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Investigating the prognostic meaning of frailty and sarcopenia definitions

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CHAPTER 1. INTRODUCTION

Since population aging is steadily increasing worldwide [1] and the probability of dying at advanced age has been constantly decreasing over the last decades [2], our healthcare and welfare systems are facing a progressive increase in costs and complexity of care. Old people are often affected by multiple, chronic conditions, take many medications and need additional time and both medical and social support to overcome adverse events compared to younger people [3,4]. In addition, it is recognized that the accumulation of diseases and their consequences do not fully explain quality of life and overall well-being [5]. It is now the time to make a shift from a disease-centered approach to a patient-centered model in order to fill in the gap between a patient's needs and expectations and the healthcare system responses. In order to promote this change in paradigm, geriatric literature has given an increasing importance to the concepts of frailty and sarcopenia.

THE IDENTIFICATION OF FRAILTY

In geriatric medicine, the term "frailty" indicates a multidimensional condition characterized by reduced capacities in several physiological systems, determining a state of increased vulnerability to stressors and susceptibility to adverse health outcomes (e.g., functional decline, falls, hospitalizations, death)[6]. It is not synonymous with comorbidity or disability, but it is a multidimensional condition that is independent of advanced age and of the burden of chronic illnesses [7,8]. The importance of frailty in geriatric medicine lies in its potential usefulness in defining a patient's «biological age», overcoming the limits of «chronological age» to describe subject's status and strength/vulnerability to negative health-related events. One of the most used images to describe the theoretical construct of frailty is the one reported in *Figure 1*: in adults, an acute endogenous or exogenous stressor leads to a

temporary disruption in homeostatic balance, producing classical signs and symptoms. In frail older persons, inadequate homeostatic mechanisms lead to the onset of heterogeneous clinical manifestations and syndromic states [9].

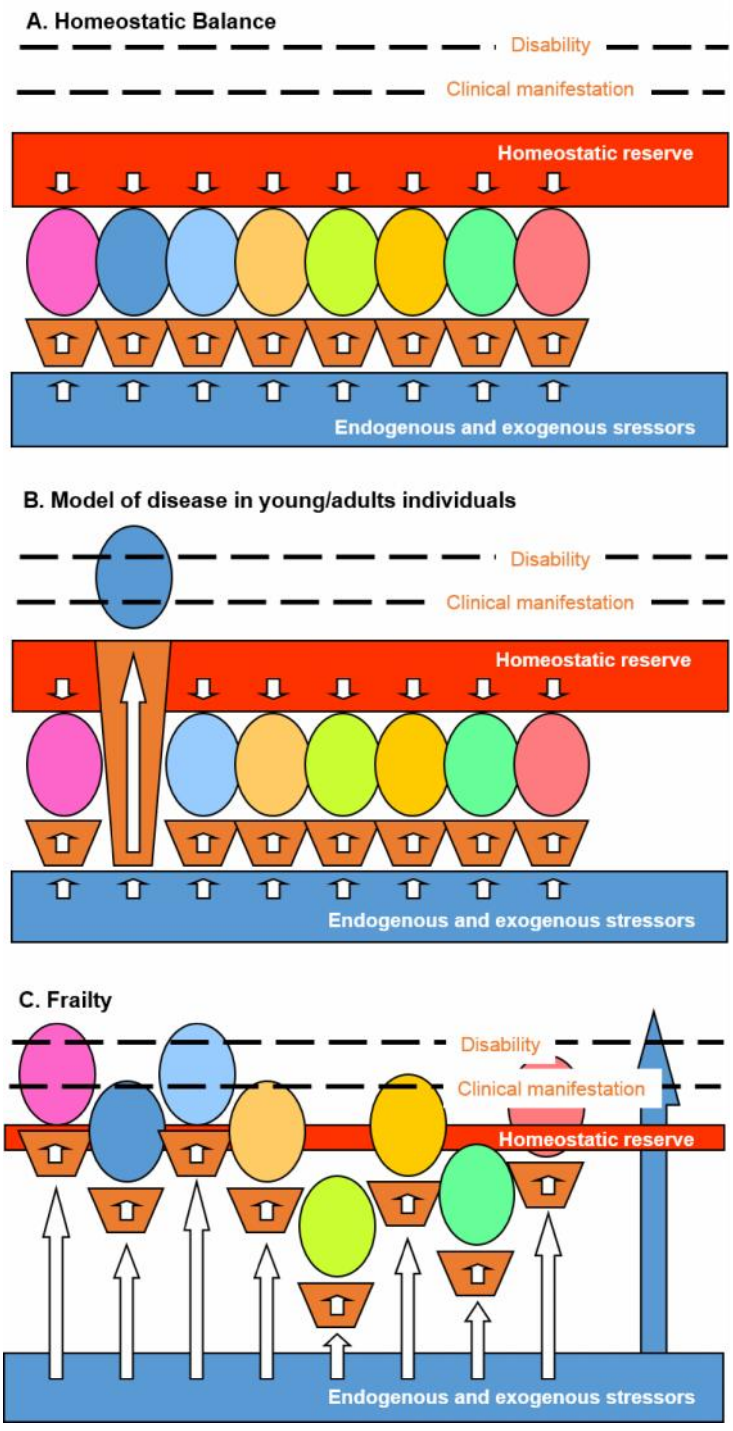


Figure 1
Frailty as the result of disruption of homeostatic balance
Adapted from Hazzard's Geriatric Medicine and Gerontology, 6th Ed.[9]

The pathophysiological background of this increased vulnerability and impaired homeostatic response has been extensively researched. In the development of physical frailty several factors may play a role, including an age-associated pro-inflammatory state, hormonal changes, structural and functional changes in the brain, nutritional factors [10,11]. Given the multidimensional nature of frailty, psychosocial factors – such as low socioeconomic position, loneliness, mood disturbances, adverse environmental conditions – play also a role in its development (*Figure 2*) [12].

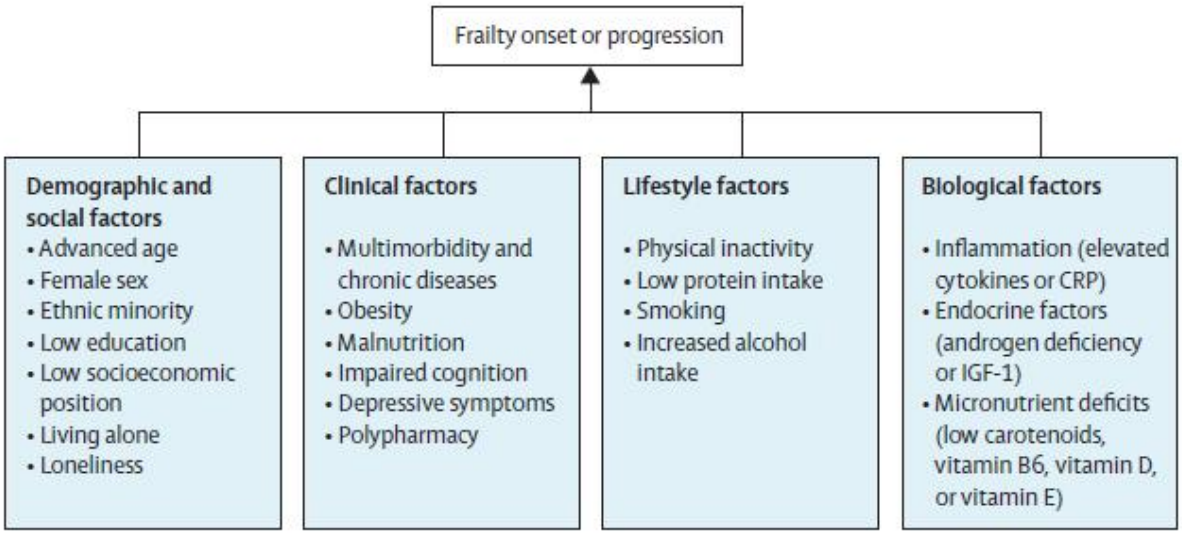


Figure 2. Risk factors for Frailty

Although experts agree on the conceptual definition of frailty, a universal accepted operational definition is still lacking. The two most common instruments are the phenotypic model, proposed by Fried and colleagues [13], and the deficit accumulation one, developed by Rockwood and Mitniski [14].

The Frailty Phenotype was derived and validated as a secondary analysis of data obtained from a prospective cohort study (the Cardiovascular Health Study) including 5,317 men and women aged 65 years and older [13]. The five variables that were associated to adverse health outcomes were used to build the instrument [13]: unintentional weight loss, self-

reported exhaustion, low physical activity, and reduced gait speed and grip strength (compared to sex- and age-specific reference values). Frailty is defined according to the presence of at least three criteria, pre-frailty when one or two factors were present, and robustness if none of the criteria was satisfied. Differently, Rockwood and Mitniski proposed a model based on the arithmetic accumulation of deficits occurring with aging [14]. The deficits are symptoms, clinical signs, abnormal laboratory values, disease states, and functional limitations, whose prevalence increases with age, that do not saturate too early, are plausibly associated to poorer health status and are sufficiently numerous (at least 30 variables) [15–17]. The so-called Frailty Index (FI) is computed as a simple ratio between the number of deficits the individual presents divided by the total of deficits taken into account.

