, cognition and sensory dysfunction), respiratory disease, arthritis/osteoporosis, fall history, sarcopenia and pain, increase the risk of frailty. These disorders indeed, can lead to functional frailty-related impairments and decrease the overall resilience [50,61-68];
- **Lifestyle factors:** social (isolation, loneliness, unmarried status, low quality of life), low income, low education, low physical activity, advanced age, female gender, rural residence, smoking, high alcohol consumption, polypharmacy [50,61,62,69].

Considering that this condition can be potentially prevented, reversed, or slowed, identifying and addressing risk factors in advance, can help the management of frailty and improve outcomes for older adults. In particular, among the different lifestyle factors, we still know very little about cultural/social influences. Thus, discovering them and their potential role in the pathophysiology of frailty becomes of great importance to establish multidimensional models of prevention and treatment. In summary, this issue deserves further exploration in the future.

1.3 Frailty and risk of adverse outcomes

As a multidimensional biopsychosocial syndrome, frailty is associated with an increased risk of adverse outcomes across various domains of health and well-being. Indeed, to date several studies proved that older adults who are frail have a higher likelihood of poor health outcomes that can affect physical, cognitive, psychological, and social aspects of an individual's life [1,30,70,71].
Among others, most common adverse outcomes associated with this condition include:

- **Risk of Falls**: Frail older adults are more prone to falls due to factors such as orthostatic hypotension, muscle weakness, balance problems, and impaired gait. Falls can result in injuries such as fractures, head trauma, and soft tissue injuries, leading to pain, disability, and decreased quality of life;

- **Hospitalization:** Frail individuals have a higher likelihood of hospital admissions due to acute illnesses, exacerbations of chronic conditions, or complications of frailty-related impairments. Hospitalization can be particularly challenging for frail older adults, as it may lead to functional decline, delirium, iatrogenic complications, and prolonged recovery periods;

- **Disability**: Frail individuals are at higher risk of experiencing declines in physical function, including limitations in activities of daily living (ADLs) and instrumental activities of daily living (IADLs). This can lead to difficulties with mobility, self-care, and independence in performing essential tasks;

- **Institutionalization:** Institutionalization refers to the transition of older adults from community-based living arrangements (such as their own homes) to long-term care facilities such as nursing homes or assisted living facilities. This is linked to the rapid decline, in frail individuals, of their ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs), resulting in the impossibility for them to live independently in the community;

- **Mortality:** Frailty is a strong predictor of mortality, with frail individuals having a higher risk of death compared to non-frail counterparts. Frail older adults are more vulnerable to adverse health events and have reduced physiological reserve to withstand acute stressors, leading to higher mortality rates across various causes of death [1,72-76].

As a consequence, frailty negatively impacts the quality of life by limiting functional independence, social participation, and overall well-being. Frail older adults may experience pain, fatigue, social isolation, and psychological distress, contributing to a diminished quality of life.

Moreover, this condition is strictly related with higher healthcare utilization, including emergency department visits, outpatient visits, and specialist consultations. Frail individuals may require more frequent medical interventions, monitoring, and support from healthcare providers to manage their complex health needs. For this reason, addressing frailty through comprehensive assessment, targeted interventions, and multidisciplinary care can help mitigate the risk of adverse outcomes and improve quality of life for older adults.

Although frailty has been considered as an age-related condition and as an extreme consequence of the normal ageing process, it has to be underlined that this is a dynamic and potentially reversible process [70,77]. In the last years, several studies have evaluated the dynamic nature of frailty. Over time, transitioning between frailty stages (not-frail, pre-frail, frail) can occur, with patients worsening, improving, or maintaining their current degree of frailty [70,78,79]. Of interest, the recent prospective analysis performed by Álvarez-Bustos et al, where the Authors aimed to explore, in a population-based longitudinal study, the existence of different frailty trajectories and their associations with adverse outcomes (disability, hospitalization, and mortality) [80]. In particular, in a representative Spanish cohort of older adults (>65 years), they supposed that prospective decreasing frailty levels along ageing were associated with a lower risk of adverse events, compared with developing or maintaining higher frailty levels. Findings from this research further confirm previous evidence of frailty related incidence of adverse outcomes in a population of community-dwelling older adults [81]. Moreover, the results identified five distinct trajectories of frailty, which support the dynamic nature of this construct. Indeed, increasing frailty trajectories or those who maintained higher frailty scores over time had higher risk of death, hospitalization, and incident or worsening disability, than those who remained non-frail [80].

1.4 Frailty implications for clinical practice and public health

Frailty is without question one of the most serious global public health challenges we are facing in the last century. Over the past decades, the rapid and progressive expansion of the ageing population, has been observed worldwide. Furthermore, demographic projections show that the growth of older age groups is expected to continue. Although it is widely known that this condition is present in millions of older adults worldwide, the global prevalence is not yet defined. This is partly due to the fact that research studies have been performed mostly in high-income countries. In addition, both different operational definitions and assessment tools of frailty are used across studies and populations. Frailty has been associated with higher healthcare utilization, including emergency department visits, outpatient visits, and specialist consultations. Frail individuals require more frequent medical interventions, monitoring, and support from healthcare providers to manage their complex health needs. Moreover, frail older adults undergoing surgical procedures are at increased risk of perioperative complications and may have poorer long-term functional outcomes compared to non-frail counterparts. Therefore, the growth in the number of older adults with frailty has brought to an increased pressure on health-care systems worldwide. The impact of frailty on health-care expenditure and use has been the subject of several recent investigations [82-87].

These studies show a clear pattern of increased health-care costs and use associated with prevalent frailty or a higher degree of frailty. The increment of health-care costs comprises: greater health-care use in inpatient, post-acute and outpatient care sectors [84,88].

Understanding and addressing frailty is essential for optimizing health-care delivery, improving outcomes, and promoting healthy aging in older populations. Effective strategies that target the prevention and management of frailty in an ageing population will probably reduce the condition's burden at the level of both the individual and the health system. Some key implications of frailty for clinical practice and public health could include:

- **Early Identification and Assessment:** Clinicians should incorporate frailty screening and assessment into routine clinical practice, particularly among older adults. Early identification of frail individuals allows timely intervention and the implementation of targeted strategies to prevent or mitigate adverse outcomes associated with frailty;
- **Multidisciplinary Care Coordination**: Frailty often requires a multidisciplinary approach involving various healthcare professionals, including physicians, nurses, physical therapists, occupational therapists, social workers, and others. Coordinated care

delivery ensures that frail individuals receive comprehensive, integrated services that address their medical, functional, and psychosocial needs;

- **Preventive Interventions:** Public health efforts should focus on promoting healthy aging and preventing frailty through lifestyle interventions, health promotion initiatives, and chronic disease management programs. Targeted interventions such as exercise programs, nutrition counseling, fall prevention strategies, and social support services can help mitigate risk factors for frailty and enhance resilience in older adults;
- **Community-Based Support Services:** Public health agencies, community organizations, and healthcare systems should invest in community-based support services that enable frail older adults to remain independent and engaged in their communities for as long as possible. These services may include home-based care, caregiver support programs, transportation services, senior centers, and social activities tailored to the needs of older adults;
- **Health Policy and Advocacy:** Policymakers and healthcare leaders should prioritize frailty prevention and management as a public health priority. This includes advocating for policies and funding initiatives that support research, education, and infrastructure development to address the needs of frail older adults and promote healthy aging across the lifespan;
- **Health Equity and Access to Care:** Programs to address frailty must consider the unique needs and vulnerabilities of diverse populations, including those from racial/ethnic minority groups, low-income communities, rural areas, and other underserved populations. Ensuring equitable access to healthcare services and resources is essential to reduce disparities in frailty outcomes and improving health equity for all older adults [82].

The integrated and collective effort of older adults, health-care professionals, researchers, and policy makers, in both frailty assessment and management, in clinical practice and public health programs and communities, will help to improve the health and well-being of elderly adults, enhance their quality of life and consequently will reduce the burden of frailty-related adverse outcomes. Although, the research on frailty condition has gained much attention in the last decades and countless studies have investigated it, the translation from research to clinical practice remains a challenge for the coming years. Future investigation will increase our understanding of how frailty and its risk factors develop during earlier stages in life and will contribute to the development of public health strategies aimed at preventing frailty and related adverse health outcomes. This research will ultimately lead to increased well-being of older adults living with frailty.

1.5 Telemedicine approach in health monitoring and disease prevention

Recent progress in telecommunication technologies has emphasized the global importance of access to healthcare. This has affected different aspects of health assistance such as methods of medical care and healthcare delivery, resulting in the possibility to remotely access to health-related services known as Telehealth or Telemedicine [89-93]. Telemedicine plays a crucial role in health monitoring and disease prevention, mainly in primary health care (PHC) context, offering numerous benefits for patients, healthcare providers, and healthcare systems [94]. Indeed, this technologic approach has various benefits, such as continuous access to health services for people, self-management promotion, patient empowerment, cost reduction of unnecessary referrals and decreasing the need for commuting to seek medical care. Moreover, physician can provide better clinical education, accelerate diagnosis, disease prevention and therapeutic interventions [89,93-96]. In this way, the health system can also overcome the issue of limited resources and facilities by utilizing telehealth [97].

In particular, telemedicine enables:

- **Remote Monitoring of Vital Signs and Health Metrics**: Vital signs, such heart rate (HR), respiration rate (RR) and blood oxygen saturation (SpO2), are recognised as essential indicators of health. Heart and respiration rates can be measured by processing electrocardiogram (ECG) signals, however, this requires multiple electrodes to be placed at different locations on the body, making the measurement inconvenient, especially during exercise, and not suitable for integration into a wearable device. Additionally SpO2, an indicator of hypoxia, cannot be extracted from ECG signals. Telemedicine, instead enables the remote monitoring of patients' vital signs, symptoms, and health metrics using wearable devices, sensors, and mobile health apps. As a consequence, patients can regularly measure and track parameters such as blood pressure, heart rate, oxygen saturation, weight, and physical activity levels, in a non-invasive, comfortable and low-cost way. In addition, healthcare providers can have access to this real-time data to monitor patients' health status, identify trends or abnormalities, and intervene promptly if necessary;

- **Chronic Disease Management**: Telemedicine supports the management of chronic conditions such as diabetes, hypertension, heart disease, COPD, and asthma by providing remote monitoring, medication management, and lifestyle coaching. Patients can receive virtual consultations with healthcare providers, participate in remote education and self-management programs, and receive personalized treatment plans tailored to their specific needs. In the last few years, interest in wearable technology for chronic diseases

management is rapidly growing, especially during and after the COVID-19 pandemic [98,99].

Specifically, considering that heart disease is the leading cause of death globally, continuous monitoring of cardiovascular dynamics has crucial relevance to improving prevention and diagnosis. In this context, telemedicine helps patients better manage their chronic conditions, prevent complications, and improve overall health outcomes;

- **Health Screening and Preventive Care**: Telemedicine facilitates the delivery of preventive care services, such as health screenings, vaccinations, and health assessments, through virtual consultations and remote monitoring. Patients can undergo screening tests, receive preventive counseling, and discuss risk factors for chronic diseases with healthcare providers via video conferencing platforms. Telemedicine increases access to preventive care services, particularly for individuals in rural or underserved areas who may face barriers to accessing traditional healthcare settings;

- **Behavioral Health and Wellness Programs**: Telemedicine supports the delivery of behavioral health services, mental health counseling, and wellness programs to promote mental well-being and prevent mental health disorders. Patients can access virtual therapy sessions, support groups, and mindfulness-based interventions for stress management, anxiety, depression, and other mental health concerns. Telemedicine removes geographical barriers to accessing mental health services and enhances privacy and confidentiality for patients seeking care;

- **Remote Health Education and Lifestyle Coaching**: Telemedicine platforms provide opportunities for patients to receive health education, lifestyle counseling, and behavior change support remotely. Patients can participate in virtual health coaching sessions, receive personalized nutrition and exercise recommendations, and access educational resources on topics such as healthy eating, physical activity, smoking cessation, and weight management. Telemedicine empowers patients to make informed decisions about their health and adopt healthier behaviors to prevent disease;

- **Patient Engagement and Empowerment**: Telemedicine and health monitoring empower patients to take an active role in managing their health and well-being. Patients can access their health data in real-time, track progress towards health goals, and communicate with

their healthcare providers more easily, leading to greater engagement and adherence to treatment plans;

- **Cost Savings and Efficiency**: Telemedicine and health monitoring can lead to cost savings and improved efficiency for healthcare systems by reducing the need for in-person visits, hospital readmissions, and emergency department visits. Remote monitoring of patients with chronic conditions can help prevent complications and reduce healthcare utilization.

1.5.1 Wearable devices

Wearable devices for health monitoring have become increasingly popular in recent years due to advancements in technology and their potential to provide continuous, real-time data on various health metrics. These devices are typically worn on the body, such as on the wrist, chest, or clothing, and can track a range of health-related parameters. Most common types of wearable devices for health monitoring include [100]:

- **Fitness Trackers**: Fitness trackers, also known as activity trackers or fitness bands, are among the most common wearable devices. They typically monitor physical activity and exercise metrics such as steps taken, distance traveled, calories burned, and heart rate. Some advanced fitness trackers may also track sleep patterns and provide insights into sleep quality;
- **Smartwatches**: Smartwatches combine the features of a traditional wristwatch with additional functionalities such as fitness tracking, heart rate monitoring, and smartphone notifications. Many smartwatches also offer built-in GPS, ECG (electrocardiogram) monitoring, blood oxygen (SpO2) monitoring, and even electrodermal activity (EDA) sensors for stress tracking;
- **Vest**: These devices are designed specifically for monitoring various health parameters and medical conditions. Examples include continuous glucose monitors (CGMs) for diabetes management, blood pressure monitors, wearable ECG monitors, pulse oximeters for oxygen saturation monitoring, and devices for monitoring respiratory rate and lung function;
- **Smart Clothing**: Smart clothing integrates wearable sensors into garments, allowing for continuous monitoring of physiological parameters such as heart rate, breathing rate, and body temperature. Smart clothing can be particularly useful for monitoring athletes during training or individuals with chronic health conditions;
- **Sleep Trackers**: Sleep trackers are designed to monitor sleep patterns and quality. They typically track metrics such as total sleep duration, sleep stages (e.g., deep, light, REM), sleep interruptions, and sleep efficiency. Some sleep trackers use actigraphy to measure movement and provide insights into sleep-wake cycles.