The two models are evidently different in their constructs [18]. The FP is more focused on screening the physical domain of frailty and can be applied at the first contact with the subject without a preliminary clinical evaluation. The FI is the result of a comprehensive geriatric assessment. Moreover, Fried and colleagues supported the hypothesis that frailty causes disability independently of (sub)clinical diseases. They explain that "the syndrome of frailty may be a physiologic precursor and etiologic factor in disability"; therefore, the FP finds its ideal application in non-disabled older subjects. On the other hand, the FI includes items of functional disability and health status in its computation (e.g. mobility limitation, illnesses); without making a clear differentiation between frailty and disability, it is applicable independently of the functional status. The FP has a categorical nature, while the FI is a continuous instrument that is particularly useful for patients' follow-up and for being retrospectively developed on a database constituted for different purposes and aims.

Many other instruments have been developed to identify older persons with a high vulnerability to stressors and during the last two decades, over 60 frailty assessment

instruments have been validated. Far from being an exhaustive list, the *Table* below reports the most extensively studied tools (modified from [19]).

Commonly used frailty instruments

	Components	**Frailty identification**
Frailty Phenotype [13]	Five criteria: weight loss, low physical activity, exhaustion, slowness, weakness	Frailty: ≥ 3 items, pre-frailty: 1-2 items, robust = 0 items
Frailty Index [17]	30+ health deficits: scores range from 0 (no deficits) to 1 (all deficits)	Continuous score; suggested cutoff score for frailty >0.25
Clinical Frailty Scale [14]	Visual chart for frailty with nine graded pictures: 1=very fit; 9=terminally ill	Frailty: score ≥ 5
FRAIL Scale [6]	Five criteria self-reported by the subject: fatigue, poor resistance, ambulation, illnesses, loss of weight	Frailty: ≥ 3 items, pre-frailty: 1-2 items, robust = 0 items
Study of Osteoporotic Fractures frailty (SOF) Index [20]	Three items: weight loss, exhaustion, unable to rise from a chair five times	Frailty: ≥ 2 items; pre-frailty: 1 item; robust: 0 items
Tilburg Frailty Indicator [21]	15 self-reported items in three domains: physical, psychological, and social	Frailty: score ≥ 5
Groningen Frailty Indicator [22]	15 self-reported items in four domains: physical, cognitive, social, psychological	Frailty: score ≥ 4
Edmonton Frailty Scale [23]	Nine items: cognition, health (2 ×), hospitalisation, social support, nutrition, mood, function, continence	Frailty: score ≥ 7
PRISMA-7 [24]	Seven self-reported items: age (>85 years), male, social support, and ADLs	Frailty: score ≥ 3
Multidimensional Prognostic Index [25]	Eight items: comorbidity, nutrition, cognition, polypharmacy, pressure sore risk, living status, ADL, IADL	Frailty: score > 0.66; pre-frailty: score 0.34-0.66; robust: score <0.34
Hospital Frailty Risk Score [26]	109 summed items from ICD-10 frailty-relevant codes from administrative hospital data. Also considered to be a case finding instrument.	Low risk: score <5; intermediate risk: score 5–15; high risk: score >15

The use of such various instruments to detect frailty has led to lack of standardization and consensus on which tool(s) should be preferentially used in clinical practice. Moreover, each instrument is able to label as frail a specific population, capturing a particular risk profile, different from the one identified by another tool. In fact, studies comparing several frailty scores reveal a low-to-moderate agreement among the available instruments in predicting the risk of adverse outcomes [27,28].

SARCOPENIA AND PHYSICAL FRAILTY: TWIN SISTERS?

Similar to frailty, there is long-standing debate about definition and measurement of sarcopenia [29]. According to the European consensus, sarcopenia is a "progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality"[30]. For decades the term sarcopenia (from the Greek "sarx" or flesh + "penia" or paucity) was used to describe the age-related decrease of muscle mass alone, without any reference to function. Past the age of 40, healthy adults lose approximately 8% of their muscle mass every 10 years, which accelerates to 15% per decade after 70 years of age [31]. Nevertheless, measurement of muscle mass seems to be inadequate to describe the complex changes that occur within sarcopenic subjects. Epidemiological studies demonstrated that muscle mass and strength are not directly related: nevertheless, the decline in muscle strength is of greater amount than the corresponding decline in muscle mass [32]. Taken individually, the reduction of muscle mass [33] and strength [34] is associated with mortality, therefore the coexistence of both conditions may identify old people at higher risk of health-related events. This is the reason why the definition of sarcopenia translated from an age-related decrease of muscle mass to the coexistence of reduced muscle mass and strength [30]. However, agreement on the

variables to be included in sarcopenia definition and on the cut-off points has not achieved yet. Among the most cited definitions, the one proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) has been recently revised (January 2019), defining cut-offs for low muscle mass and strength and reduced physical performance [30].

The correct identification of sarcopenia is even more important if we consider its contribution in understanding and identification of frailty. Sarcopenia is closely related to physical frailty and has been described as its biological substrate [35–37]. As depicted in *Figure 3*, sarcopenia and physical frailty largely overlap. According to the phenotypic model, frailty may be exemplified as "vicious cycle" in which, among multiple physical risk factors and diseases, sarcopenia and age-related muscle dysfunction are the major contributing features in the pathogenesis of disability and dependency (*Figure 4*).

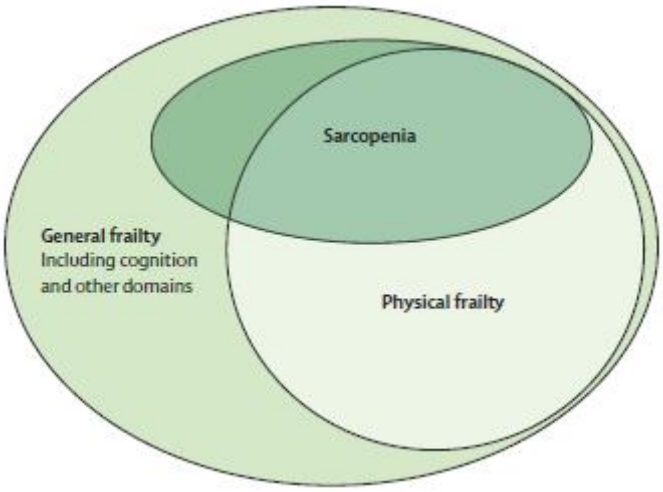


Figure 3. Overlap between sarcopenia and physical and general frailty [29]

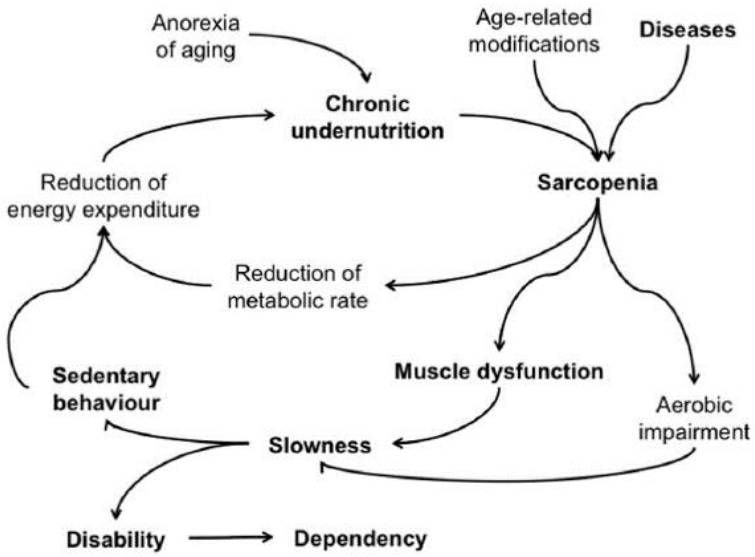


Figure 4. The vicious cycle of frailty [13]

It is worth remembering that multidimensional frailty (general frailty in *Figure 3*) and sarcopenia are conceptually different: sarcopenia relies only on the musculoskeletal system, whereas the pathophysiology of frailty is more multifactorial and complex, representing the outcome of intrinsic and extrinsic changes during the life history trajectory. In fact, although the two entities overlap, there is little concordance between definitions of sarcopenia and definitions of frailty [38].