These wearable devices often sync data to companion mobile apps or cloud platforms, allowing users to track their health metrics over time, set goals, and receive personalized insights and recommendations. However, it's essential to consider factors such as accuracy, reliability, data privacy, and user comfort when selecting and using wearable devices for health monitoring.

Additionally, consulting with a healthcare professional can help individuals interpret the data and make informed decisions about their health and wellness.

Wearable devices (wearables) are already revolutionizing biomedicine through mobile and digital health by enabling continuous, longitudinal health monitoring outside of the clinic.

New wearables-based analytic platforms are coming online at an unprecedented rate and are transforming quality and accessibility of healthcare everywhere from hospital intensive care units (ICUs) to in-home chronic disease management to resource-limited field settings [100].

Many wearable sensors exist for use in consumer health and medical research and some devices are already being integrated into standard clinical practice (**Figure 3**). There are already several findings to support the use of wearable sensors combined with tailored algorithms for continuous, longitudinal monitoring, for example, for detection of abnormal heart conditions, hypertension, diabetes, for example (**Figure 3**). Further, these tools can be used in specific settings to target extreme healthcare costs, for example, by reducing emergency room visits and hospital readmission rates, improving postsurgical and rehabilitation outcomes, assisting with aging in-home, and preventing serious, preventable and costly medical events. Wearable sensors have an extremely broad variety of applications to specific areas of medicine, enabling monitoring of acute and chronic conditions and overall health both in and outside of the clinical setting. Ongoing studies are exploring ways in which this longitudinal data can be used to change the paradigm of medicine from a reactive to a proactive health system. mobile health interventions. Additional benefits of wearable sensors in the field setting include their applicability in environments where rapid medical care is needed and often not readily available, for example, at the scene of accidents, in military settings, athletics and in resource-constrained environments. In this context, Photoplethysmography (PPG) represents a possible way to replace ECG techniques for vital sign monitoring in wearable device systems. PPG sensors are widely embedded in wearable devices due to their ease of use, and lower cost compared to ECG sensors. Indeed, Photoplethysmography (PPG) is a popular, non-invasive, and low-cost optical technique that can provide useful information about the cardiovascular system, aiming to reveal autonomic dysfunctions and peripheral vascular diseases during daily life. In fact, due to its simplicity and versatility, this technology can be used to develop wearable and wireless devices for out-of-hospital monitoring of both healthy and pathological subjects.

In PPG-based physiological monitoring, single or multiple light sources are adopted with specific illumination wavelengths. The light passing through, or reflected from, the skin tissue indicates changes in blood volume and is captured by a photodetector [101]. From the periodic changes in the PPG signal, it can be extracted readings of Heart Rate, Respiratory Rate, and SpO2 [102,103].

However, even if technology has successfully increased the comfort of PPG sensors, in terms of wearability, dimensions and battery life, scientific research is still working on several issues, such as, poor sensor contacts, which leads to acquiring signals corrupted by noise and motion artifacts (Mas), especially during physical activity [103]. Motion artefacts (MAs) represent a significant difficulty in obtaining the desired PPG signal during physical activity. These may be generated by a motion-induced variation in the distance between the optical sensor and skin surface, contact pressure modulation, and by hemodynamic effects [104]. MA-corrupted PPG signals may significantly reduce the accuracy and stability of physiological monitoring [105]. Although several approaches and methods have been recently proposed in order to reduce MAs, the accuracy and robustness of these methods in many realistic situations is still poor.

Of note, in a recent study performed by Zheng X. et al, Authors aimed to suppress MAs and obtain reliable physiological readings using the part of the pulsatile signal, captured by a multi-wavelength illumination optoelectronic patch sensor (mOEPS), that minimizes the residual between the measured signal and the motion estimates obtained from an accelerometer. As a consequence, they proposed a robust and low complexity Minimum Residual (MR) method that effectively extract the physiological parameters, HR, RR and SpO2 by utilizing signals acquired from the mOEPS integrated with an triaxial accelerometer, during physical activity [103]. The performance of the method in reducing both in-band and out-of-band frequencies of MAs has been evaluated through two protocols with 34 subjects engaged in the study. The MA-suppressed PPG signal, obtained through MR, enables the calculation of the heart rate (HR) with an average absolute error of 1.47 beats/min for the IEEE-SPC datasets, and the calculation of HR and respiration rate (RR) to 1.44 beats/min and 2.85 breaths/min respectively for our in-house datasets. Oxygen saturation (SpO 2) levels calculated from the minimum residual wave forms were consistently. These outcomes demonstrate that MR is capable of effective suppression of MAs for a range of physical activity intensities and to achieve real-time signal processing for wearable health monitoring [103].

However, in general there are also several limitations to the use of wearable technology in healthcare, such as high device cost, not complete compatibility across platforms and lack of standardized data. In conclusion, many technical and regulatory hurdles remain, that when addressed, will improve the adoption of wearable sensors for healthcare [100].

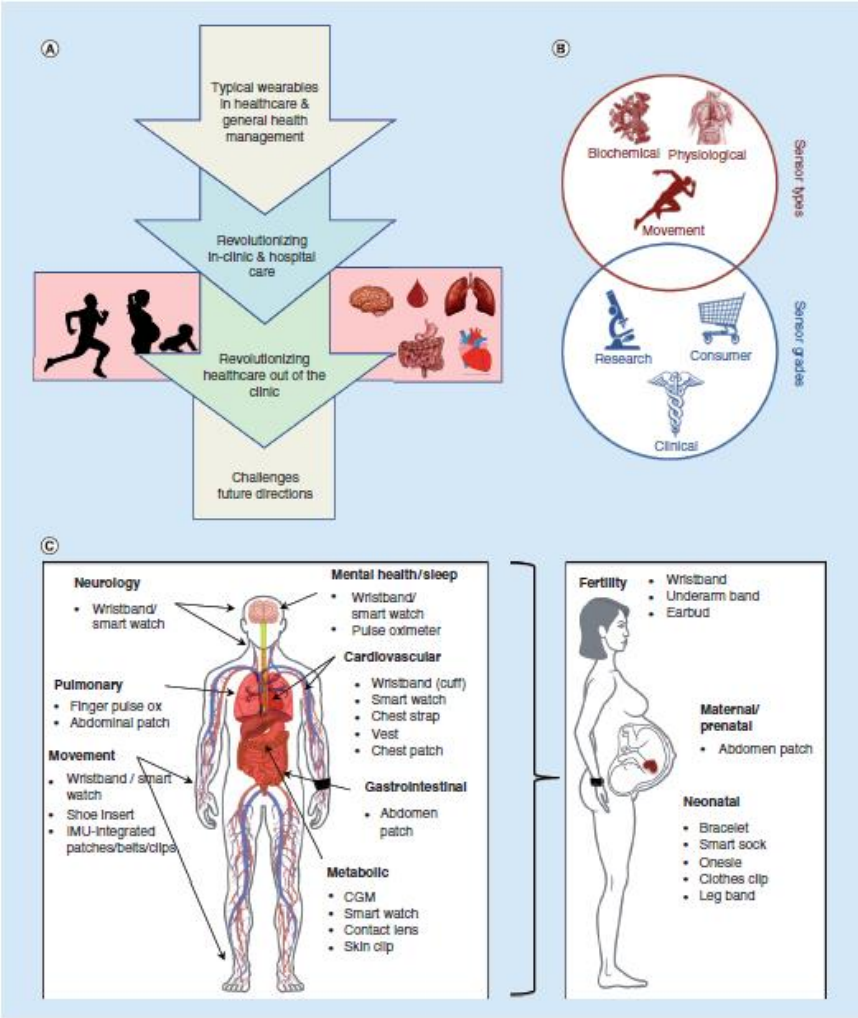


Figure 3 – A wide variety of wearable devices facilitate personalized healthcare. (A) Overview diagram of review paper showing major topics covered. (B) The three major wearable sensor types (red) and sensor grades (blue). (C) Wearable devices for use in metabolic, cardiovascular and gastrointestinal monitoring; sleep, neurology, movement disorders and mental health; maternal, pre- and neo-natal care; and pulmonary health and environmental exposures. IMU: Inertial measurement unit; CGM: Continuous glucose monitoring [Dunn J, Runge R, Snyder M. Wearables and the medical revolution. Per Med. 2018;15(5):429-448].

1.6 Telemedicine for frailty prevention

The increasing ageing population worldwide and all the age-related adverse health outcomes of recent years, have further contributed to underline the urgent need of an efficient healthcare service, in order to support well-being and better quality of life in elderly adults [106]. An important evolution in healthcare delivery is occurring, made possible by the technological revolution in wearable sensors systems, the Internet of Things (IoT), and the potential of employing machine learning, deep learning and artificial intelligence [107]. The treatment of many medical conditions is guaranteed to benefit from the use of wearable and IoT technology [107]. Therefore, wearable sensors and IoT applications have some potential for a low-cost remote monitoring, supporting independent living, reducing falls among older adults, and early detection of various long-term conditions [106].

Wearable Devices (WD) are essentially composed by:

- A sensor that generates an electrical signal;
- A transducer that analyzes and transmits the signal;
- Accessories, garments or clothes where the sensors-transducer system is integrated, that allow permanent and pervasive evaluation of health-related outcomes [108].

The use of wearable devices (WDs) and technology to evaluate and monitor physical activity and health-related outcomes in order to maintain overall health, preserve motor control, cardiovascular, metabolic and cognitive performance throughout the aging process will certainly be advantageous [109]. In particular, the use of WD have the potential to play a significant role in assessing and managing frailty by providing continuous monitoring of its various health parameters and functional abilities [110,111].

The most common uses of wearable devices in frailty assessment and management are:

- *Activity Monitoring*: The use of wearable devices, such as fitness trackers and smartwatches have been widely increased during the last years, also in older adults. This has made possible the constant monitoring of individuals' physical activity levels, including several parameters such as distance traveled, steps taken and performance duration. Collecting this information provides also insights into changes in mobility, functional status and energy expenditure, which are important indicators of frailty risk;
- *Gait Analysis*: By using wearable sensors and accelerometers, it is possible to assess walking speed, gait variability and stride length. Investigating on gait parameters can support the identification of modification in mobility, balance and prevent functional decline.

- *Sleep Monitoring*: Several devices have the ability of "sleep tracking", reporting data on sleep duration, disturbances and quality, identifying sleep-related problems, common in older adults, that may affect their quality of life in and increase frailty risk.
- *Vital Signs Monitoring:* heart and respiratory rate, blood pressure, pulse rate variability and oxygen saturation can be registered in a real-time manner. This allows early detection of changes in health status indicative of possible frailty-related complications;
- *Fall Detection and Prevention*: Wearable devices with fall detection features can automatically detect falls and alert caregivers or emergency responders in the event of an emergency. Fall detection capabilities can provide older adults with added safety and confidence in their daily activities, reducing the risk of fall-related injuries and frailty progression;
- *Medication Adherence:* The use of a reminder alert can support older adults in their daily medication routine. This feature is essential to manage chronic conditions and avoid complications related to frailty development.

Despite Wearable Devices' massive availability and constant evolution, their actual utility to measure these outcomes and extensive use by the elderly population continues to be limited [111].

In **Figure 4 is** showed the overview model of wearable sensors systems and are listed four key areas which are currently limiting the wider clinical adoption of wearable technology, especially among older adults.

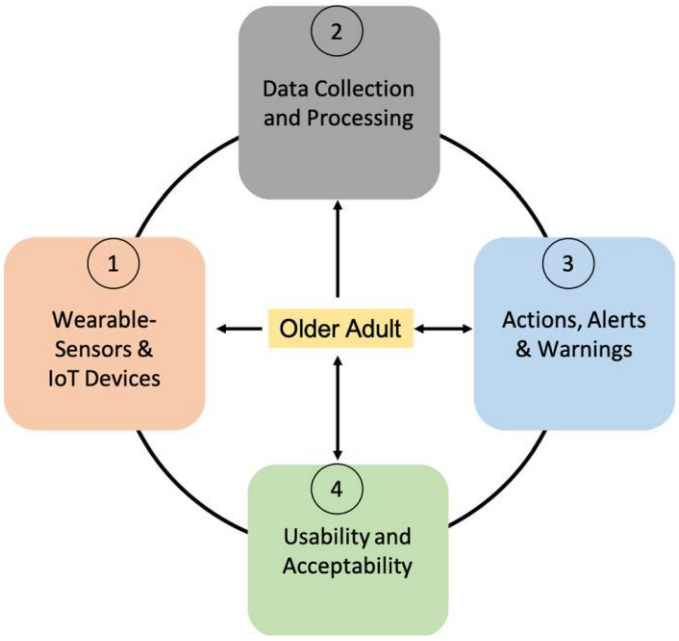


Figure 4 Overview of WS and IoT-based systems [106]

Major limitations are represented by specific devices technical challenges that can make difficult the access to all information collected. These problems need to be fully understood and resolved before the WS, and IoT-based wearable sensing and IoT-based monitoring applications can be successfully used to support older people at home. Moreover, further attention has to be kept on aspects such usability, accuracy, privacy and data security when wearable device will be selected and implemented for frailty monitoring in older adults.

Chapter 2: Aims of the study

The aim of this PhD research project, performed at the Department of Epidemiology and Prevention of the IRCCS Neuromed, Pozzilli, in collaboration with the Department of Medicine and Health Sciences "V. Tiberio" of University of Molise, Campobasso, was to conduct a pilot study on the pre-frail population aged 65 years or more, residents in Molise region. In this context, the principal purpose of the present pilot study was to standardize a protocol to develop a useful model to enhance local care in small population isolates, by remotely monitoring the health status of pre-frail subjects and to improve the progression of the frailty condition, in order to support a healthy ageing for future investigation including a larger number of individuals.

In addition, the present pilot study aimed to:

- Quantify the necessary timeframes for the subject's recruitment and examination activities, including questionnaires and functional tests administration;
- Calculate the training time needed to explain the use of the wearable device to the recruited elderly individuals;
- Assess the responsiveness of pre-frail subjects, during the preliminary screening, the baseline visits and the monitoring period;
- Estimate whether the selected cohort is representative of a larger population;
- Evaluate the compliance of pre-frail individuals with the wearable device use.

Chapter 3: Material and Methods

3.1 Study population

The present work is a pilot study that enrolled 135 individuals aged 65 years and more, randomly recruited from the general population of Molise region in Southern-central Italy between May 2023 and January 2024, on whom has been investigated frailty condition.

Exclusion criteria were refusal to sign the Informed Consent form, disturbances in understanding or willingness, age < 65 years, residence out from Molise, physical or mental disorders, clinical history of cardio and cerebrovascular diseases, being a wearer of a medical devices (such as pacemaker or prosthesis) who can affect the use of the "wearable device" or being incapable to complete specific functional tests. The project complies with the Declaration of Helsinki and was approved by IRCCS Neuromed ethical committee. The protocol of this study has been registered on https://classic.clinicaltrials.gov/: ID: NCT05173870, before starting the recruitment. Thirty-six percent of subjects refused to participate after the explanation of the project engagement.

Eight subjects, were excluded because they weren't resident in Molise region. For the present study the final study population was of 78 individuals.

3.1.1 Screening phase

In the screening phase, trained researchers provided detailed description of the project protocol and informed individuals about the specific procedures. All the participants who agreed to participate, provided written informed consent. Then it has been assessed their frail status, through the *AGILE* survey. Finally, 30 individuals, whose *AGILE* score ranged (0-3), corresponding to the "*Light*"/ "pre-frail" category, were included into the pilot study.

3.1.2 Baseline visit

After signing the informed consent, to the 30 pre-screened pre-frail elderlies, it has been administered structured questionnaires and has been performed specific practice test, to further evaluate frail condition and to collect information on physical activity, dietary habits, lifestyles, self-perception health status, cognitive assessment, drug use and clinical history of the major chronic disease (CVD, cancer etc). Blood pressure (BP) and anthropometric measurements has been performed using standardized methods. Additionally, a venous blood sample has been collected. After the analyses of routine biochemical and molecular parameters, the remaining part has been stored in liquid nitrogen in a dedicated biobank at the IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) NEUROMED, for any future molecular analysis.

3.2 Lifestyle variables assessment

Information on sociodemographic, lifestyle and clinical variables were self-reported and obtained by interviewer-administered questionnaires. Education was based on the highest qualification attained and was categorized as none, primary school graduation, lower secondary school graduation, high school graduation, university graduation. Job position was categorized as manual, non manual work, retired, housewife. Subjects were classified as “non-smokers”, “current smokers” or “former smokers”, as they self-reported. Drinking habits were classified as: abstainer, regular drinker, occasional drinker, former drinker, alcohol addiction, non-responder.

Body weight and height were measured on a standard beam balance scale with an attached ruler, in subjects wearing no shoes and only light indoor clothing. Body mass index (BMI) was calculated as kg/m^2 and then grouped into three categories as normal (≤ 25), overweight (> 25; < 30) or obese (≥ 30 kg/m^2). Waist circumference, measured in cm, was measured in the middle between the twelfth rib and the iliac crest according to the National Institutes of Health’s National Heart, Lung, and Blood Institute Guidelines [112], and hip circumference, measured in cm, was measured around the buttocks. Arm circumference, measured in cm, was measured between the lateral margin of the coracoacromial process of the scapula and the inferior margin of the olecranon process of the ulna, with the subject in an upright position, flexing the elbow at 90 degrees. Calf circumference measurement is carried out with the subject in an upright position and feet approximately 20 cm apart. BP was measured by an automatic device (OMRON-HEM-FL31) [113] three times on the non-dominant arm and the last two values were taken [114]. Measurements were made in a quiet room with comfortable temperature with the participants lying down for at least 5 minutes.

Personal history of clinical events was self-reported. Participant reports of physician-made diagnoses of several disorders and accurate information on the use (frequency, dose, compliance) of medication for any disease, were also collected during the recruitment. Use of medications was collected and categorized as no/yes/non-responder.

3.3 Blood collection and laboratory procedures

Blood samples were obtained by a venipuncture using the vacutainer system between 8.30 a.m. and 1.00 p.m. from participants who had fasted and had refrained from smoking for at least two hours before the visit. The samples were taken using the vacutainer system.

3.3.1 Blood markers of CVD risk

Serum lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) and Glycated hemoglobin were assayed by enzymatic reaction methods using an automatic analyzer (ILab ARIES Instrumentation Laboratory, Milan, Italy). Quality control for lipids and glycated hemoglobin was obtained by a commercial standard (Ser 1 and Ser 2) provided by the IL and an in-house serum standard pool. The coefficients of variability were respectively 5.25% and 2.53% for blood total cholesterol; 5.04% and 5.0% for HDL-cholesterol; 4.2% and 4.3% for triglycerides, and 1.70% and 1.72% for glycated haemoglobin. Glycated haemoglobin (HbA1c), is haemoglobin with glucose attached. The higher is the level of blood glucose, the more glycated haemoglobin is formed. Once the glucose binds to the haemoglobin, it remains there for the whole life of the red blood cells, normally about 120 days. Therefore, the HbA1c test, evaluates the average amount of blood glucose concentration over the last 3 months by measuring the percentage of glycated haemoglobin. This assay is intended for the screening and diagnosis of diabetes in general population. Glycated haemoglobin is measured from EDTA whole blood fresh samples. Final data are expressed as %HbA1c, or mmol/mol. Normal levels of glycated haemoglobin are <5.7%, <39 mmol/mol. Cut-off for diabetes diagnosis is ≥ 6.5%, 48 mmol/mol. A value of Hb1Ac comprised to 5.7-6.4% , 39-47 mmmol/mol is considered as pre-diabetic condition, in conclusion values 5.9-8%, 42-64 mmol/mol are considered as controlled diabetic.

3.4 Frailty assessment

The "*AGILE"* screening questionnaire. This is a frailty tool originated from the growing need to quickly identify frail elderly, but also to investigate "multidimensional" frailty. Thus, *AGILE* was built by selecting, among the 40 items of "*Italian version of Frailty Index (IFI)*", the 10 ones most predictive of mortality, in order to homogeneously represent the four domains of "multidimensional" frailty: physical, mental, nutritional and socio-economic.

Thus, the items were selected as following (**Figure 5**):

– *Physical frailty*: (1) "Feel everything is an effort" (#21 of *IFI*), (2) "Help up/down stairs" (#8 of *IFI*), (3) "Grip strength" (#38 of *IFI*), calculated by the mean of three measurements made using a Jamar® hydraulic dynamometer;

– *Mental frailty*: deficits in two *Mini Mental State Examination (MMSE)* items (#34 of the *IFI*): (4) temporal orientation (date/month/year) and (5) delayed recall of the three words "bread house cat" (referred to the patient at the beginning of the questionnaire); (6) Feel depressed (#22 of *IFI*);

– *Nutritional frailty*: (7) "Weight loss over 4.5 Kg in the last year" (#15 of *IFI*); (8) "Help in eating" (#5 of *IFI*);

– *Socio-economic frailty*: using two items of the Social Support Scale (SSS) (#24 of the *IFI*): (9) "Financial help from family members" and (10) "Physical help from family members".

All the binary variables have been coded using "0" to indicate the absence and "1" the presence of a deficit, except for the two items selected from the SSS where in the original scoring system the absence of help corresponds to "1" and the presence of help to "0". The *AGILE* scores were then divided into tertiles: light (0–3), moderate (4–7) and severe frailty (8–10) [115].

n.	Item	Score	Frailty domain
1	Feel everything is an effort	yes = 1; no = 0	**Physical**
2	Help up/down stairs	yes = 1; no = 0	
3	Grip strength[(1)]	yes = 1; no = 0	
4	Temporal orientation deficit[(2)]	yes = 1; no = 0	**Mental**
5	Delayed recall deficit[(3)]	yes = 1; no = 0	
6	Feel depressed	yes = 1; no = 0	
7	Weight loss over 4.5 kg in the last year	yes = 1; no = 0	**Nutritional**
8	Help in eating	yes = 1; no = 0	
9	Financial help from family members	yes = 0; no = 1	**Socio-economic**
10	Physical help from family members	yes = 0; no = 1	

[(1)]≤30 Kg in men, ≤20 Kg in women at hand-held dynamometer
[(2)]The subject does not refer the exact date (day/month/year)
[(3)]The words "bread-house-cat" are referred to the subject at the beginning of the questionnaire and then asked to the subject at this time of the questionnaire

Figure 5 - The 10 items of AGILE tool with relative scoring system divided by domain of frailty (physical, mental, nutritional and socioeconomic) [115].

The *"Italian Frailty Index (IFI)"* is a valid measure of frailty after the comprehensive geriatric assessment in an Italian cohort of non-institutionalized patients, derived from a validated scale used in a cohort of New Haven (Connecticut, USA) in the Yale Precipitating Events Project study [29]. This tool has been constructed by counting health deficits defined as defined as symptoms, signs, disabilities and diseases, including ordinal and binary variables. The *"Italian Frailty Index (IFI)"* incorporates a set of criteria to assess various domains associated with frailty, including physical, cognitive, and social aspects. In particular, it evaluates the disability in basic and instrumental activities of daily living including impaired grip strength and walking, comorbidity, self-rated health, and depression. The resulting *"Frailty Index"* embraces information on 40 deficits that are measured in routine assessments of older adults. *Jamar Plus+* digital handgrip dynamometer was used to determine the grip strength at both hands, left and right (**Figure 6**). All binary variables were coded, using the "0" to indicate the absence and "1" the presence of deficit. For intermediate response, we used "0.25," "0.5"and "0.75" (i.e., *MMSE* less than 10 = 1, 0.75 for scores ≥10 and ≤17, 0.5 for scores ≥18 and ≤20, 0.25 for scores >20 and <24, indicating a grading of cognitive impairment from 1 = severe dementia to 0.25 = mild cognitive impairment, and to 0 = no dementia). In order to better define "socioeconomic" and "nutritional" frailty, with respect to original "frailty index," the item #24 (feel lonely) and item #39 (usual pace) has been substituted in *IFI* by "*Social support Score*" (>13 = 1; 6–13 = 0.5 and 1–5 = 0) and by *Mini Nutritional assessment* (<17 = 1; 17–23.5 = 0.5 and 24 = 0) (**Appendix 1**) [116].



Figure 6 – Jamar Plus+ digital handgrip dynamometer was used to determine the grip strength at both hands, left and right, to determine weakness. For each hand two tests are made and the measurements that appear on the display of the dynamometer are collected: grip strength (kg), average between the two measures made for each hand (AVG, kg), standard deviations (SD, kg) and coefficient of variation (CV, kg).

As before mentioned, the "IFI" comprises additional tests who makes possible to analyze all the different frailty domains. It includes:

- The *"Social Support Scale (SSS)"*, is a quick tool used to measure an individual's perceived level of social support. Social support refers to the assistance, encouragement, and resources that individuals receive from their social network, including friends, family, and community members. It plays a crucial role in promoting mental health, well-being, and resilience, particularly during times of stress or adversity [117] (**Figure 7**).

Scala supporto sociale

1. Stato civile	Vedovo o celibe = 1	Coniugato = 0
2. Figli viventi	No = 1	Sì = 0
3. Fratelli e sorelle viventi	No = 1	Sì = 0
4. Frequenza di rapporti familiari	Mai, raramente = 1	Spesso, di frequente = 0
5. Con chi abita	Solo = 1	In compagnia = 0
6. Aiuto finanziario da parte dei familiari	No = 1	Sì = 0
7. Rapporti stretti con parenti non familiari	No = 1	Sì = 0
8. Aiuto concreto da parte dei familiari	No = 1	Sì = 0
9. Con quante persone del vicinato si vede almeno una volta a settimana?	Nessuno = 1	Almeno una = 0
10. Ha amici intimi?	No = 1	Sì = 0
11. Frequenza rapporti?	Mai, raramente = 1	Spesso, di frequente = 0
12. Frequenta posti pubblici?	Mai, raramente = 1	Spesso, di frequente = 0
13. Frequenta cinema-teatri?	Mai, raramente = 1	Spesso, di frequente = 0
14. Frequenta associazioni di volontariato-ricreative?	Mai, raramente = 1	Spesso, di frequente = 0
15. Legge i giornali?	Mai, raramente = 1	Spesso, di frequente = 0
16. Ascolta radio e/o vede TV?	Mai, raramente = 1	Spesso, di frequente = 0
17. Si prende cura dei bambini?	Mai, raramente = 1	Spesso, di frequente = 0
Totale		

Dalla analisi della tabella si ottiene uno score in cui i punteggi più alti individuano i soggetti con un basso livello di supporto sociale: il più basso livello si individua con un punteggio di 17