PREVALENCE AND IMPACT OF FRAILTY AND SARCOPENIA

Given that different operational definitions of frailty were used across studies and that research data are mainly available from high income countries, the global impact of frailty is unknown. A systematic review, collecting data from 21 studies and more than 61,500 community-dwelling older persons [39], reported a great variety of prevalence across studies, ranging from 4.0% to 59.1%: nevertheless, restricting the analyses to studies using the FP, average prevalence was 9.9% (95% C.I.: 9.6-10.2) and 44.2% (95% CI 44.2-44.7) for frailty

and pre-frailty, respectively. A recent meta-analysis on frailty prevalence in 22 European countries involved in the ADVANTAGE Joint Action project confirmed a great heterogeneity, nevertheless the prevalence was higher in non-community based studies compared to community-based studies (45% vs 12%) and lower using the physical phenotype (12%) as compared to all other definitions (16%)[40]. These findings are consistent with data from Asian countries, such as South Korea (prevalence of robust, prefrail, and frail elders: 48.4%, 42.3%, and 9.3%, respectively) [41] or Japan (prevalence of frailty: 11.3%) [42]. Data from Central and South America reveal a potentially higher prevalence among older people in those regions [43,44]. For example, in the Costa Rican Study on Longevity and Healthy Aging, the prevalence of frailty increases from 17.8% among 60- to 79-year-old participants to 57.0% among those 80 years and older [45].

Prevalence of frailty is higher among nursing home residents (19-76%) [46] and in particular disease categories, such as people with malignancies (42%) [47], HIV infection (5-29%) [48] and end stage renal disease (37%) [49]. Frailty is more common in advanced ages: its prevalence increases from 4% among people with 65–69 years to 26% among people older than 85 years. Finally, a higher prevalence was found in women compared with men [39,50] and among lower socioeconomic conditions and ethnic minorities [13].

It should be mentioned that frailty is a dynamic process and transitions across frailty states may vary from individual to individual [51]. In a study by Gill and colleagues[52], nondisabled individuals aged 70 years or older were followed over time to explore changes in frailty status (measured using FP). Among the 754 participants, 57.5% had at least one transition between any two of the three frailty states during the 54-month follow-up period. According to data from an Italian longitudinal cohort study, 32.6% had one transition in their frailty status over a 4.4-years follow-up[53]. Nevertheless, data about frailty transitions and trajectories are scarce and harmonization among studies is needed[54].

A great variability has been reported also for the prevalence of sarcopenia. Its estimates are affected both by the choice of muscle mass and muscle function cut off points and by the study setting. In community dwelling older people, a recent review reported that sarcopenia prevalence according to the original 2010 EWGSOP definition was 12.9% (95% confidence interval: 9.9-15.9%)[55]. Using the abovementioned definition, the estimated prevalence was 41.4% among institutionalised older adults[56] and 34.7% among those in the acute care[57].

MEASURES OF ASSOCIATION VERSUS PREDICTIVE VALUE

Frailty has been consistently shown to be a risk factor for falls, disability, hospitalizations, post-operative complications and mortality [7,51,58,59]. The results of a meta-analysis [60], based on 31 articles studying 13 negative health outcomes and 158,764 community-dwelling older adults, showed that frailty significantly increases the risk for developing negative health events irrespectively of the definitions used (physical approach or deficit accumulation or multidomain approach). Overall, frailty was associated with a 1.8-2.3-fold risk for mortality, a 1.6-2.0-fold risk for loss of activities of daily living (ADLs), a 1.2-1.8-fold risk for hospitalization, a 1.5- to 2.6-fold risk for physical limitation, and a 1.2- to 2.8-fold risk for falls and fractures. Literature review demonstrated also that mortality risk raises progressively with increasing number of phenotypic components and deficits [61].

Most research on frailty has studied it as a risk factor for adverse outcomes (hence calculating relative measures of association) while much less attention has been devoted to the prognostic performance of the frailty score in terms of calibration and discriminative capacity. Strong statistical associations between an outcome and a marker, in fact, do not necessarily imply that the marker can discriminate between persons likely to have the outcome and those who do not [62]. Our group observed that among community-dwelling

older people frail subjects according to FP has a 4.2-times greater probability of dying compared to robust ones, but this association did not translate into good sensitivity and positive predictive values [63]. These results are consistent with those obtained from sub-analysis of other population-based studies [64,65]. The probability of dying or becoming disabled in frail people is relatively low, and therefore FP cannot be used with confidence when trying to identify people who will experience the outcome. On the other hand, the probability of not developing the outcome in non-frail people is high, allowing identifying with confidence elderly people who will not experience the outcomes. As a consequence, the available frailty scores, including FP, may be of limited value for both screening and diagnostic purposes in daily practice. The discrepancy between a strong association and a poor prognostic performance is not surprising. Actually it is very common that scoring systems strongly associated with a given outcome have a poor capacity to identify people who will actually develop the outcome itself [62]. In order to consider a marker/scale effective for classifying people according to their future outcome, in fact, we need extremely strong associations between the marker/scale and the outcome of interest, expressed by very high odds ratio values that are rarely seen in epidemiological studies.

RATIONALE OF THE THESIS

The concepts of frailty and sarcopenia are gaining increasing importance both in Geriatric medicine and in many other disciplines, including social sciences, as two related though distinct conditions that may contribute to the transition from successful ageing to disability, which may represent the target for preventative interventions. The approach to detect frail persons is still lacking a standardization, since a great variety of operational definitions have been developed over the last years. Current instruments to diagnose frailty seem to be useful

to identify older people who would not develop adverse outcomes (high specificity) but not for screening purposes (low sensitivity). This limitation may lay both in the definition of frailty itself and in the identification of the outcome (e.g. disability). In addition, the criteria for identification of sarcopenia, that is one of the physical hallmarks of frailty, have been recently revised (European Working Group on Sarcopenia in Older People 2) and new cut-points for diagnosis of low muscle mass and low muscle strength have been proposed [30]. The effect of applying this new algorithm with regards to sarcopenia prevalence and identification of people at risk of adverse outcomes is unknown.

AIM AND OUTLINE OF THE THESIS

The aim of the thesis was to clarify the predictive power of FP and the individual contribution of low muscle mass and low muscle strength towards adverse outcomes among community-dwelling older people. We analyzed data from the InCHIANTI Study, a population-based study of older persons living in the Chianti geographic area (Tuscany, Italy), designed to investigate the factors contributing to the decline of mobility in older persons and including 1150 subjects of 65 years and older [66].

In the next sections the design and aims of these studies are summarized.

Chapter 2 presents the results of a study that was part of this PhD program with the purpose of evaluating an alternative approach to identify frailty in order to improve its predictive value towards incident disability.

Since the FP has low sensitivity towards the identification of older people who will lose one or more activities of daily living, in the study summarized in *Chapter 3* we examined the discriminative capacity of the FP towards the identification of patterns of disabilities in an extended list of tasks.

Chapter 4 presents the results of a third study that was part of this PhD program aiming at studying changes in prevalence of low muscle strength and low muscle mass according to the European Working Group of Sarcopenia in Older People 2 definition, and their individual contribution towards mortality and incident mobility disability in a cohort of community-dwelling older people.

Chapter 5 discusses the findings of the abovementioned studies, their impact and future directions for research on factors contributing to loss of independence in elderly people.

EXPERIMENTAL STUDIES

CHAPTER 2. CLUSTERS OF FUNCTIONAL DOMAINS TO IDENTIFY OLDER PERSONS AT RISK OF DISABILITY

Costanzo L, Pedone C, Cesari M, Ferrucci L, Bandinelli S, Antonelli Incalzi R. Geriatr Gerontol Int. 2018 May;18(5):685-691. doi: 10.1111/ggi.13226.

ABSTRACT

*Aim***.** To date, there is no consensus on which set of variables should be used to identify older persons at risk of disability in activities of daily living (ADLs). This study aimed at 1) evaluating how different deficits cluster in a population of community-dwelling older persons, and 2) investigating whether the discriminative capacity of physical performance measures towards the development of disability might be improved by adding psychological, social and environmental indicators.

Methods. Data are from 709 non-disabled older persons participating in the InCHIANTI Study. We performed a cluster analysis of twelve deficits in multiple functional domains, selected from the available frailty assessment instruments. Then, participants were assigned to group, based on the obtained clusters of variables. For each group, we measured the prognostic capacity and the predictive ability for 6-year disability.

*Results***.** The analysis revealed a "physical" cluster (including weight loss, reduced grip strength/gait speed/physical activity, impaired balance, environmental barriers) and a "psychosocial" cluster (e.g. living alone, depression, low income). Thus, subjects were classified into four groups according to the presence of physical and/or psychosocial cluster. Compared to the "fit" group, the relative risks of becoming disabled in the "physical", "psychosocial", and "mixed" deficit groups were 2.23 (95%CI 0.71-7.00), 1.52 (95%CI 0.62-3.75), and 6.37 (95%CI 2.83-14.33), respectively. The positive and negative predictive values

for the "physical", "psychosocial", and "mixed" deficit groups were, respectively, 9% and 87%, 6% and 83%, 27% and 94%.