Supporto sociale buono: 1–5

Supporto sociale discreto: 6–13

Supporto sociale scarso: 14–17

Figure 7 – Social Support Scale

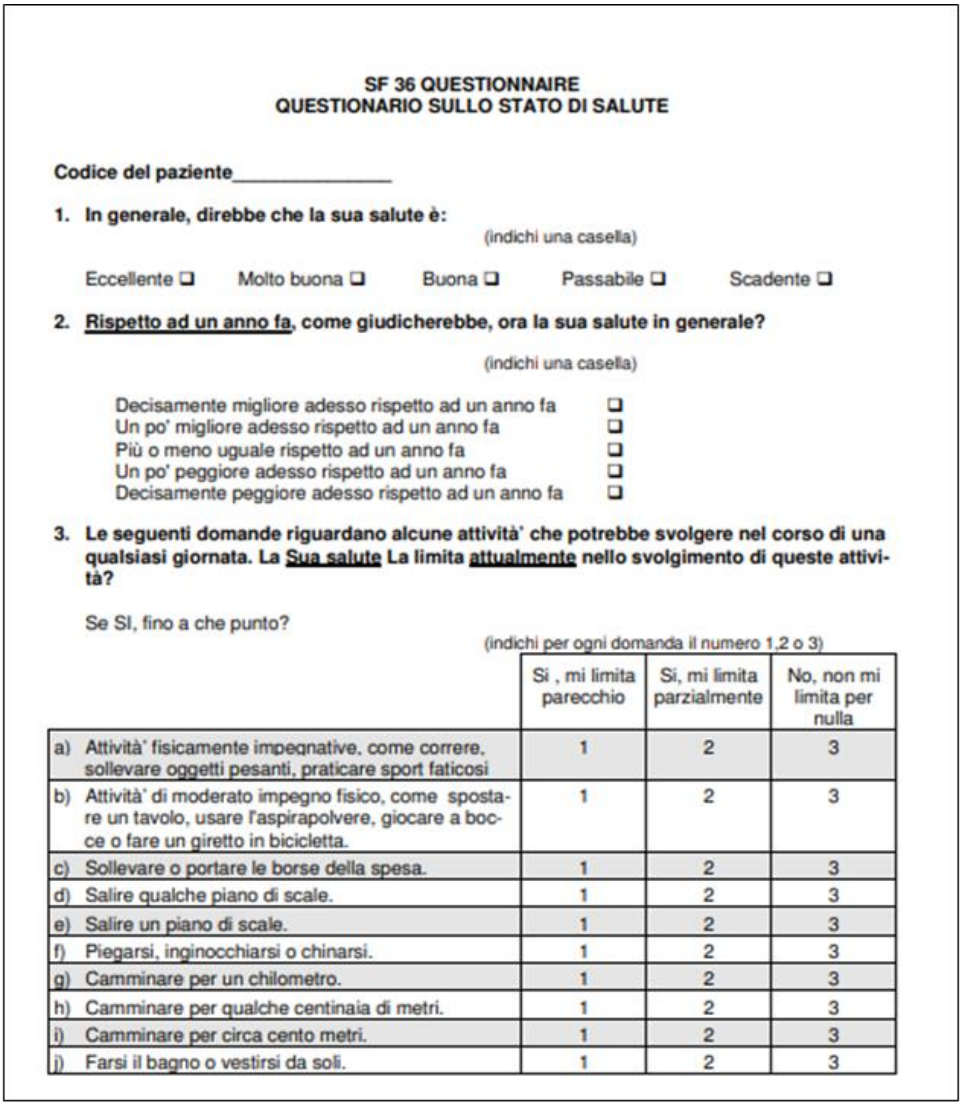
- The *"Mini Mental State Examination (MMSE)*" evaluates various cognitive domains, including orientation, registration, attention and calculation, recall, language, and visuospatial skills. Each correct response is assigned a score, and the total score is calculated by summing the scores across all items. The maximum score on the MMSE is 30 points, with higher scores indicating better cognitive function. Scores below a certain threshold (typically <24) may suggest cognitive impairment, although the cutoff may vary based on factors such as education level and cultural background. A MMSE score < 10 corresponded to a 1 point in IFI item; 11-17 = 0.75; 18-20= 0.25 e >24 = 0. This means a range from 1 (severe dementia) to 0.25 (light cognitive impairment) and 0 (no deficit) (**Appendix 1**) [118];
- The *"Mini Nutritional Assessment (MNA)"* estimates various aspects of nutritional status, including anthropometric measurements, dietary intake, mobility, psychological stress or acute disease, and self-assessment of nutritional status. It has been constructed to investigate elderly adults at risk of malnutrition. It consists of 18 items with a maximum total score of 24. Total *MNA* score <17 = 1 point in IFI; 17–23.5 = 0.5 and 24 = 0 (**Appendix 1**).

The *"Physical Activity Scale for the Elderly (PASE)"* is a self-report questionnaire designed to assess physical activity levels in older adults. It was developed as a simple and reliable tool to measure various aspects of physical activity in older populations, including leisure, household, and occupational activities. typically consists of items that inquire about the frequency and duration of various physical activities performed over the past week, distinguished in 3 different groups (leisure-time, housework and job-related work), and it is characterized by 4 levels answers for the first group, and binary (yes/no) for the remaining categories. Participants are asked to indicate how often they engage in each activity and for how long. Scores on the *PASE* can be calculated by summing the total time spent on all reported activities, weighted by intensity level.

The scale provides a comprehensive measure of overall physical activity levels, allowing researchers and healthcare professionals to assess the extent to which older adults are engaging in physical activities and to monitor changes over time. The *PASE* has been validated for use in older adult populations and has been shown to be a reliable tool for assessing physical activity levels in various settings, including research studies, clinical practice, and community health programs. It helps identify individuals who may be at risk of low physical activity levels and allows for the development of targeted interventions to promote physical activity and improve health outcomes in older adults (**Appendix 1**) [119].

The "*Health-related quality of life (HRQL)"* was assessed by using the validated Italian version of the *"Short form health survey (SF-36)"*. It was standardized in 1992 as a self-report measure of functional health and well-being. The SF-36 was designed to be a brief yet comprehensive measure of general health status. The questionnaire consists of eight scales yielding two summary measures: physical and mental health. The physical health measure includes four scales of physical functioning (10 items), role-physical (4 items), bodily pain (2 items), and general health (5 items). The mental health measure is composed of vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items). A final item, termed self-reported health transition, is answered by the subject but is not included in the scoring process. The SF-36 offers a choice of recall format at a standard (4 week) or acute (1 week) time frame (**Figure 8)** [120].

In particular, for the physical domain and for social functioning and role limitation due to emotional problems, the lowest score corresponds to the best health and the highest with the worst. For vitality and mental health instead, the lowest score resulted with the worst mental health while the highest is the best.



SF 36 QUESTIONNAIRE
QUESTIONARIO SULLO STATO DI SALUTE

Codice del paziente_____

1. **In generale, direbbe che la sua salute è:**

(indichi una casella)

Eccellente ❑ Molto buona ❑ Buona ❑ Passabile ❑ Scadente ❑

2. **Rispetto ad un anno fa, come giudicherebbe, ora la sua salute in generale?**

(indichi una casella)

Decisamente migliore adesso rispetto ad un anno fa ❑
Un po' migliore adesso rispetto ad un anno fa ❑
Più o meno uguale rispetto ad un anno fa ❑
Un po' peggiore adesso rispetto ad un anno fa ❑
Decisamente peggiore adesso rispetto ad un anno fa ❑

3. **Le seguenti domande riguardano alcune attività' che potrebbe svolgere nel corso di una qualsiasi giornata. La Sua salute La limita attualmente nello svolgimento di queste attività?**

Se SI, fino a che punto?

(indichi per ogni domanda il numero 1,2 o 3)

	Si , mi limita parecchio	Si, mi limita parzialmente	No, non mi limita per nulla
a) Attività' fisicamente impegnative, come correre, sollevare oggetti pesanti, praticare sport faticosi	1	2	3
b) Attività' di moderato impegno fisico, come spostare un tavolo, usare l'aspirapolvere, giocare a bocce o fare un giretto in bicicletta.	1	2	3
c) Sollevare o portare le borse della spesa.	1	2	3
d) Salire qualche piano di scale.	1	2	3
e) Salire un piano di scale.	1	2	3
f) Piegarsi, inginocchiarsi o chinarsi.	1	2	3
g) Camminare per un chilometro.	1	2	3
h) Camminare per qualche centinaia di metri.	1	2	3
i) Camminare per circa cento metri.	1	2	3
j) Farsi il bagno o vestirsi da soli.	1	2	3

Figure 8 – First page of the Official Italian version SF-36 questionnaire. Through 36 multiple questions different aspects are investigate such asphysical activity, role and physical health, physical pain, health in general, vitality, social activities, role and emotional state, mental health. There is also a question about changing health status over the last year [Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-483].

The "*Bone Densitometry Test"*, performed by GE Lunar Achilles Express instrument, a validated medical device which uses ultrasound waves to measure bone density in the heel bone.

Studies of fracture risk prediction show that ultrasonometry of the heel using Achilles is an economical alternative to DEXA. Achilles Express is a compact, cost-effective solution to evaluate the risk of osteoporotic fracture in elderly individuals. This test is a quick and non-invasive screening tool for assessing bone health, particularly for detecting osteoporosis fracture risk, a condition characterized by weak and brittle bones, most common in elderly individuals. The rationale at the basis of this examination is that bone density in the heel bone correlates with bone density in other parts of the body, such as the spine and hip, where osteoporosis-related fractures commonly occur. By measuring the density of the heel bone, healthcare providers can estimate the overall bone density and assess the risk of fractures. The Achilles bone densitometry tests are generally performed in outpatient settings, and they are painless and quick. However, it's important to note that while this test can provide valuable information about bone health, it may not be as accurate or comprehensive as other bone density tests, such as dual-energy X-ray absorptiometry (DXA) scans. In general, the exam is performed on right heel, if the subject has never had fractures, otherwise it is used the left heel. Before of starting the measurement, the healthcare operator indicates some personal information of the individuals such sex and age. This information is important because risk of osteoporosis is different among men and women and age classes. In particular, women in menopausal status have a higher risk of osteoporosis. Then healthcare operator put some alcohol on both heel and instrument membranes. Membranes are filled with hot water and push a little pressure on the heel. Measurement lasts less than a minute, after the end the instrument gives a report, easy to understand with the highlights on individual's bone health. Achilles Express reports are concise and easy to interpret. The individual's result is expressed as a T-score and compared to the reference population on the color-coded graph. Achilles T-scores are valid and based on the World Health Organization (WHO) definition of osteoporosis simplifying result interpretation and patient management [121].

Results are expressed by following parameters:

- STIFFNESS Index with WHO graph;
- T-score;
- Young Adult percentage;
- Age-Matched percentage;
- Z-score.

The Achilles Express ultrasonometer measures ultrasound variables of the os calcis to provide a clinical measure called the STIFFNESS INDEX. The STIFFNESS INDEX indicates risk of osteoporotic fracture in postmenopausal women comparable to bone mineral density (BMD) as measured by x-ray absorptiometry at the spine or hip. STIFFNESS INDEX results expressed as T-scores are used to assist physicians in the diagnosis of osteoporosis in the same way as are T-scores obtained by x-ray absorptiometry. T-score can be utilized, in conjunction with other clinical risk factors, to provide a comprehensive skeletal assessment. The STIFFNESS INDEX has a precision error in older women comparable to that of x-ray absorptiometry which makes it suitable for monitoring bone changes. Therefore, T-score makes possible to to categorize individuals in: "Low-risk", "Medium-risk" and "High-risk" category respectively.

- "Low-risk": there is a low chance of having a osteoporotic fracture, compared to other people of the same age;
- "Medium-risk": the risk of ostoporotic fracture reflects the average risk of individuals with the same age;
- "High-risk": there is a high possibility to have osteoporotic fracture, compared to other individuals at the same age [121].

After the Achilles examination, to the 30 pre-frail elderly individuals it has given a report of the test, and it has been suggested to consult their physicians in order to decide the best procedure according to the test results (**Appendix 1**).

3.5 Dietary information

The Mediterranean diet is characterized by high consumption of fruits, vegetables, whole grains, legumes, nuts, seeds, and olive oil, along with moderate consumption of fish, poultry, and dairy products, and low consumption of red meat. A high adherence to the Mediterranean diet has been associated with numerous health benefits, including reduced risk of cardiovascular disease, improved cognitive function, and lower incidence of chronic diseases. The Adherence to the Mediterranean diet was evaluated by the *"Mediterranean Diet Score (MDS)",*., used to assess how closely an individual's dietary habits align with the traditional Mediterranean diet pattern, through the evaluation of mean consumption of their food groups (vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, fish, alcohol, and monounsaturated to saturated fat ratio) (**Figure 9**) [122]. For typical Mediterranean diet food groups (fruits, vegetables, grains, legumes, and fish) points have been assigned as follow:

- 2 points to the highest consumption category;
- 1 point to the medium category;
- 0 point to the lowest category.

Otherwise, for not typical Mediterranean diet food groups (meat and meat products, dairy products) it has been assigned:

- 2 points to the lowest category;
- 1 point to the medium category;
- 0 point to the highest category.

For alcohol, was used the alcohol unit categories (1 alcohol unit = 12 g alcohol), assigning 2 points to the medium category (1-2 alcohol units/day), 1 point to the lowest category (<1 alcohol unit/day) and 0 points to the highest consumption category (>2 alcohol units/day).

Finally, olive oil was introduced as part of the proposed score for its importance in the typical Mediterranean diet and the beneficial effect of its consumption on health and longevity:

- 2 points = regular use;
- 1 point = frequent use;
- 0 points = occasional use).

The final *MDS* ranges from 0 to 18 points corresponding to lowest and highest adherence respectively [122].

FRUIT *1 portion: 150 g*	<1 portion/d 0	1–1·5 portions/d 1	>2 portions/d 2	
VEGETABLES *1 portion: 100 g*	<1 portion/d 0	1–2·5 portions/d 1	>2·5 portions/d 2	
LEGUMES *1 portion: 70 g*	<1 portion/week 0	1–2 portions/week 1	>2 portions/week 2	
CEREALS *1 portion: 130 g*	<1 portion/d 0	1–1·5 portions/d 1	>1·5 portions/d 2	
FISH *1 portion: 100 g*	<1 portion/week 0	1–2·5 portions/week 1	>2·5 portions/week 2	
MEAT AND MEAT PRODUCTS *1 portion: 80 g*	<1 portion/d 2	1–1·5 portions/d 1	>1·5 portions/d 0	
DAIRY PRODUCTS *1 portion: 180 g*	<1 portion/d 2	1–1·5 portions/d 1	>1·5 portions/d 0	
ALCOHOL *1 Alcohol Unit (AU) = 12 g*	<1 AU/d 1	1–2 AU/d 2	>2 AU/d 0	
OLIVE OIL	Occasional use 0	Frequent use 1	Regular use 2	**TOTAL:**

Figure 9 – Literature-based Adherence score to the Mediterranean diet (range: 0–18 points). Portion sizes derive from the calculation of mean value of weighted medians (or means) ±2 SD coming from all the cohort studies investigated [Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014;17:2769-2782].

3.6 Wearable device:

Wearable devices are electronic devices that are worn on the body or incorporated into clothing or accessories. Some common types are: smartbands, patches, smart-clothes, fitness trackers, smartwatches, health monitoring devices and sleep trackers.

These instruments allow multiple biometric readings to be remotely collected on a daily basis such as: blood pressure, heart and respiratory rate, temperature, position and quality of sleep.

During the baseline visits, pre-frail individuals have been equipped and formed to the use of a wearable device. The wearable devices and telemedicine instruments were provided, free of charge, by the company Aebiosystem, specialized in digital services for well-being and market leader for telemedicine and telemonitoring systems and for remote management of patients and doctors and management of health data.

3.6.1 Easy O2 ring

The device used during this project is the Easy O2 ring (**Figure 10**) [*https://www.aebiosystem.com/*].

Easy O2 Ring was designed to offer continuous and remote monitoring of patients' saturation and heart rate. The device consists of a measurement system capable of monitoring the following parameters directly:

- Continuous monitoring of oximetry;
- Continuous heart rate monitoring;
- Pedometer function;

Easy O2 Ring transmits via the Bluetooth interface to any device equipped with BLE communication. In order to allow the use of the AEB Health tele-monitoring application, it can be associated with the Easy Link accessory (ET-LINK-G1), which allows the data collected to be transported to the cloud, through connection to a Wi-Fi. This is the only wearable device on the market that allows instant, punctual and continuous monitoring.

- Main features:

  ▪Instant and real measurement of 2 vital parameters;

  ▪Accuracy of measurements comparable to those of bench-top devices;

  ▪Continuous monitoring of the patient even remotely thanks to the App compatible with Apple® and Android™ mobile devices;

  ▪Operating range 30m.

- Sampling Frequency:
    - Saturimetry can be sampled at fixed sampling intervals as follows: 1 minute, 2 minutes, 5 minutes, 15 minutes, 30 minutes and 60 minutes.
    - The sampling rate of the accelerometer is 10Hz.

Alarm thresholds can be entered for the both saturimetry and heart rate, upon the occurrence of which the device instantly reports data to the server. The device can be used continuously on the same patient for up to 30 days.



Specifiche Standard

Sensoristica	Sensore per la saturimetria Sensore per il battito cardiaco Contapassi
Batteria	Alimentazione: 3,7 V CC Specifiche: a litio ricaricabile con cavo (in dotazione)
Condizioni Operative	Temperatura: 34°C ~ 43°C Umidità: 15 ~ 85% senza condensa Pressione: 700 ~ 1060hPa
Condizioni di trasporto	Temperatura: 5°C ~ 55°C Umidità: 15 ~ 85% senza condensa Pressione: 500 ~ 1060hPa
Condizioni di stoccaggio	Il dispositivo ha una scadenza di 5 anni dalla data di fabbricazione e va stoccato come di seguito riportato: Temperatura: 23°C+/-5°C con umidità relativa al 50%
Grado Impermeabilità	IP24

Figure 10 Easy O2 ring: Standard Technical tools [*https://www.aebiosystem.com/*].

3.7 Statistical Analyses

All continuous variables were tested for normality using Shapiro's test and are reported as means ± standard deviation (SD). Categorical variables are reported as frequencies and percentages. IFI score and its related domains are reported as median and interquartile range (IQR). AGILE score and its domains were reported as mean and standard deviation.

AGILE and IFI score was categorized in "light", "moderate" and "severe frailty" separately for men and women, as reported by Liguori et al., and Abete et al. (**Figure 5 and Appendix 1**) [115].

The data analysis was generated using SAS/STAT software, Version 9.4 of the SAS System for Windows[a]2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA. [124].

Chapter 4: Results

During this PhD research project, from May the 4th 2023 to January the 16th 2024, 135 elderly Molise residents aged 65 years and older were enrolled, screened for frailty condition, at the Department of Epidemiology and Prevention of the IRCCS Neuromed, Pozzilli. Thirty-six percent of subjects refused to participate after the explanation of the present project engagement. Eight subjects, were excluded because they weren't Molise resident. For the present work, the final study population was of 78 individuals (mean age 70.2 ± 4.3 SD years, 46.1% women). During the screening phase, at the moment of recruitment, no one of the subjects had history of cardiovascular diseases, including stroke, angina, myocardial infarction, thrombosis nor had revascularization surgery.

We calculated the *AGILE* score and determined distribution of frailty in the total sample (N=78, mean score 3.2). In **Figure 11** it is showed the distribution of the analysed elderly population, according frailty classification and stratified by sex. In particular, the "*Light*" category was composed for the 61.8% by men (mean score 2, mean age 70.5 ± 4.6 SD years) and for 38.2% by women (mean score 3, mean age 69.8 ± 3.1 SD); the "Moderate" for 36.4 % by men (mean score 5.0, mean age 70.7 ±4.9 SD years), and the "Severe" only by 1 woman with score= 8 and age 75.8 (**Table 1**).

The mean AGILE score was 3 in women and 2 in men respectively. Moreover, considering the distribution of the four domains proposed by Liguori et al. [115], the prevalence of "physical frailty" was higher in women than in men, both in the "Light" and in the "Moderate" category (**Table 1**). In addition, the grip strength, determined using Jamar Plus+ digital handgrip dynamometer, was lower in women than in men (mean ±SD: 20.76 ± 4.71 vs 37.1 ± 8.77 Kg, for right harm and 18.75 ± 5.18 vs 33.3 ± 8.86 Kg, for left harm respectively, $P<0.0001$. Same findings have been observed for "Mental frailty" and "Nutritional frailty" mean scores both in "Light" and in "Moderate" category (**Table 1**). Otherwise "Socio-economic frailty" mean score was the same in both genders.

Table 1. Distribution of study population according to AGILE classification

Distribution	Whole Sample	Women	Men
Light (range 0-3)			
N (%)	55 (70.5)	21 (38.2)	34 (61.8)
Agile Score (mean, SD)	2	3	2
Age, years (mean, SD)	70.2 ±4.1	69.8 ±3.1	70.5 ±4.6
"Physical frailty" score (mean, SD)	0.25 ±0.081	0.33 ±0.49	0.16 ±0.37
"Mental frailty" score (mean, SD)	0.16 ±0.36	0.24 ±0.44	0.088 ±0.29
"Nutrional frailty" score (mean, SD)	0.039 ±0.20	0.048 ±0.22	0.029 ±0.17
"Socio-economic" frailty score (mean, SD)	1.95 ±0.22	1.91 ±0.44	2
Moderate (range 4-7)			
N (%)	22 (28.2)	14 (63.6)	8 (36.4)
Agile Score (mean, SD)	4.9	4.9	5
Age, years (mean, SD)	70.1 ±4.8	69.8 ±4.9	70.7 ±4.9
"Physical frailty" score (mean, SD)	1.48 ±0.72	1.54 ±0.66	1.43 ± 0.79
"Mental frailty" score (mean, SD)	1.46 ±0.87	1.29 ±1.0	1.63 ±0.74
"Nutrional frailty" score (mean, SD)	0.036 ±0.13	0.071 ±0.27	0
"Socio-economic" frailty score (mean, SD)	1.96 ±0.13	1.93 ±0.27	2
Severe (range 8-10)			
N	1 (1.3)	1 (100)	/
Agile Score	8	8	/
Age, years (mean, SD)	75.8	75.8	/
"Physical frailty" score (mean, SD)	3	3	/
"Mental frailty" score (mean, SD)	2	2	/
"Nutrional frailty" score (mean, SD)	1	1	/
"Socio-economic" frailty score (mean, SD)	2	2	/

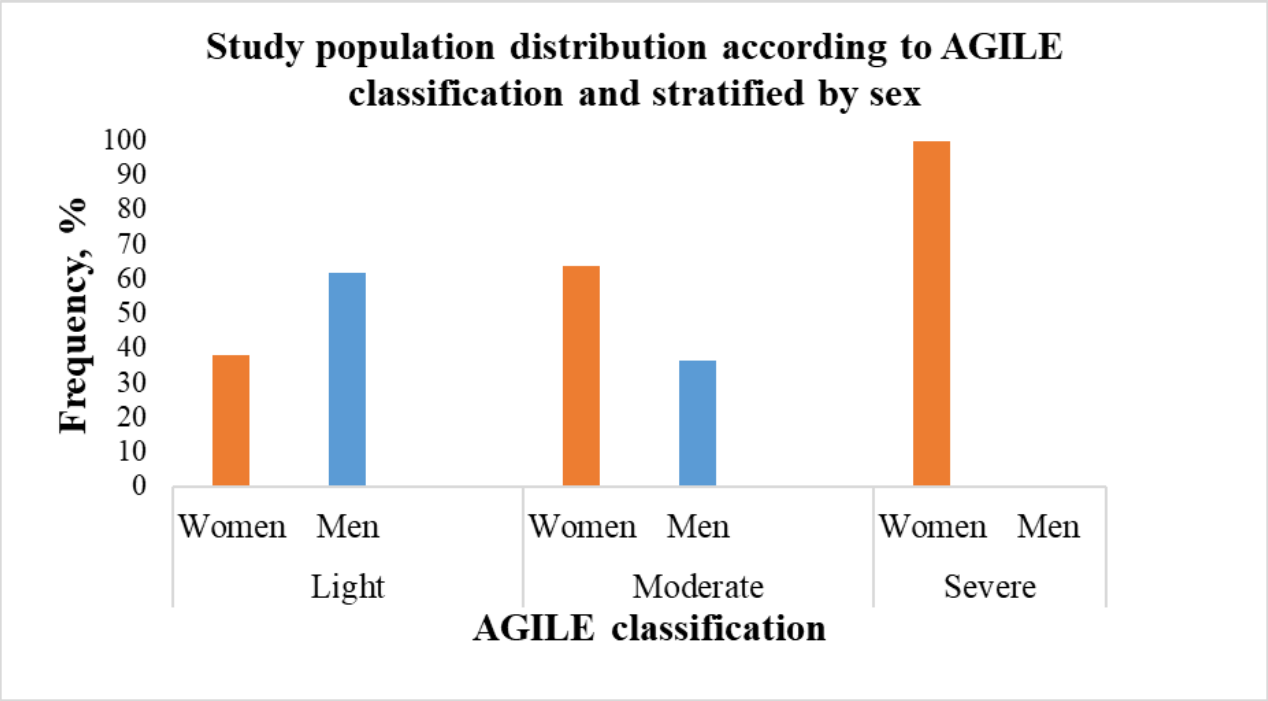


Figure 11. Distribution of sample study according AGILE classes

Findings from the screening phase allowed us to identify and select 55 individuals of the "Light" / pre-frail category, to be potentially included in the pilot study. All the 55 subjects have been called to be invited to participate to the recruiting phase of the project. Of these, 13 refused to be involved for personal or working issues, or because in that moment they were out of region.

Among November 20th 2023 to January the 16th 2024, it has been performed baseline visits of the 30 pre-frail individuals (number decided by the study protocol) (mean age 71.5 ±4.6 SD years,73.3% men, **Table 1**) of which it has been further investigated pre-frail condition.

The characteristics of the study population are showed in **Table 2,** whole sample and stratified by sex. Of note men were older than women (mean ±SD: 71.7±5.0 vs 70.9±3.4 years). Moreover, men had more heterogeneous education level, with 59.1% having high school diploma. In contrast, women 50% had high school diploma and 50% were graduated. The majority of the population was retired. Women had a higher mean BMI, were mainly non-smokers and abstainers than men. In contrast, men had higher mean blood pressure and heart rate than women. Even if all individuals have mean systolic pressure of 148.0 ±19.6 SD mmHg and mean diastolic of 79.0 ±7.7 SD mmHg, only the 56.7% of them are under pharmacological treatment for hypertension (**Table 2**).

Table 2. Characteristics of 30 pre-frail individuals stratified by sex

Characteristics	Whole Sample	Women	Men
N (%)	30	8 (26.7)	22 (73.3)
Age, years (mean ± SD)	71.5 ± 4.6	70.9 ± 3.4	71.7 ± 5.0
Education (%)			
Middle school diploma	13.3	/	18.2
High School diploma	56.7	50.0	59.1
University degree	30.0	50.0	22.7
Job position (%)			
Non manual	10.0	12.5	9.1
Retired	86.7	75.0	90.9
Housewife	3.3	12.5	/
BMI, Kg/m^2 (mean ± SD)	28.7 ± 4.1	30.3 ± 6.1	28.1 ± 3.0
Smoking habit			
Non smoker	46.7	62.5	40.9
Smoker	6.6	12.5	4.6
Former smoker	46.7	25.0	54.5
Alcohol consumption			
Abstainer	36.7	62.5	27.3
Drinker	30.0	0.0	40.9
Occasional drinker	33.3	37.5	31.8
Former drinker	0	/	/
Alcohol addiction	0	/	/
Non-responder	0	/	/
Systolic BP, mmHg (mean ± SD)	148 ± 19.6	141 ± 17.1	150 ± 20.3
Diastolic BP, mmHg (mean ± SD)	79 ± 7.7	77 ± 6.6	80 ± 7.9
Heart rate, bpm (mean ± SD)	67 ± 8.0	69 ± 3.5	66 ± 9.0
Anti-hypertensive drug (%)	56.7	50	59.1

To confirm the pre-frail status determined by the AGILE score, during the baseline visit frailty was also evaluated by the "*Italian Frailty Index*" (IFI). The IFI median score (Interquartile Range, IQR) was higher in women than in men (median (IQR): 4.3 (3.4-5.8) and 3.0 (1.8-4.0)), respectively. This confirmed the selection of pre-frail individuals for the recruitment phase of the project (**Table 3**).

However, considering the distribution of the four domains of frailty, the "*Italian frailty index*" evaluated differences in phenotypic frailty among women and men. Indeed, the prevalence of "Physical frailty", considered as the disability in basic and instrumental activities of daily living including impaired grip strength and walking, was higher in women than in men.

Focusing on the "Socio-economic frailty", investigated by the Social Support Scale, 63.3% had "good social support" (range 1-5), and 36.7% had "moderate social support" (range 6-13) (**Table 3**).

Table 3. Distribution of Frailty Scores in 30 pre-frail elderly

Characteristics	**Whole Sample**	**Women**	**Men**
N (%)	30 (100)	8 (26.7)	22 (73.3)
IFI Score (median, IQR)	3.0 (2.0-4.5)	4.3 (3.4-5.8)	3.0 (1.8-4.0)
Light (%)	100	100	100
Social Support Score (median, IQR)	5.0 (4.0-7.0)	5.0 (4.0-6.5)	4.5 (4.0-7.0)
Good (%)	63.3	62.5	63.6
Moderate (%)	36.7	37.5	36.4

Table 4 shows nutritional information of 30 pre-frail elderly individuals. According to the *"Mini Nutritional Assessment (MNA)"*, the 53.4% of study population has a "normal" nutritional status, the 43.3% is at "risk of malnutrition" and the remaining 3.3% is "malnourished" (**Table 3**).