Conclusions. As expected, physical and psychosocial deficits cluster predominantly into different groups. Even when both are considered simultaneously, the ability to predict incident disability is still insufficient.

BACKGROUND

Several instruments have been developed to operatively recognize the frailty syndrome [67,68]. Each instrument is based on the evaluation of a combination of different deficit indicators, that, if present, poses the individual at risk of adverse outcomes. Some authors recognized frailty mainly as a biological syndrome, proposing physical signs and/or symptoms as diagnostic criteria. In this category falls the well-known Frailty Phenotype (FP) [13]. Other researchers, instead, have proposed the addition of other domains to the physical one in order to better capture the elders at risk of adverse outcomes, in line with the view of frailty as a multidimensional condition [69]. A relevant issue regarding the available frailty assessment instruments concerns their ability to predict adverse outcomes: although it is better for the multidimensional questionnaires than for the FP, it seems to be still suboptimal [63,70–72]. Moreover, to date, no data about the predictive ability of composite scales (including both measures of physical performance as well as evaluation of psychological, environmental and social domains) are available.

In this study, we evaluated how several deficits conceptually belonging to different domains (physical, psychological, social, environmental) actually cluster in a cohort of community-dwelling older persons. We also investigated whether a multidimensional approach may increase the prognostic and discriminative capacity of physical performance measures towards incident disability.

METHODS

Data source and definition of deficits

We used data from people of 65 years and older participating in the "Invecchiare in Chianti" (InCHIANTI) study[66]. The characteristics of these dataset has been previously described. Deficit indicators were selected based on a literature search. Among the physical deficits, we included the modified Fried's criteria [13] and impaired balance [73,74], that were defined as follows. Unintentional weight loss was intended as a reduction in weight >4.5 kilograms in the past 12 months. Exhaustion was described as a feeling of needing an effort to do everything, and was considered present if the participant reported it for more than 3 or 4 days in the last week. Reduced physical activity was defined as having performed less than 2-4 hours of light exercise per week. Walking speed was evaluated over a 4.57 m course with the patient taking two walks at usual pace. The mean of the two walks was considered, and those with a walking speed below the lowest sex- and height-specific quintiles were considered slow walkers. Grip strength was measured using a hand-held dynamometer. The average of two measurements was used, and those with results lower than the sex- and BMI-specific quintiles were considered as having poor muscle strength. Balance was measured following the design of the Short Physical Performance Battery [75]. The balance test is composed by three subtests (i.e., side-by-side stand, semi-tandem, and tandem) to obtain a score from 0 (worst performers) to 4 (best performers). Impaired balance was defined as a summary score of 0 or 1.

According to literature evidence, psychological deficits selected for the study were cognitive impairment [76,77], depression [76,78], and poor coping ability [79]. A Mini Mental State Examination score [80] below 24 (corrected for education and age) defined cognitive impairment. The Center for Epidemiological Studies Depression scale (CES-D, 20-item version)[81] was used to measure depressive symptoms. A CES-D cut-point of 16 was used to identify individuals at risk for clinical depression. Poor coping capacity was

considered present if the participant had not tried to solve a difficult situation occurred in the previous six months or agreed with one of the two statements "I have no control over what is happening around me" or "I'm unable to solve any of my problems".

Finally, social and environmental deficits were also included [13,76,79,82,83]. Living alone was defined as the absence of any co-habitant. Architectural barriers were defined as the presence of indoor and/or outdoor physical obstacles limiting the use of one or more rooms in the house and/or the move from/to home. Low income was considered present when the participant reported financial problems.

Performance measures and disability

The widely used Katz's index of ADLs [84] (including the capacity of independent dressing, moving in and out of bed, using the toilet, washing, eating, and control urine and fecal continence) was used to measure the functional status [85]. Incident disability was defined as the loss of at least one ADL occurred during the study follow-up.

Sample selection

From the original study population (N=1308), 936 participants aged ≥ 65 years and without ADL impairment at baseline were selected. Then, participants with missing values for any deficit measures (N=168) and those with no follow-up information (N=59) were excluded, leaving the analytical sample to 709 individuals. The 59 participants lost during the follow-up were older, were more likely to be frail (46% had reduced gait speed) and 46 of them died before the 3-year follow-up visit.

Statistical analysis

Descriptive statistics were used to present demographic characteristics of the study population and the prevalence of deficits. We performed a hierarchical cluster analysis to group the deficit indicators without any *a priori* hypothesis. Cluster analysis is a multivariate analysis that attemps to form "clusters" of objects that are "similar" to each other but differ

among clusters. On the basis of clusters of variables, we then divided the study population into groups. We therefore examined the prognostic capacity of each group by calculating relative risks for incident disability. The discriminative capacity was evaluated calculating the sensitivity, specificity, PPV and NPV for the same outcome.

Statistical analysis was performed using R 3.1 for Linux (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The population included 709 older persons (mean age: 73.4 years, SD: 6.5, 56.3% women). The general characteristics of the population are reported in *Table 1.1*. At baseline, more than half of participants suffered from hypertension, about one third had osteoarthritis and chronic renal failure, 20% of population was diagnosed with heart failure, while the prevalence of diabetes mellitus, peripheral artery disease and chronic obstructive pulmonary disease was around 10%. Compared to fit, participants who became disabled at follow-up were more likely to be female and had a higher prevalence of chronic illnesses, with the exception of diabetes mellitus and chronic obstructive pulmonary disease, while cancer was more prevalent among non-disabled participants.

In *Table 1.2* we reported the prevalence of the selected deficits. According to the FP, 5.9% of baseline sample was frail: this prevalence raised to 19.6% among people who became disabled at follow-up. Among Fried et al's criteria, weight loss had a low prevalence (4.9%), which was not higher among people who lost one or more ADLs at follow-up. More that 40% of the cohort reported to have coping problems, nearly 30% had cognitive decline and 20% lived alone. As expected, these and the remaining deficits had a higher prevalence among people who developed disability at follow-up.

As shown in *Figure 1.1*, the cluster analysis of the deficits revealed two clusters: the "physical" one combined weight loss, poor grip strength, slow gait speed, low physical activity, presence of architectural barriers, and impaired balance; the "psychosocial" cluster included six deficits: depressive symptoms, poor coping capacity, cognitive impairment, exhaustion, living alone, and financial difficulties. As expected, in the "physical" cluster, there is a close link among all the variables, in particular grip strength, physical activity and walking speed; in the "psychosocial" cluster, depression and coping problems are closer to cognitive decline than to other deficits (*Figure 1.1*). Once obtained the results of the cluster analysis, four groups of participants were then identified: 1) the "fit" group, including subjects with no deficit (N=142); 2) the "physical deficit" group, subjects with at least one physical deficit indicator (N=53); 3) the "psychosocial deficit" group, including subjects with at least one psychosocial deficit (N=280); 4) the "mixed deficit" group, consisting of subjects with deficits included in both clusters (N=234).

Over the 6 years of follow-up, 92 participants reported incident ADL disability. Compared to the "fit" group, the relative risks of becoming disabled in the "physical", "psychosocial", and "mixed" deficit groups were 2.23 (95%CI 0.71-7.00), 1.52 (95%CI 0.62-3.75), and 6.37 (95%CI 2.83-14.33), respectively.

The predictive capacity of this classification is summarized in *Table 1.3*. The probability that a subject in the "physical deficit" group would develop disability was 9.4% (positive predictive value, PPV), while the probability of the same outcome for a subject not belonging to the "physical deficit" group was 86.7% (negative predictive value, NPV). The corresponding values for the "psychosocial deficit" and "mixed deficit" groups were PPV=6.4% and NPV=82.7%, and PPV=26.9% and NPV=93.4%, respectively (*Table 1.3*). Similar results were found when analyzing the predictive value of the classical FP.

DISCUSSION

In this study, we analyzed how several deficits pertaining physical, psychological, social and environmental domains cluster in a representative population of community-dwelling older persons. The examined deficits clustered in two groups: one composed of measures concerning the physical domain and the other gathering psychological, social and environmental measures. When deficits belonging to both clusters were present, the risk of developing disability was greater.

Our findings support the theory that frailty is not a mere physical phenomenon, but the result of multidimensional deficits pertaining to different domains [68,69,86,87]. Frailty is a dynamic condition exposing older persons to an increased risk of disability and adverse outcomes. An approach focused on the physical issues and underestimating the multidomain complexity of the individual may insufficiently capture the frailty condition, misclassifying the individuals potentially amenable of *ah hoc* preventive interventions. Indeed, psychological, social and environmental factors are all associated with dependency in later life [13,76,79,82,83,88], therefore deficit in these domains may contribute to define the frailty syndrome.