In particular, men were mostly in "normal" status, while women were prevalently at risk of malnutrition. Moreover, it has been assessed the Adherence to the Mediterranean Diet, through the administration of the specific questionnaire. Data showed that 16.7% of pre-frail individuals had a "*high*", the 73.3% had a "*medium-high*" and the 10.0% had "*medium-low*" adherence respectively. There was no difference between women and men in the adherence to MD.

Table 4. Dietary information in population study

Characteristics	**Whole Sample**	**Women**	**Men**
N (%)	30 (100)	8 (26.7)	22 (73.3)
Mini Nutritional Assessment (median, IQR)	26.0 (22.0-28.0)	22.0 (19.-22.5)	27.0 (23.0-28.0)
Normal (%)	53.4	12.5	68.2
Malnutrition risk (%)	43.3	75.0	31.8
Malnutrition (%)	3.3	12.5	/
Mediterranean Diet Score (median, IQR)	11.0 (10.0-12.0)	10.0 (8.5-11.5)	11.0 (10.0-12.0)
High adherence (%)	16.7	/	22.7
Medium-high adherence (%)	73.3	75.0	72.7
Medium-low adherence (%)	10.0	25.0	4.6

No one of the pre-frail elderlies showed a cognitive impairment (Mini Mental State examination, median (IQR): 30.0 (29.5-30.0), **Table 5**). Considering self perception of health, repling to "How do you judge your health?" question 16 of IFI, we observed that women had a worse perception of their health and quality of life compared to men. Indeed, as shown in **Table 5**, 12.5% judged their health "decent" and 87.5% described it as "good". In contrast, men had a higher perception of their health, with a 68.2% reporting "good" health status, 22.7" "very good" and 9.1% " excellent" (**Table 5**).

Table 5. Cognitive frailty and IFI-6

Characteristics	Whole Sample	Women	Men
N (%)	30 (100)	8 (26.7)	22 (73.3)
Mini Mental State Examination (median, IQR)	30.0 (29.0-30.0)	30.0 (29.5-30.0)	30.0 (29.0-30.0)
Self-health perception			
Decent (%)	3.3	12.5	/
Good (%)	73.3	87.5	68.2
Very good (%)	16.7	/	22.7
Excellent (%)	6.7	/	9.1

In this context, it has been also assessed the health related quality of life by the SF-36 survey.

Table 6 showed that women had worse physical functioning (SF36_phy), a higher role limitation due to physical and emotional problems (SF36_rp and SF36_re), stronger body pain (SF36-bp) and in general have a worse perception of their health, when compared to men. In addition, regarding the mental domain, women had lower vitality (SF36_vit), worse social functioning and mental health (SF36_mh) than men (**Table 6**). These data as a consequence reported that not only women had a higher risk of frail condition, but also that pre-frail women have a worse health related quality of life.

Table 6. Health related quality of life

Health related quality of life domanins	Components	Whole Sample	Women	Men
	N (%)	30 (100)	8 (26.7)	22 (73.3)
Physical Domain	**SF36_phy (mean, SD)**	0.6 ± 1.0	1 ± 1.41	0.46 ± 0.80
	SF36_rp (mean, SD)	1.3 ± 2.3	2.9 ± 3.2	0.70 ± 1.6
	SF36_bp (mean, SD)	1.57 ± 2.0	2.13 ± 2.10	1.36 ± 1.99
	SF36_gh (mean, SD)	7.77 ± 2.57	8 ± 1.77	7.68 ± 2.83
Mental Domain	**SF36_vit (mean, SD)**	7.3 ± 2.47	6.0 ± 3.12	7.82 ± 2.06
	SF36_soc (mean, SD)	0.4 ± 1.22	1.0 ± 1.85	0.18 ± 0.85
	SF36_re (mean, SD)	0.87 ± 1.85	1.63 ± 2.39	0.59 ± 1.59
	SF36_mh (mean, SD)	9.63 ± 2.17	9.50±1.85	9.68 ± 2.32

Information on Physical Domain of frailty have been implemented by the "*PASE"*. For the list of questions refers to **Appendix 1**. Question from 1 to 6 reported data on "How often?" pre-frail individuals have performed a specific activity in the last 7 days, such as activity while sitting, walking, light, moderate and intense physical activity and specific exercises to increment muscular strength. Question from 7 to 9 instead, included information on "Have you done?" only to know if they did or not some peculiar activities such as house chores, electrical repairs, gardening or housekeeping.

No great differences have been observed among women and men (PASE_SCORE mean ±SD: 14.13 ± 1.81 vs 6.86 ± 3.72). The majority of individuals has not been physically active in the last 7 days.

In particular, they never perform any light or moderate or intense physical activity (PASE1, 3 to 6, **Table 7**). They mainly did activities while they were sitting or everyday housework chores (PASE7 and 8, **Table 7**). The only exception is that 63.34% of pre-frail individuals often (5-7 days) went out for a walk (PASE2, **Table 7**).

Table 7. Physical Activity Scale for Elderly

	Whole Sample				**Women**				**Men**			
How often?	Never	Rarely	Sometimes	Often	Never	Rarely	Sometimes	Often	Never	Rarely	Sometimes	Often
PASE1 (%)	0	3.3	6.7	90.0	0	0	12.5	87.5	0	4.6	4.5	90.9
PASE2 (%)	13.3	10.0	13.3	63.4	25	25	25	25	9.1	4.5	9.1	77.3
PASE3 (%)	86.7	0	10.0	3.3	100	0	0	0	81.8	0	13.6	4.6
PASE4 (%)	100	0	0	0	100	0	0	0	100	0	0	0
PASE5 (%)	96.7	3.3	0	0	100	0	0	0	95.5	4.5	0	0
PASE6 (%)	93.3	0	3.3	3.4	100	0	0	0	91.0	0	4.5	4.5
Have you done?	Not		Yes		Not		Yes		Not		Yes	
PASE7 (%)	0		100		0		100		0		100	
PASE8 (%)	23.3		76.7		0		100		31.8		68.2	
PASE9A (%)	80.0		20.0		100		0		72.7		27.3	
PASE9B (%)	63.3		36.7		75.0		25.0		59.1		40.9	
PASE9C (%)	70.0		30.0		87.5		12.5		63.6		36.4	
PASE9D (%)	23.3		76.7		25.0		75.0		22.7		77.3	
PASE_SCORE (mean ±SD*)*	16.1 ± 3.5				14.1 ± 1.8				16.9 ± 3.7			

Pre-frail women had higher levels of both serum total cholesterol and HDL than men (mean ±SD: 192.0± 27.9 and 57.4 ± 9.8 vs 176.4 ± 23.3 and 50.7 ± 12.4 mg/dL, respectively, **Table 8**). Glycated emoglobin levels, were slightly higher in women than in men too (**Table 8**). Even if both women and men levels of glycated hemoglobin suggested that all the pre-frail individuals were to be considered as diabetic, however, only 10% of them were under diabetes drug treatment. Otherwise, it has to be considered that a single measurement of glycated hemoglobin is not enough to assess diagnosis of diabetes. Further investigation are needed. Indeed to pre-frail individuals, together with the delivery of blood tests results it has been suggested to report these data to their physician.

Table 8. Cardiovascular risk factors

Characteristics	**Whole Sample**	**Women**	**Men**
N (%)	30 (100)	8 (26.7)	22 (73.3)
Total Cholesterol, mg/dL mean (SD)	180.7 ± 25.1	192.0 ± 27.9	176.4 ± 23.3
HDL Cholesterol, mg/dL	55.5 ± 12.0	57.4 ± 9.8	50.7 ± 12.4
LDL Cholesterol, mg/dl, mean (SD)	128.2 ± 25.2	134.6 ± 32.5	125.8 ± 22.2
Triglycerides, mg/dL median (IQR)	133.8 ± 72.6	131.9 ± 32.4	134.5 ± 83.5
Lipid-lowering drug, (%)	33.0	50.0	22.3
Glycated hemoglobin, mean (SD)	53.9 ± 14.8	58.3 ± 8.0	52.3 ± 16.6
Diabetes drug, (%)	10.0	25.0	4.6

The bone densitometry test showed that elderly pre-frail individuals have a mean Stiffness index = 96 ± 15 SD. According to Achilles parameters, women had a worse bone health, when compared to men. Indeed, when categories have been analysed, only 50% of them was at "*low*" risk of osteoporotic fracture. In contrast, men were mainly at "*low*" risk (**Table 9**).

Table 9. Achilles Test report

Characteristics:	**Whole Sample**	**Women**	**Men**
N (%)	30 (100)	8 (26.7)	22 (73.3)
Stiffness Index, mean (SD)	96 ± 15	85 ± 14	100 ± 14
% Young Adult, mean (SD)	95 ± 13	90 ± 13	97 ± 17
T-score, mean (SD)	-0.5 ± 1.2	-0.9 ± 1.2	-0.3 ± 1.2
% Age-Matched, mean (SD)	127 ± 18	123 ± 18	128 ± 18
Z-score, mean (SD)	1.74 ± 1.12	1.43 ± 1.05	1.85 ± 1.15
Categories:			
Low-risk (%)	70	50	77.3
Medium-risk (%)	23.3	25	22.7
High-risk (%)	6.7	25	0.0

Data on remote monitoring are not available yet because the monitoring phase is still in process.

Chapter 5: Discussion

In the present study population of elderly Molise residents, the overall prevalence of pre-frailty was 38.2% in women and 61.8 % in men; and the prevalence of frailty was 63.6% in women and 36.4% in men. Despite the small sample, this is in line with data from literature, where it has been showed that both at European level [125] and globally [126,127], the frailty and pre frailty incidence rates, among community-dwelling older adults, were significantly higher in women than men.

The majority of these studies used the "*Frailty Index*" tool to evaluate the frailty condition in general population. This tool, as before mentioned, provides a continuous measure of frailty, allowing a comprehensive way to evaluate an individual's health status across multiple domains, taking into account the complexity of frailty [24-26]. This confirms that *"Frailty Index"* is an efficient, diffuse and rapid instrument to measure frailty in community and primary care. Indeed, it has been widely used in research and clinical practice to assess frailty and guide interventions aimed at improving the health and well-being of older adults. Therefore, the choice of using the *AGILE* score for the screening phase of the present study, which is derived from the "*Italian Frailty Index*", supports the comparability and the truthfulness of our data. Of note, the main advantage of using AGILE and Frailty Index score, is that they can be rapidly and easily administered in the general population, by non-physician health professionals. Through the *AGILE* assessment, it has been identified 55 individuals belonging to the "*Light*" / pre-frail category, to be potentially included in the present pilot study. Among these 30 pre-frail individuals (mean age 71.5 ±4.6 SD years) have been choosen to further investigate pre-frail condition. This categorization was confirmed also by the administration of the "*Italian Frailty Index*", during baseline visits. Considering the distribution of the four domains of frailty (physical, socio-economic, nutritional and mental), the "*Italian frailty index*" showed different phenotypic frailty among women and men. The prevalence of "*Physical frailty*", considered as the disability in basic and instrumental activities of daily living including impaired grip strength and walking, was higher in women than in men. This finding has been also previously observed by several studies [128,129] where the "*Physical frailty*" has been mainly related to exhaustion, slowness, grip strength impairment and weakness. In a recent study in particular, it has been found that, there was higher prevalence of exhaustion (40.8% vs. 21.0%) and weakness (21.0% vs. 18.0%) among women compared to men, respectively [48]. In addition, we observed that also the grip strength, determined using Jamar Plus+ digital handgrip dynamometer, was lower in women than in men for both right left harms. Grip strength parameter has been proved to be the most discriminant component among men and women, together with physical activity [129] Our data, in line with this previous study, suggested that grip

strength and physical activity as a proxy measure of frailty, which can increase the precision of screening without a large additional investment of time, training, or cost.

Physical activity has been further investigated by the administration of "*PASE*" survey. No great differences have been observed among women and men. The major part of individuals has not been physically active in the last 7 days. In particular, they never performed any light or moderate or intense physical activity. Instead, they mainly did activities while they were sitting or everyday housework chores.

Focusing on the "*Socio-economic frailty*", investigated by the Social Support Scale, 63.3% of elderly individuals had "good social support" (range 1-5), while 36.7% had "moderate social support". It is widely known from literature that there is a relationship between social factors and health [130]. Social integration (marriage, family relationships, friendships, church and civic communities, volunteering) is known to be a beneficial aspect for individuals health. Indeed, social integration both prevents health problems, and accelerate the recovery time after clinical conditions occurrence [131]. Moreover, a higher number of social relationships, is inversely related to the onset of clinical problems [132,133].

The presence of chronic diseases, such as, diabetes, cardiovascular risk factors (hypertension, orthostatic hypotension, atherosclerosis, atrial fibrillation, heart failure and vascular diseases), increase the risk of frailty. These disorders indeed, can lead to functional frailty-related impairments and decrease the overall resilience. All the 30 pre-frails individuals showed hypertension (mean systolic pressure of 148.0 ±19.6 SD mmHg and mean diastolic of 79.0 ±7.7 SD mmHg). Otherwise, only the 56.7% of them were under pharmacological treatment for this condition. Hypertension has been widely found in previous studies associated with frailty, although the root cause is still matter of debate [134]. Frailty and hypertension often coexist in older people, but there have been few studies regarding their relationship with each other and with antihypertensive treatment. As frailty may affect the risk-benefit ratio of hypertension therapy and increase the prevalence of hypertension, it is important to assess for each patient whether hypertension is combined with frailty [135].

For this reason, it is essential to further investigate how to manage individuals with both these conditions, in order to understand prevention strategies in hypertensive older individuals. Together with hypertension, others common cardiovascular risk factors have been also investigated in the 30 pre-frail participants of the present pilot study. It has been observed that pre-frail women had higher levels of both serum total cholesterol and HDL than men. In addition, in both women and men levels of glycated hemoglobin, showed that all the pre-frail individuals were to be considered as diabetic. However, only 10% of them, were under diabetes drug treatment. Altogether, these

observations are in line with literature data who reported that CVD risk factors and diabetes and are both the most common comorbidities found in elderly individuals and the major risk factors for frailty [50,61-63].