Our results show that the abnormalities in the physical domain are not significantly associated with an increased risk of incident disability. This finding may seem in contrast with available literature reporting physical impairment (especially slow gait speed) as strongly and independently associated with adverse outcomes [89,90]. However, it must be noted that the strength of the association reported in our study is similar to what reported in the literature. It is likely the small number of persons included in the "physical deficit" group (n=53) and the low incidence of outcome in the sample (13%) may have limited the statistical power of the analysis.

Interestingly, four of the Fried and colleagues' criteria clustered in the "physical" deficit group, whereas the "exhaustion" criterion was part of the psychosocial cluster. This might be

(at least partly) due to the fact that the exhaustion criterion was derived by questions retrieved from a scale measuring depressive symptoms (i.e., CES-D), thus a domain different from the physical one.

The ability of FP of capturing not only the physical domain of frailty, but also the psychosocial one, may help explaining why frailty measures not including gait speed and grip strength are still associated with adverse outcomes [63]. Recently, in a cohort of 8,684 community-dwelling older people, Op het Veld and colleagues [91] reported that, compared to non-frail participants, the FP is associated with worse scores in social (e.g. social network type), psychological (e.g. psychological distress, mastery), and physical (e.g. chronic diseases) domains. These data may support our finding that the FP includes markers characterizing the two different clusters.

Our data confirm that predictive ability of commonly used deficit indicators remains relatively poor. The probability of becoming disabled among people identified at risk according to the presence of physical and/or psychosocial deficits is relatively low, and none of the markers can singularly be used as screening test for this syndrome. In fact, the PPV was higher when physical and psychosocial deficit indicators were simultaneously considered (PPV 27%), but still far from providing a sufficient detection. This finding is consistent with previous literature [63,70,71,92] indicating that commonly used frailty assessment instruments are not particularly sensitive at identifying older persons at risk of negative health-related events. The available instruments might be rather used for detecting fit individuals, due to the high specificity. Improving the predictive validity of current instruments is thus necessary in order to plan effective interventions aimed at preserving independent function in later life.

A limitation of our study may arise from the relatively small size of the whole sample (709 participants) and of each group, that could explain the non-significant association with

incident disability (with the exception of the mixed deficit group). Secondly, the relatively low prevalence of the outcome (13%), could have affected sensitivity and PPV, that were low for incident disability among all three groups (physical, psychosocial and mixed). However, similar results (PPV=0.38) would have been reported for the "mixed" deficit group even in a hypothetical scenario with 20% of incident disability.

In conclusion, the results of our analysis let us identify among community-dwelling older people different risk "profiles" for incident disability, in particular a group mainly characterized by physical deficits and another identified by a psychosocial impairment. These findings are in line with previous recommendations describing frailty as a multidimensional phenomenon, thus requiring individualization of its management. Unfortunately, even applying more holistic parameters for detecting frailty, the predictive capacity remains inadequate. It is conceivable that latent and still unrecognized factors, such as interaction with healthcare system, incident life events, biomarkers of frailty, may contribute to disability, rendering the identification of elders at risk a challenging task. In this context, specific research should be continued in the field in order to enrich or modify the current operational definitions of frailty with the aim of improving the capacity to discriminate the older persons in the need of preventive actions.

TABLES AND FIGURES

Table 1.1. Characteristics of the population at baseline and of participants disabled and non-disabled* at 6-year follow-up.

	All	Non-disabled at follow-up	Disabled at follow-up
N	709	617	92
Age, mean (SD)	73.4 (6.5)	73.4 (6.5)	73.4 (6.5)
Sex (female), %	56.3	54.9	65.2
Hypertension, %	61.5	60	71.7
Heart failure, %	21.9	20.3	32.6
Ischemic heart disease, %	9.4	8.9	13
Cerebrovascular disease, %	3.8	3.1	8.7
Diabetes mellitus, %	12.1	12	13
Chronic obstructive pulmonary disease, %	10.3	10.2	10.9
Chronic renal failure, stages III-V†, %	33.8	28.8	67.8
Parkinson's disease, %	2	1.1	7.6
Peripheral artery disease, %	15.9	14.1	28.3
Hip or knee osteoarthritis, %	30.7	28.7	44.6
Dementia, %	1.4	1.1	3.3
Cancer, %	5.6	6.2	2.2

** Disability: loss of at least one Katz's activity of daily living at follow-up*
† Creatinine-clearance was estimated by Cockcroft-Gault equation

Table 1.2. Prevalence of deficits in the baseline population and among the disabled and non-disabled participants at six-year follow-up.* Data are expressed as percentages

	All	Non-disabled at follow-up	Disabled at follow-up
Weight loss	4.9	5	4.3
Exhaustion	16.8	16	21.7
Low physical activity	13.5	10	37
Low walking speed	17.5	12.8	48.9
Low grip strength	17.2	14.7	33.7
Frailty (3 or more FP criteria)	5.9	3.9	19.6
Impaired balance	6.5	3.2	28.3
Cognitive decline	27.5	25.9	38
Depression	31	28	51.1
Living alone	18.2	17.2	25
Environmental barriers	8.2	5.8	23.9
Coping problems	42	39.2	60.9
Low income	9.3	9.1	10.9

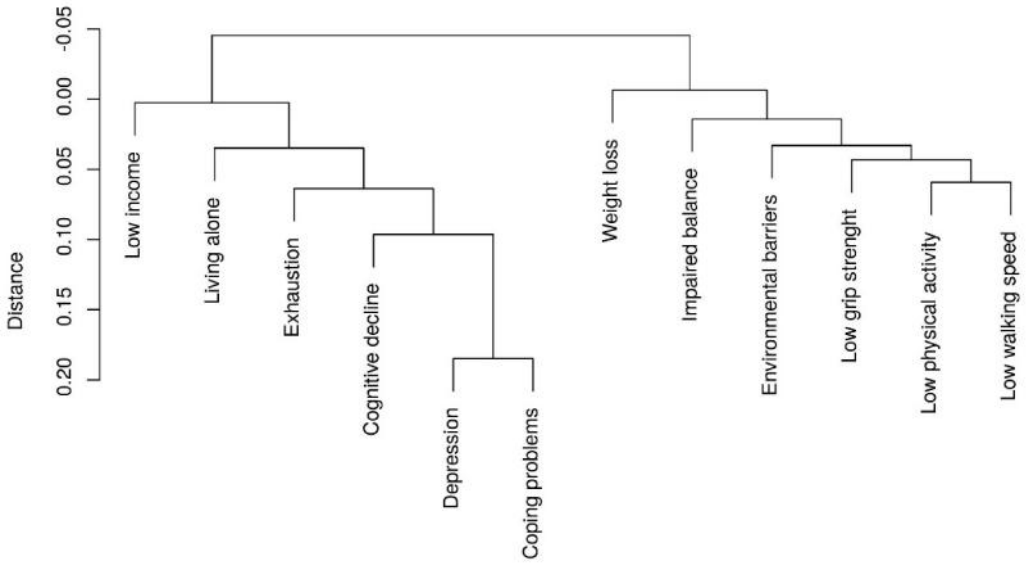
** Disability: loss of at least one Katz's activity of daily living at follow-up*

Table 1.3. Sensitivity, Specificity, Positive and Negative Predictive Values (PPV, NPV) of the three groups of deficit indicators for incident disability*

Groups	Sensitivity	Specificity	PPV	NPV
Fit (n=142)	Ref.	Ref.	Ref.	Ref.
Physical deficit (n=53)	.054	.922	.094	.867
Psychosocial deficit (n=280)	.196	.575	.064	.827
Mixed deficit (n=234)	.685	.722	.269	.939

**loss of at least one ADL at follow-up*

Figure 1.1. Dendrogram resulting from cluster analysis testing the distribution of deficit indicators in the population.



CHAPTER 3. PREDICTIVE CAPACITY OF FRAILTY PHENOTYPE TOWARDS PATTERNS OF DISABILITY IDENTIFIED USING LATENT CLASS ANALYSIS

Costanzo L, Cesari M, Ferrucci L, Bandinelli S, Antonelli Incalzi R, Pedone C. J Am Med Dir Assoc. 2019 Aug;20(8):1026-1031. doi: 10.1016/j.jamda.2018.12.018

ABSTRACT

*Aim***.** Frailty Phenotype (FP) has low sensitivity towards the identification of older people who will lose one or more activities of daily living (ADL). Nevertheless, the definition of disability in terms of ADLs may not resemble the pattern of functional impairment occurring during aging. The aim of this study was to examine the discriminative capacity of the Frailty Phenotype (FP) towards the identification of patterns of disabilities in an extended list of tasks, identified among community-dwelling older people.