Nutritional domain has been the first aspect identified as both characteristic and risk factor for frailty condition, already in 2001, when Fried et al. proposed for the first time, the operational definition "*Phenotype of frailty*". Indeed, the unintentional weight loss of ≥10 pounds in prior year or, at follow-up, of ≥ 5% of body weight in prior year (by direct measurement of weight), have always represented the main parameter to recognise this condition. Nutritional information of the 30 pre-frail elderly, therefore has been collected. According to the "MNA", it has been observed that only the 53.4% of the cohort investigated had a "normal" nutritional status. In particular, women against men were prevalently at "risk of malnutrition". In addition, results showed that there is no difference in Adherence to the Mediterranean Diet among women and men, however more than 70% had a "medium-high" adherence to this dietary pattern. Poor nutrition might contribute to frailty, but on the other hand frailty might also affect dietary intake, for example by impairments in going shopping, chewing, or swallowing. Based on our data, it is not possible to decide, whether a Mediterranean diet prevents frailty or whether the diet is altered by frailty or comorbidity which might contribute to nutritional risk. Although we did not find difference in the MD score, probably due to the small sample size of our study, our findings show that a "medium-high" adherence to MD could contribute to protect elderly individuals from frailty incidence or to slow its progression. This is in line with the well-known association of between Adherence to a traditional Mediterranean Diet and lower incidence of several chronic diseases in several cohorts worldwide [136-138].

Cognitive impairment referred as a decline in cognitive function is considered one of the common age-related changes in nervous system [139,140,141]. It can range from mild cognitive impairment (MCI), which may not significantly interfere with daily functioning, to severe forms such as dementia, where there is a notable decline in memory, thinking skills, and the ability to perform everyday activities. As expected, cognitive impairment and frailty are two interconnected aspects commonly observed in the elderly population. This can be explained by the fact that these two conditions can share underlying biological mechanisms and common risk factors, In the end, cognitive impairment and frailty can exacerbate each other's effects. As a consequence, managing cognitive impairment and frailty in the elderly are crucial for optimizing outcomes and improving the quality of life for elderly individuals affected by these conditions. In the present study, of note, no one of the pre-frail elderlies showed a cognitive impairment, as resulted by the Minimental State Examination test.

Another important aspect of the management of frailty is the health-related quality of life. Data from the present PhD project showed that women had a higher role limitation due to physical and emotional problems (SF36_rp and SF36_re), stronger body pain (SF36-bp) and in general have a worse perception of their health, when compared to men. Moreover they reported also lower vitality, worse social functioning and mental health. These data, as a consequence, reported that not only women had a higher risk of frail condition, but also that pre-frail women have a worse health related quality of life. This interesting observation make us understand that not only social support, but also the self-perception of health is essential in order to improve the prognosis and the recovery from a chronic disease.

Epidemiological studies in men and women have shown that frailty is linked with an increased risk of falls and future fractures due to several factors such as muscle weakness, balance problems, and impaired gait [75,142,143]. Falls can result in injuries such as fractures, head trauma, and soft tissue injuries, leading to pain, disability, and decreased quality of life. In addition, the risk of osteoporosis is typical condition of elderly individuals. However, there are surprisingly few studies which have looked at the link between bone health and frailty. To this extent we measured bone health of pre-frail individuals through the "*Bone Densitometry Test"*. According to parameters resulting of this tool, women again reported a worse bone health, when compared to men, Only the 50% of them, indeed, showed a "low-risk" of osteoporotic fracture. In contrast, men were prevalently at "low" risk. Although it is widely known that this condition has a negative effect on elderly quality of life, the assessment of "bone health" in elderly individuals, might help in the management of frailty condition. This might result in timely treatment and prevention of the syndrome.

Chapter 6: Conclusions

Frailty is a condition of increased vulnerability to stressors due to age-related decline in physiologic reserves across neuromuscular, metabolic, and immune systems. In general, frailty is expressed as a multifactorial dysfunctional framework which includes physical, psychological, cognitive, economic and social spheres and which leads to a serious deterioration in the quality of life. Due to the great impact of this condition, developing interventions programs aiming to prevent the progression of frailty towards the independence loss, is essential to support healthy ageing.

Even if strictly connected, it has to be considered that frailty doesn't occur in all elderly adults. This is essential in order to assess health management of elderly individuals. Preventing frailty and its consequences, therefore is the most important challenge of the present aging society. There is the urgent need for a universally valid characterization of the clinical syndrome of frailty and also the research of a validated tool useful to timely recognize it. This PhD pilot study provides a complete evaluation of the several domains of frailty domains: nutritional, physical, psychological, social and biochemical. The main aim of the present project was to standardize a protocol to develop a useful model for enhancing local care in small population, by remotely monitoring the health status of pre-frail individuals over 65. Findings from the present project demonstrated that the selected study population of 30 pre-frail elderly residents in Molise region is representative of a larger population. This statement is proved by the fact that all the results observed for the different domain of frailty were in line with previous data from epidemiological studies who investigated aspect of frailty in larger populations worldwide. Of note, our study is one of the few epidemiological studies who investigated frailty management and prevention in an Italian cohort. Moreover, this research describes the most commonly used frailty components and the corresponding indicators in contemporary publications. These findings can be used to guide the development of a standardized protocol for frailty in future studies, with larger populations. Healthcare professionals, can use these frailty components and their corresponding indicators to comprehensively identify frail older adults from physical, psychological and social perspectives to provide holistic care to meet the multidimensional healthcare needs of this vulnerable population. In addition, data may support the debate and the elaboration of public policies focused on frailty syndrome in order to deal with the demographic growth of the country and the higher life expectancy of the population. The choice of use "*AGILE*" and "*Italian Frailty Index*" two simple and ready to use frailty assessment tools, has confirmed the validity of these instruments. The association between poor nutritional intake and frailty was demonstrated in numerous recent studies. Consequently, the goal will be to raise the general dietary intake of high-quality food to provide sufficiently both macro and micronutrients. In the present study, it has been observed that major part of the pre-frail population had a "medium-

high" adherence to the Mediterranean Diet. In the future, clinical trials should evaluate whether an intervention promoting MD is able to prevent frailty. In contrast, to the association between frailty and cognitive impairment, in the present study no-one of the pre-frail individuals presented cognitive impairment, measured by the Mini Mental State Examination. Moreover, a novelty of the present study has been the use of SF-36 questionnaire, to estimate the mental and physical health self-perception in pre-frail women and men. Common chronic diseases in elderly and frail individuals, have been confirmed by the data from the present study. Another strength of this PhD project has been the evaluation of bone health by *"Bone densitometry test*". Considering the prevalence of this condition and its negative effect on elderly quality of life, the assessment of "bone health" in elderly individuals, might help in the management of frailty condition, resulting in timely treatment and prevention of the syndrome.

The increasing ageing population worldwide and all the age-related adverse health outcomes of recent years, have further contributed to underline the urgent need of an efficient healthcare service, in order to support well-being and better quality of life in elderly adults. Many wearable sensors have been already been integrated in clinical use and have a wide variety of applications to specific areas of medicine, enabling monitoring of acute and chronic conditions and overall health. In particular, vital signs, such heart rate (HR), respiration rate (RR) and blood oxygen saturation (SpO2), are recognized as essential indicators of health. In addition, the remote monitoring of patients' vital signs, symptoms, and health metrics using wearable devices, sensors, and mobile health apps represents a non-invasive, comfortable and low-cost approach for patients to regularly measure health parameters, and for health professionals to have access to this real-time data to monitor patients' health status, identify trends or abnormalities, and intervene promptly if necessary. Considering the presence of comorbidity in elderly individuals and all the adverse age-related outcome who increase the risk of frailty occurrence, the possibility to continuously monitor vital signs as heart rate variability, as a proxy of orthostatic hypotension occurrence and of risk of falls prevention, in elderly individuals, is the major novelty of the present study. This evaluation is achievable thanks to the use of *O2 Ring* wearable device who is equipped with a PPG sensor, able to measure, among others parameters, heart rate variability. This pilot study put the basis for developing a useful model to enhance local care in small population isolates, by remotely monitoring the health status of pre-frail individuals over 65 years. Results from the remote monitoring with *O2 Ring* will give further information of the potential use of PPG sensors, in wearable device, to evaluate and prevent frailty in elderly populations. Findings from this study could provide valuable insights for both the management and the prevention of frailty in older individuals, in order to promote healthy aging.

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Appendix 1

ITALIAN FRAILTY INDEX

1. Aiuto nel lavarsi	SI = 1	No = 0			
2. Aiuto nel vestirsi	SI = 1	No = 0			
3. Aiuto nel sedersi o alzarsi dalla sedia	SI = 1	No = 0			
4. Aiuto nel camminare in casa	SI = 1	No = 0			
5. Aiuto nel mangiare	SI = 1	No = 0			
6. Aiuto nella cura della casa	SI = 1	No = 0			
7. Aiuto nell'utilizzare il bagno	SI = 1	No = 0			
8. Aiuto nel salire o scendere le scale	SI = 1	No = 0			
9. Aiuto nell'alzare 4.5 kg	SI = 1	No = 0			
10. Aiuto nel fare la spesa	SI = 1	No = 0			
11. Aiuto nei lavori di casa	SI = 1	No = 0			
12. Aiuto nel preparare i pasti	SI = 1	No = 0			
13. Aiuto nell'assumere i farmaci	SI = 1	No = 0			
14. Aiuto nella gestione del denaro	SI = 1	No = 0			
15. Perdita di più di 4.5 kg di peso nell'ultimo anno	SI = 1	No = 0			
16. Giudizio sulla propria salute	Scarsa = 1	Discreta = 0.75	Buona = 0.5	Molto buona = 0.25	Eccellente = 0
17. Come è cambiata la sua salute nell'ultimo anno?	Peggiorata = 1	Migliorata/stessa = 0			
18. Persistenza a letto almeno 1/2 giornata per motivi di salute, nell'ultimo mese?	SI = 1	No = 0			
19. Riduzione della solita attività nell'ultimo mese?	SI = 1	No = 0			
20. Uscire	<3 Giorni = 1	≥3 Giorni = 0			
21. Affaticarsi per qualsiasi cosa	Spesso = 1	Qualche volta = 0.5	Rara-mente = 0		
22. Sentirsi depresso	Spesso = 1	Qualche volta = 0.5	Rara-mente = 0		
23. Sentirsi infelice	Spesso = 1	Qualche volta = 0.5	Rara-mente = 0		
24. Social support score (vedi allegato 1)	>13 = 1	6–13 = 0.5	1–5 = 0		
25. Avere difficoltà a mettersi in moto	Spesso = 1	Qualche volta = 0.5	Rara-mente = 0		
26. Ipertensione	SI = 1	Sospetta = 0.5	No = 0		
27.Angina pectoris	SI = 1	Sospetta = 0.5	No = 0		
28. Insufficienza cardiaca cronica	SI = 1	Sospetta = 0.5	No = 0		
29. Ictus	SI = 1	Sospetta = 0.5	No = 0		
30. Cancro	SI = 1	Sospetta = 0.5,	No = 0		
31. Diabete	SI = 1	Sospetta = 0.5	No = 0		
32. Artrosi	SI = 1	Sospetta = 0.5	No = 0		
33. Broncopneumopatia cronica	SI = 1	Sospetta = 0.5	No = 0		
34. MMSE	<10 = 1	11–17 = 0.75	18–20 = 0.5	20–24 = 0.25	>24 = 0

35. BMI	<18.5, ≥30 = 1		25–<30 = 0.5		18.5–24.9 = 0
36. Picco flusso espiratorio = _____L/min 1 = _____ 2 = _____ 3 = _____	≤340 (uomo), ≤310 (donna) = 1		>340 (uomo), >310 (donna) = 0		
37. Forza muscolare sollevamento = Kg 1 = _____ 2 = _____ 3 = _____	≤12 (uomo), ≤9 (donna) = 1		>12 (uomo), >9 (donna) = 0		
38. Forza muscolare presa = Kg 1 = _____ 2 = _____ 3 = _____	Uomo = 1		Uomo = 0		
	BMI ≤24,	Kg ≤29	BMI ≤24	Kg >29	
	BMI 24.1–28	Kg ≤30	BMI 24.1–28	Kg >30	
	BMI >28	Kg ≤32	BMI >28	Kg >32	
	Donna = 1		Donna = 0		
	BMI ≤23	Kg ≤17	BMI ≤23	Kg >17	
	BMI 23.1–26	Kg ≤ 17.3	BMI 23.1–26	Kg >17	
	BMI 26.1–29	Kg ≤18	BMI 26.1–29	Kg >18	
	BMI >29	Kg ≤21	BMI >29	Kg >21	
39. Mini nutritional Assessment (vedi allegato 2)	<17 = 1		17–23.5 = 0.5		24 = 0
40. Tempo impiegato per percorrere 4 metri con passo rapido (sec)	>10 = 1		≤10 = 0		
Totale					

MINI MENTAL STATE EXAMINATION

1. *Orientamento spazio-temporale*

   II paziente sa riferire il giorno del mese, l'anno, il mese, il giorno della settimana e la stagione. [0] [1] [2] [3] [4] [5]

   II paziente sa riferire il luogo in cui si trova, a quale piano, in quale città, regione, stato. [0] [1] [2] [3] [4] [5]

2. *Memoria*

   L'esaminatore pronuncia ad alta voce tre termini (casa, pane, gatto) e chiede al paziente di ripeterli immediatamente. [0] [1] [2] [3]

   L'esaminatore deve ripeterli fino a quando il paziente non li abbia imparati (max 6 ripetizioni). Tentativi n.

3. *Attenzione e calcolo*

   Far contare per sette all'indietro, partendo da 100. Fermarsi dopo le prime 5 risposte.

   Se il paziente avesse difficoltà di calcolo, far scandire all'indietro la parola "MONDO" una lettera alla volta. [0] [1] [2] [3] [4] [5]

4. *Richiamo delle tre parole*

   Richiamare i tre termini precedentemente imparati. [0] [1] [2] [3]

5. *Linguaggio*

   II paziente deve riconoscere due oggetti.

   Come si chiama questo? (indicando una matita). Come si chiama questo? (indicando un orologio). [0] [1] [2]

   Invitare il paziente a ripetere la frase "TIGRE CONTRO TIGRE". [0] [1]

6. *Esecuzione di un compito su comando.*

   Invitare il paziente ad eseguire correttamente i seguenti ordini:

   prenda un foglio con la mano destra,

   Io pieghi a metà,

   Io butti dal tavolo. [0] [1] [2] [3]

   Presentare al paziente un foglio con la seguente scritta: "Chiuda gli occhi".

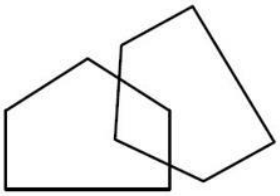
   Invitare il paziente ad eseguire il comando indicato [0] [1]

   Far scrivere al paziente una frase formata almeno da soggetto e verbo. [0] [1]

   Far copiare al paziente il disegno indicato. [0] [1]

   (Il materiale delle ultime due prove va conservato)

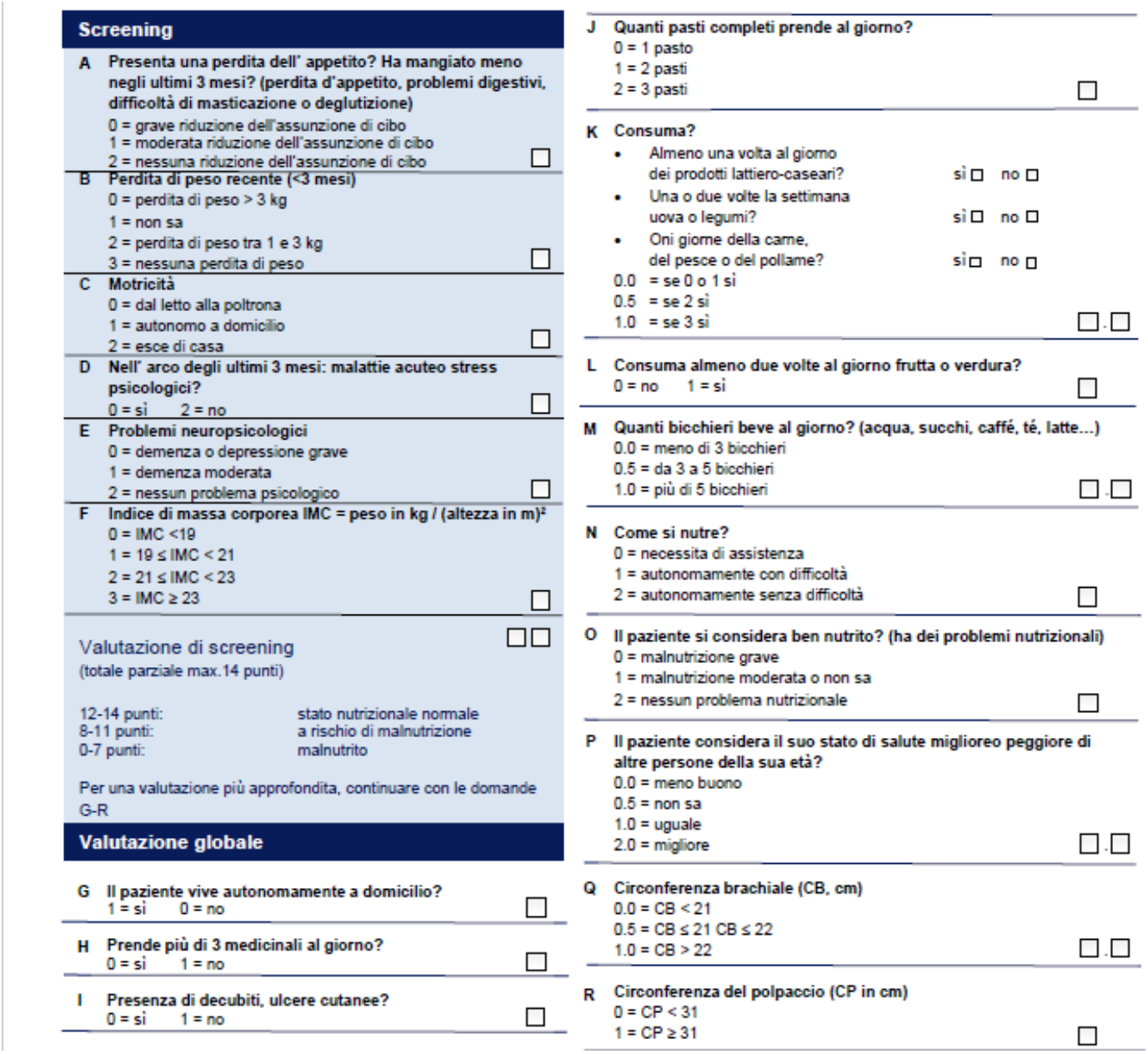
Disegno



Frase

PUNTEGGIO COMPLESSIVO /30

MINI NUTRITIONAL ASSESSMENT



Screening

A **Presenta una perdita dell' appetito? Ha mangiato meno negli ultimi 3 mesi? (perdita d'appetito, problemi digestivi, difficoltà di masticazione o deglutizione)**
0 = grave riduzione dell'assunzione di cibo
1 = moderata riduzione dell'assunzione di cibo
2 = nessuna riduzione dell'assunzione di cibo ☐

B **Perdita di peso recente (<3 mesi)**
0 = perdita di peso > 3 kg
1 = non sa
2 = perdita di peso tra 1 e 3 kg
3 = nessuna perdita di peso ☐

C **Motricità**
0 = dal letto alla poltrona
1 = autonomo a domicilio
2 = esce di casa ☐

D **Nell' arco degli ultimi 3 mesi: malattie acuteo stress psicologici?**
0 = sì 2 = no ☐

E **Problemi neuropsicologici**
0 = demenza o depressione grave
1 = demenza moderata
2 = nessun problema psicologico ☐

F **Indice di massa corporea IMC = peso in kg / (altezza in m)²**
0 = IMC <19
1 = 19 ≤ IMC < 21
2 = 21 ≤ IMC < 23
3 = IMC ≥ 23 ☐

Valutazione di screening ☐☐
(totale parziale max.14 punti)

12-14 punti: stato nutrizionale normale
8-11 punti: a rischio di malnutrizione
0-7 punti: malnutrito

Per una valutazione più approfondita, continuare con le domande G-R

Valutazione globale

G **Il paziente vive autonomamente a domicilio?**
1 = sì 0 = no ☐

H **Prende più di 3 medicinali al giorno?**
0 = sì 1 = no ☐

I **Presenza di decubiti, ulcere cutanee?**
0 = sì 1 = no ☐

J **Quanti pasti completi prende al giorno?**
0 = 1 pasto
1 = 2 pasti
2 = 3 pasti ☐

K **Consuma?**
- Almeno una volta al giorno dei prodotti lattiero-caseari? sì ☐ no ☐
- Una o due volte la settimana uova o legumi? sì ☐ no ☐
- Oni giorne della carne, del pesce o del pollame? sì ☐ no ☐

0.0 = se 0 o 1 sì
0.5 = se 2 sì
1.0 = se 3 sì ☐.☐

L **Consuma almeno due volte al giorno frutta o verdura?**
0 = no 1 = sì ☐

M **Quanti bicchieri beve al giorno? (acqua, succhi, caffé, té, latte...)**
0.0 = meno di 3 bicchieri
0.5 = da 3 a 5 bicchieri
1.0 = più di 5 bicchieri ☐.☐

N **Come si nutre?**
0 = necessita di assistenza
1 = autonomamente con difficoltà
2 = autonomamente senza difficoltà ☐

O **Il paziente si considera ben nutrito? (ha dei problemi nutrizionali)**
0 = malnutrizione grave
1 = malnutrizione moderata o non sa
2 = nessun problema nutrizionale ☐

P **Il paziente considera il suo stato di salute miglioreo peggiore di altre persone della sua età?**
0.0 = meno buono
0.5 = non sa
1.0 = uguale
2.0 = migliore ☐.☐

Q **Circonferenza brachiale (CB, cm)**
0.0 = CB < 21
0.5 = CB ≤ 21 CB ≤ 22
1.0 = CB > 22 ☐.☐

R **Circonferenza del polpaccio (CP in cm)**
0 = CP < 31
1 = CP ≥ 31 ☐

[Vellas B, Villars H, Abellan G, et al. Overview of MNA® - Its History and Challenges. J Nut Health Aging 2006; 10: 456-465.Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini Nutritional Assessment (MNA-SF). J. Geront 2001; 56A: M366-377; Guigoz Y. The Mini-Nutritional Assessment (MNA®) Review of the Literature – What does it tell us? J Nutr Health Aging 2006; 10: 466-487. ® Société des Produits Nestlé SA, Trademark Owners.© Société des Produits Nestlé SA 1994, Revision 2009. Per maggiori informazioni : www.mna-elderly.co].

PHYSICAL ACTIVITY SCALE FOR ELDERLY

Lo score del PASE SCALE test è calcolato per ciascuna attività, moltiplicando l'ammontare del tempo (h/d) o la partecipazione (Si/No) per un peso attività-specifico. Il PASE totale è ottenuto sommando i singoli PASE score.

Negli gli ultimi 7 giorni:

1. Quante volte ha svolto attività stando seduto come leggere, guardare la televisione o fare qualche lavoretto?

Mai (Passare al punto 2) Raramente (1-2 gg) Qualche volta (3-4 gg) Spesso (5-7 gg)

1a) Quali sono queste attività?

1b) In media, nei giorni indicati, quante ore ha dedicato ad esse?

Meno di 1 h 1-2 h 2-4 h Più di 4 h

2. Quante volte è andato a passeggiare fuori casa per una qualsiasi ragione (svago, allenamento, a piedi al lavoro, a spasso con il cane, ecc.)?

Mai (Passare al punto 3) Raramente (1-2 gg) Qualche volta (3-4 gg) Spesso (5-7 gg)

2a) In media, nei giorni indicati, quante ore ha dedicato a camminare?

Meno di 1 h 1-2 h 2-4 h Più di 4 h

2b) Qual è la distanza percorsa negli ultimi 7 gg?

Meno di 1 km 1-2 km 2-4 km Più di 4 km

2c) Quante rampe di scale ha salito in totale negli ultimi 7 gg? (1 rampa=10 gradini)

Meno di 1 rampa 1-2 rampe 2-4 rampe Più di 4 rampe

3. Quante volte si è impegnato in uno sport leggero, o attività ricreativa (passeggiare in bicicletta, giocare a bocce, yoga, tai chi, pescare dalla barca o attività simili)?

Mai (Passare al punto 4) Raramente (1-2 gg) Qualche volta (3-4 gg) Spesso (5-7 gg)

3a) Quali sono queste attività?

3b) In media, nei giorni indicati, quante ore ha dedicato ad esse?

Meno di 1 h 1-2 h 2-4 h Più di 4 h

4. Quante volte si è impegnato in uno sport moderato, o attività ricreativa, come tennis in doppio, ballo o attività simili?

Mai (Passare al punto 5) Raramente (1-2 gg) Qualche volta (3-4 gg) Spesso (5-7 gg)

4a) Quali sono queste attività?

4b) In media, nei giorni indicati, quante ore ha dedicato ad esse?

Meno di 1 h 1-2 h 2-4 h Più di 4 h

5.Quante volte si è impegnato in uno sport faticoso, o attività ricreativa, come jogging, nuoto, ciclismo, tennis singolo, danza aerobica, sci (pista o fondo) o attività simili?

Mai (Passare al punto 6) Raramente (1-2 gg) Qualche volta (3-4 gg) Spesso (5-7 gg)

5a) Quali sono queste attività?

5b) In media, nei giorni indicati, quante ore ha dedicato ad esse?

Meno di 1 h 1-2 h 2-4 h Più di 4 h

6. Quante volte ha fatto esercizi specifici per incrementare la forza muscolare?

Mai (Passare al punto 7) Raramente (1-2 gg) Qualche volta (3-4 gg) Spesso (5-7 gg)

6a) Quali sono queste attività?

6b) In media, nei giorni indicati, quante ore ha dedicato ad esse?

Meno di 1 h 1-2 h 2-4 h Più di 4 h

7. Ha svolto attività stando seduto come leggere, guardare la TV o fare qualche lavoretto? Si No

6MWT (6-MINUTES WALKING TEST)

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (see Table 2 for the Borg scale and instructions).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself.
You will probably get out of breath or become exhausted.
You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones.
You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."
Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly. "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready."

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

Pretreatment and posttreatment comparisons
Lung transplantation (9, 10)
Lung resection (11)
Lung volume reduction surgery (12, 13)
Pulmonary rehabilitation (14, 15)
COPD (16–18)
Pulmonary hypertension
Heart failure (19, 20)
Functional status (single measurement)
COPD (21, 22)
Cystic fibrosis (23, 24)
Heart failure (25–27)
Peripheral vascular disease (28, 29)
Fibromyalgia (30)
Older patients (31)
Predictor of morbidity and mortality
Heart failure (32, 33)
COPD (34, 35)
Primary pulmonary hypertension (10, 36)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

WORKSHEET

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _ _ _

TABLE 2. THE BORG SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: “Please grade your level of shortness of breath using this scale.” Then ask this: “Please grade your level of fatigue using this scale.” At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

ACHILLES REPORT

In its official document of 2005, the "International Society of Clinical Densitometry" recommends that peripheral densitometry devices have to be used for osteoporotic fracture risk assessment, rather than for the diagnosis of osteoporosis. The T-score provided for this test classifies individuals into three categories:

• **low risk**, not presumably exposed to the risk of osteoporotic fracture.

• **medium risk**, moderate risk of osteoporotic fracture, where further measurements, specifically central DEXA, should be considered based on the presence of other risk factors.

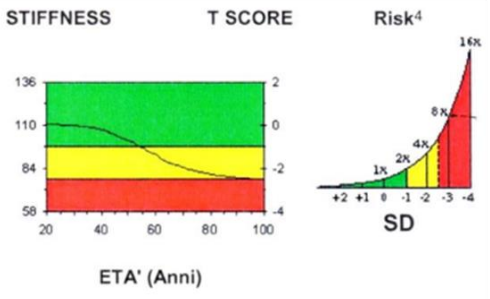
• **high risk**, high probability of osteoporotic fracture, if other risk factors are present, and therefore need for DEXA examination for definitive diagnosis.

BONE DENSITOMETRY DATA

Device: Achilles Express

ID Subject	Name	
Date of Birth	Test Date	
Stiffness Index	Piede	Sex
%Young Adult	T Score	Height
% Age-Matched	Z Score	Weight

Graph for Men



Graph for Women