*Methods***.** This was a longitudinal cohort study including 997 subjects of 65 years and older selected from the InCHIANTI Study population. Using latent class analysis, we assessed the pattern of 3-year changes in twenty-four functional tasks. Then, we calculated the discriminative capacity of the FP for each pattern of disability. Analyses were stratified by gender.

Results. In both men and women, we recognized three classes: stable function (SFC); disability in complex tasks (CDC); global functional disability (GDC). Among women, ability of FP to identify subjects in GDC showed sensitivity=0.42, specificity=0.98, positive and negative predictive values 0.75 and 0.91; the corresponding values for prediction of CDC were 0.13, 0.98, 0.68 and 0.75. Similar results were obtained among men.

Conclusions. Over three years, older people of the InCHIANTI population remained largely functional stable, some persons developed deficiency in complex tasks, and a minority developed global functional disability. Trying to predict these three patterns may be useful for the care of older people in order to promote individualized interventions to reduce

the burden of disabilities and their consequences. To this purpose, FP showed a fairly good capacity to identify people at risk of functional decline, but further studies are needed to identify instruments with better prognostic capacity.

BACKGROUND

Epidemiological studies have shown that the majority of older persons are disabled in the last years of life [93].Older adults with disabilities have worse quality of life, are at higher risk of institutionalization, hospitalization, and mortality and require greater healthcare expenditure compared to their fit counterparts [94–96]. With the progressive increase in average life expectancy, preserving functional independence of older adults and/or compressing lifetime disability into a shorter period before death have become primary goals for geriatric medicine. To this purpose, early identification of older people at risk of functional disability is essential in order to recognize potential treatable conditions and carry out timely countermeasures.

In the last twenty years, the concept of frailty has gained importance as a state of increased vulnerability to stressors and susceptibility to adverse outcomes, such as disability, institutionalization and death [10]. Among the proposed operational definitions of frailty, the Frailty Phenotype (FP) is one of the most known and frequently used and it is based on the evaluation of five criteria (exhaustion, involuntary weight loss, poor handgrip strength, slow gait speed, inactivity) [13]. The FP and other frailty definitions are strongly and independently associated with incident disability in epidemiological studies [13,97–99], but some papers have recently shown that the ability of current frailty instruments to discriminate people who will actually become disabled is poor [63,70,100]. This means that, among old people identified as frail according to the FP, only a small proportion will develop disability, therefore this instrument is of limited usefulness for screening purposes.

It should be noted that in the abovementioned studies, disability has been assessed through loss of one (or more) basic activities of daily living (defined as Katz ADL Index [84]) or instrumental activities of daily living (Lawton IADL Scale [101]). We hypothesized that the concept of frailty may be able to catch a transition from an independent status to a pattern of functional limitations rather than predicting the development of disability in a default set of ADLs. During aging, the disablement process may differ among individuals, leading to a variable loss of functional abilities, ultimately affecting the capacity of living independently. The resulting pattern of functional limitations may not necessarily be caught by the inability in performing one specific task among ADLs or IADLs.

In this study, we aimed at verifying whether a number of classes, characterized by co-occurrence of incident impairments in an extended list of functional tasks (including not only basic ADLs, but also IADLs and mobility), can be identified in a population of community dwelling older people. Then, we measured discriminative capacity of FP towards the recognition of these disability classes.

METHODS

Study population

We used data from people of 65 years and older participating in the "Invecchiare in Chianti" (InCHIANTI) study [66], a population-based study designed to investigate the factors contributing to the decline of mobility in older persons. The participants in the study were randomly selected from the populations of two town areas in the Chianti region: Greve in Chianti and Bagno a Ripoli (Tuscany, Italy). The study protocol was approved by the Italian National Institute of Research and Care on Aging ethical committee. The eligible participants were interviewed at their homes by trained study researchers using a structured questionnaire aimed at investigating their health status, physical and cognitive performance,

and other factors possibly related to loss of independence in late life. The interview was followed by a physical examination at the study clinic. The first wave of the study started in 1998 and participants were followed-up with evaluations every three years.

Measures of frailty and disability

At baseline, frailty was defined using adapted Fried et al.'s criteria [13]. Unintentional weight loss was defined as a reduction in weight >4.5 kilograms in the previous 12 months. Exhaustion was defined as a feeling of needing an effort to do everything and was considered present if the participant reported it for more than 3 or 4 days in the last week. Reduced physical activity was defined as having performed less than 2-4 hours of light exercise per week. Walking speed was evaluated over a 15 feet course with the patient taking two walks at usual pace. The mean of the two walks was considered, and those with a walking speed below the lowest quintile as adjusted for sex and height were considered slow walkers. Finally, grip strength was measured for the dominant limb using a hand-held dynamometer. The average of two measurements was used, and those with a grip strength below the sex and BMI (quartiles) specific 20th percentile was considered to have low grip strength. Subjects were then identified as "robust" when none of the criteria was present, "pre-frail" in the case of one or two indicators, "frail" when three or more criteria were present.

At 3-year follow up, data about the capacities in an extended list of 24 functional tasks were collected through interviews. The tasks were derived from the items used to assess disability in a subanalysis of the Cardiovascular Health Study [102] combined with those used in the European Longitudinal Study on Aging [103]. Then, we completed the list adding the missing Katz's ADL (urine and fecal continence) [84] and the three remaining Lawton's IADL (doing the laundry, using public transportation, taking medications correctly) [101]. Disability in each task was considered present when a person was unable of doing the task or if he/she required another person's help.

Sample selection

From the original study population, we selected participants with age ≥ 65 years (N: 1155). Thereafter, we excluded participants with any missing data for the functional tasks (N: 158), leaving 997 participants available for analysis. The excluded subjects were slightly older (mean age 77.8 years vs. 75.1 years) and with a higher prevalence of women (66% vs. 55%) but with the same proportion of frail subjects (10% vs. 11%) in comparison with the selected participants.

Analytic approach

Using latent class analysis (LCA), we assessed whether incident or worsening disability in the individual 24 tasks aggregates into classes. LCA is a technique used to classify individuals into mutually exclusive types, or latent classes, based on their pattern of response on a set of categorical variables. We used this method to test our study hypothesis that the InCHIANTI population comprises a number of subpopulations (classes) characterized by co-occurrence of impairments in the examined 24 functional tasks. Considering that trajectories and burden of disabilities differ between men and women [104], we stratified the analyses by gender. We evaluated the number of latent classes needed by comparing goodness-of-fit of models with different number of classes, using Bayesian Information Criterion (BIC). Once obtained the classes, we measured discriminative capacity of the FP for each pattern of worsening disability, over a 3-year follow-up, by calculating contingency tables to obtain sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). We also compared this discriminative capacity with that of FP for prediction of loss of at least one Katz's ADL.

All the analyses were performed using R 3.3 for Linux (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The cohort included 997 subjects, 550 women (mean age 75.7 years) and 447 men (mean age 74.3 years). Baseline characteristics are summarized in *Table 2.1*. According to FP, 69 women and 40 men were frail at baseline. Women had a greater prevalence of impairment in the 24 functional tasks when compared to men, especially regarding some abilities such as walking 400 mt, doing heavy houseworks, cutting toenails, carrying a shopping bag and using public transportation. We included in the LCA 857 people who were alive and completed functional evaluation at 3-year follow-up (mean age: 73.8 years, 56% women). Both in men and women subgroups, the evaluation of BIC showed an improvement of goodness of fit with increasing number of classes up to three and only marginal improvement thereafter. Accordingly, we chose a three classes model. LCA was stratified according to sex and the three latent classes are represented in *Figure 2.1*. The first one (SFC, stable function class) was characterized by substantially preserved ability in all the examined tasks; in this class only 28% of women and 14% of men reported difficulty in cutting toenails. The second class (CDC, disability in complex activities) showed, in both genders, a prevalence of 50% and higher of some incident or worsening disabilities (difficulty in climbing stairs, walking 400mt, doing heavy housework, cutting toenails, carrying shopping bags) and, in men, a prevalence of 51% of inability in bathing. The third class (GDC, global functional disability) grouped persons with difficulties in the majority of the 24 tasks in both sexes. SFC grouped 80% of men and 62% of women, CDC included 16% of men and 26% of women, and the corresponding values for GDC were 4% and 12%. CDC and GDC comprised participants who were older and with a higher prevalence of FP, compared to people included in SFC. *Table 2.2* summarizes the prevalence of disabilities according to each class.

The interplay among FP, disability classes and death is shown in *Table 2.3*. Of the robust women, 78.3% were included in SFC, 15.3% in CDC, 3.2% in GDC and 3.2% died. Only

25% of frail women at baseline were included in GDC and 34.2% died before the 3-year follow-up. Similar results were obtained among men (*Table 2.3*).

Then, we analyzed the discriminative capacity of the FP with respect to identification of longitudinal changes in disability. In women, FP showed sensitivity=0.13, specificity=0.98, PPV=0.68, NPV=0.75 to identify CDC. Similarly, concerning the capacity to predict GDC, FP had sensitivity=0.42, specificity=0.98, PPV=0.75, NPV=0.91. The corresponding values for the prediction of loss of at least one Katz's ADL were sensitivity=0.44, specificity=0.94, PPV=0.44, NPV=0.94. We found similar results among men (*Table 2.4*).

DISCUSSION

According to the results of our study, community dwelling older persons participating in the InCHIANTI Study showed three patterns of functional decline after a three-year follow-up: most subjects remained functionally stable (SFC), some persons developed deficiency in more complex tasks (CDC), and a minority developed global functional disability (GDC). The ability of FP to predict development of CDC and GDC showed high specificity and NPV, as expected, but also a fairly good PPV, especially when compared to the prediction of loss of at least one Katz's ADL.

Despite many differences concerning population sampling, definition of disability and methodological aspects, our data resemble those reported by Yu and colleagues [105] who identified three distinct ADL and IADL disability trajectories among 3186 older adults in Taiwan based on a 11-year follow-up survey: maintained function, progressive disability and consistent disability. Differently from these authors, our aim was not analyzing the trajectories of individual disabilities or synergy scores over a timeframe but verifying if the FP was able to predict the pattern of functional loss defined by LCA. The fact that we described three patterns of disabilities similar to those identified by Yu and colleagues

reinforces our findings and makes them generalizable. Prediction of these three patterns may help promoting individualized interventions to reduce the burden of disabilities and their consequences. For example, in subjects belonging to SFC, fostering the involvement in physical and social activities may help maintaining a good performance status as long as possible; for older people in the GDC, the use of assistive devices can be an important strategy to preserve residual independence and prevent further deterioration; for older adults belonging to CDC, early interventions and management of chronic diseases may prevent the entrance in a spiral of rapid functional decline.

At 3-year follow-up, prevalence of CDC and GDC was higher among women than men. This finding is in line with that previously reported in several population-based studies, which found that women had a higher incidence of ADL disability compared to men [106–109]. In the Framingham Heart Study, women reported greater functional limitation and physical disability than men on each of three different self-report measures of physical functioning [110]. Nevertheless, recent data reported that, when adjusting for socioeconomic, health, and social relations indicators, incidence of functional disability was similar between genders [111,112]. Moreover, gender differences in disability trajectories may be explained in part by higher initial levels of disability among older women [113], as observed also in our cohort (*Table 2.1*).

Our study shed light on the capacity of FP to predict the pattern of worsening disability. When looking at the percentage distribution of robust, pre-frail and frail people across the three latent classes (*Table 2.2*), the FP identifies well people belonging to the SFC (78.3% of fit women and 90% of fit men are included in SFC), but frail persons have the same probability to be included in the three classes. When analyzing the predictive ability of the FP for the identification of CDC and GDC, we obtained a high NPV (range of values from .75 to .98) and a modestly good PPV (range of values from .60 to .75). Our findings strengthen the

previously reported data about the high specificity and NPV of FP towards loss of ADLs [63,64,70,71]. Nevertheless, the PPV we found for the prediction of CDC and GDC is rather better than the corresponding value for the loss of one Katz's ADL (PPV=.44 among women, .33 among men). Therefore, when considering as an outcome the pattern of disability in an extended list of tasks, the FP showed a quite good capacity to discriminate among people who remained functionally stable and those who developed dependency. More studies are needed to confirm these data and to further improve the discriminative capacity of frailty assessment instruments.

Our cohort is representative of the real world of old outpatients, since it derives from an over 65 community-dwelling Italian population. Moreover, we used an innovative approach to detect disability, including not only Katz's ADL index, that has high floor and ceiling effects and therefore may show difficulty in identifying milder or earlier onset of disability [114].

Despite these strengths, this study has some limitations. First, although the entire cohort is relatively large, the stratification of analyses according to gender and the low prevalence of frailty contributed to shrink the population at risk of developing the outcome, introducing a potential bias in our results. Second, since we studied only the FP, our results cannot be extended to other frailty indicators, despite the evidence from literature that predictive ability for ADL disability is similar for other current assessment instruments [115]. Third, we used self-reported measures of disability. Previous studies have noted discrepancies in ratings between self-reported and performance based functional measures [116]. However, the use of self-reported data is a common practice when investigating disabilities in older adults, since they are strongly associated with performance-based functional scores and more accurately reflect personal abilities for interacting with the real world [117]. Moreover, concerning discrepancy among men and women, two studies comparing self-reported function with

observed performance found no gender differences in the reporting of disability [118,119]. Fourth, in our analysis we cannot exclude that functional decline is the result of major events (e.g. falls) rather than progressive aging. However, we can assume that as in other population-based studies, in our cohort FP was associated with functional deterioration irrespective of intercurrent events. Finally, since we analyzed data from a community in central Italy, our findings regarding disability patterns may not be translated to other communities. It should be noted, though, that the prevalence of baseline frailty was similar to the one reported in other large European and US population studies [40,120].

In conclusion, when considering as an outcome the pattern of disability in an extended list of tasks, instead of loss of one or more Katz's ADL, the ability of the FP to identify people at risk of functional decline modestly improves. This study highlights the fact that the prognostic capacity of frailty assessment instruments depends also on the definition of the outcome. More research is encouraged in order to identify the best instrument for the prediction of future disability and to implement relative countermeasures.

TABLES AND FIGURES

Table 2.1. Baseline characteristics of the entire cohort according to sex.

	Women	Men
N	550	447
Age, mean (SD)	75.7 (7.8)	74.3 (7)
Frail (FP), %	12.6	9
Indoor mobility, %	5.6	4.7
Outdoor mobility, %	11.5	6.7
Using stairs, %	10.7	6.9
Walking 400mt, %	14.6	8.5
Daily shopping, %	16.9	10.6
Washing face and arms, %	5.1	3.6
Bathing, %	16.2	12.3
Dressing, %	8.7	7.6
Eating, %	3.3	3.1
Cooking a simple meal, %	10.7	9.5
Using the toilet, %	6.2	5.1
Getting in and out of bed, %	6.2	6
Doing light housework, %	10.9	11.3
Doing heavy housework, %	24.5	15.2
Cutting toenails, %	28.2	15.9
Raising arms up over head, %	3.5	3.4
Using fingers to grasp or handle,%	9.6	4.9
Carrying a shopping bag, %	22.4	10.7
Urine and fecal continence, %	7.3	4
Using the telephone, %	9.1	6.7
Doing the laundry, %	13.7	11.8
Using public transportation, %	25.5	12.9
Taking medications correctly, %	9.3	7.6
Managing home finances, %	16.9	12

Table 2.2 Prevalence of baseline frailty (according to Frailty Phenotype) and 3-year-follow-up inability in doing activities of daily living according to the three classes obtained by the latent class analysis.

	SFC		CDC		GDC	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
N	297	303	123	59	59	16
Age at baseline, mean, SD	72.1 (5.5)	71.9 (5.4)	75.7 (6.7)	76.6 (7.2)	82.7 (6.5)	80.2 (7)
Frailty (FP) at baseline, N (%)	6(2)	3(1)	17(14)	12(20)	25(42)	7(46)
At least one ADL lost at baseline, N (%)	17 (5.7)	6(2)	2(2.3)	8(13.5)	12(20.3)	4(25)
Indoor mobility, N (%)	0	0	11(9)	13(22)	51(88)	11(69)
Outdoor mobility, N (%)	0	0	44(36)	16(27)	46(78)	13(81)
Using stairs, N (%)	23(8)	21(7)	59(48)	30(51)	41(69)	14(88)
Walking 400mt, N (%)	9(3)	12(4)	66(54)	35(59)	42(71)	15(94)
Daily shopping, N (%)	6(2)	0	54(44)	29(49)	43(73)	14(88)
Washing face and arms, N (%)	3(1)	3(1)	7(6)	2(3)	43(73)	15(94)
Bathing, N (%)	3(1)	6(2)	45(37)	30(51)	49(83)	14(88)
Dressing, N (%)	3(1)	3(1)	30(25)	24(41)	53(90)	16(100)
Eating, N (%)	0	3(1)	1(1)	2(3)	34(58)	13(81)
Cooking, N (%)	0	0	12(10)	12(20)	47(80)	16(100)
Using the toilet, N (%)	0	0	2(2)	8(15)	51(86)	15(94)
Getting in and out of bed, N (%)	0	0	25(20)	22(37)	52(88)	15(94)
Doing light housework, N (%)	0	0	33(27)	23(39)	50(85)	13(81)
Doing heavy housework, N (%)	32(11)	15(5)	79(64)	36(61)	35(59)	9(56)
Cutting toenails, N (%)	83(28)	42(14)	64(52)	35(59)	35(59)	12(75)
Raising arms over head, N (%)	6(2)	3(1)	17(14)	8(15)	34(58)	9(56)
Using fingers to handle, N (%)	17(6)	6(2)	39(32)	18(31)	40(68)	16(100)
Carrying shopping bags, N (%)	41(14)	12(4)	65(53)	29(49)	33(56)	13(81)
Urine and fecal continence, N (%)	30(10)	27(9)	33(27)	16(27)	35(59)	9(56)
Using the	3(1)	3(1)	15(12)	16(27)	38(64)	12(75)

telephone, N (%)						
Doing the laundry, N (%)	0	0	19(16)	19(32)	39(66)	11(69)
Using public transportation, N (%)	12(4)	3(1)	42(34)	11(19)	28(47)	11(69)
Taking medications, N (%)	6(2)	3(1)	18(15)	18(31)	38(64)	15(94)
Managing home finances, N (%)	18(6)	6(2)	45(37)	21(36)	34(58)	10(62)

SFC: stable function; CDC: disability in complex activities; GDC: global functional disability; FP: Frailty Phenotype (frailty is defined as the presence of at least three of five criteria); ADL: activities of daily living

Table 2.3. Percentage distribution of the three latent classes and death according to Frailty Phenotype and sex.

	ROBUST		PRE-FRAIL		FRAIL	
	Women %	Men %	Women %	Men %	Women %	Men %
SFC	78.3	90	50	56.3	15.8	20.3
CDC	15.3	5.2	28.3	22.6	25	20.3
GDC	3.2	0.9	10.6	3.5	25	12.1
Death	3.2	3.9	11.1	17.6	34.2	47.3

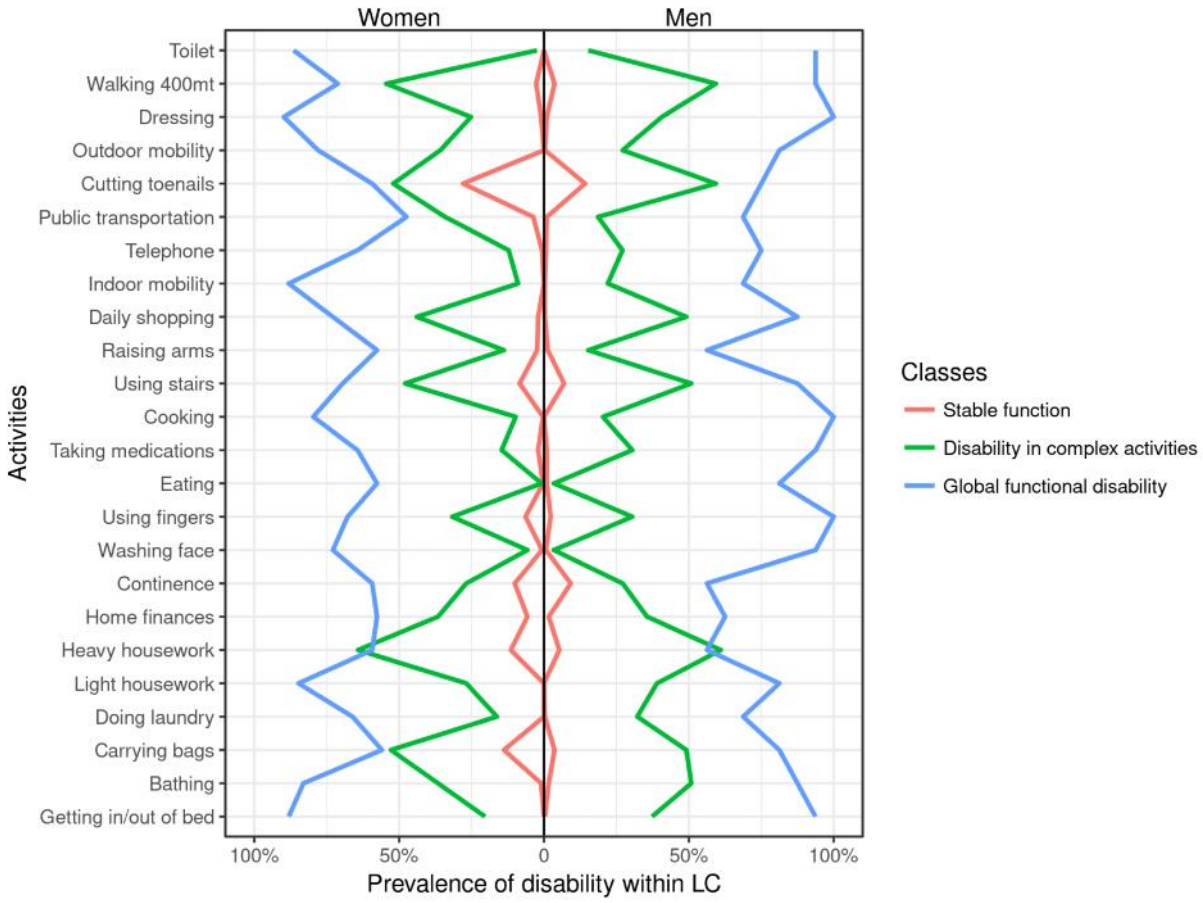
SFC: stable function class; CDC: disability in complex activities; GDC: global functional disability

Table 2.4. Predictive capacity of frailty for the identification of classes of disability in complex activities (CDC) and global functional disability (GDC) and for loss of at least one Katz's activities of daily living (ADL) at three-year follow-up.

	Sensitivity	Specificity	PPV	NPV
Women				
CDC	0.13	0.98	0.68	0.75
GDC	0.42	0.98	0.75	0.91
Loss of one Katz's ADL	0.44	0.94	0.44	0.94
Men				
CDC	0.20	0.99	0.73	0.87
GDC	0.46	0.99	0.60	0.98
Loss of one Katz's ADL	0.28	0.95	0.33	0.95

Frailty was defined as the presence of at least three criteria of the Frailty Phenotype
CDC: disability in complex activities; GDC: global functional disability; PPV: positive predictive value; NPV: negative predictive value.

Figure 2.1. Proportion of disability in each functional task, in women and men, according to the classes obtained by latent class analysis.
The lines represent the proportion of people developing individual disabilities within each latent class. LC: latent class



CHAPTER 4. IMPACT OF LOW MUSCLE MASS AND LOW MUSCLE STRENGTH ACCORDING TO EWGSOP2 AND EWGSOP1 IN COMMUNITY-DWELLING OLDER PEOPLE

Costanzo L, De Vincentis A, Di Iorio A, Bandinelli S, Ferrucci L, Antonelli Incalzi R, Pedone C. J Gerontol A Biol Sci Med Sci. 2020 Mar 11. [Epub ahead of print] doi: 10.1093/gerona/glaa063

ABSTRACT

*Background***.** A universal definition of sarcopenia is still lacking. Since the European criteria have been recently revised, we aimed at studying prevalence of low muscle strength (LMS) and low muscle mass (LMM), as defined according to the European Working Group of Sarcopenia in Older People (EWGSOP) 2 and 1 definitions, and their individual contribution towards mortality and incident mobility disability in a cohort of community-dwelling older people.

Methods. Longitudinal analysis of 535 participants of the InCHIANTI study. LMS and LMM were defined according to criteria indicated in the EWGSOP2 and 1. Cox and log-binomial regressions were used to examine association with mortality and 3-year mobility disability (inability to walk 400m).

*Results***.** We observed a lower prevalence of the combination LMM/LMS according to EWGSOP2 compared to EWGSOP1 (3.2% vs.6.2%). Using the new criteria, all sarcopenia components were associated with mortality, although the hazard ratio[HR] for the group LMM/LMS was no longer significant after adjustment for confounders (LMM: HR 2.69,95% C.I.:1.04-6.94; LMS: HR 3.18,95% C.I.:1.44-7.01; LMM/LMS: HR 2.95,95% C.I.:0.86-10.16). Using EWGSOP1, LMS alone was independently associated with mortality (HR 4.43,95% C.I.:1.85-10.57). None of the sarcopenia components conferred a higher risk of mobility disability.

Conclusions. The EWGSOP2 algorithm leads to a reduction in the estimated prevalence of sarcopenia defined as combination of LMM/LMS. The finding that, independent of the

adopted criteria, people with LMS and normal mass have a higher mortality risk compared to robust individuals, confirms that evaluation of muscle strength has a central role for prognosis evaluation.

BACKGROUND

Given the current and expected growth in the geriatric population worldwide, the promotion of healthy aging has been set among the priorities of public health authorities. Recently, the World Health Organization introduced the concept of intrinsic capacity (the whole person's physical and mental capacities) in order to promote an appropriate assessment of the needs of the aging population and the maintenance of an individual's functional ability [121]. Locomotion has been recognised as one of the domains constituting intrinsic capacity [122], which may be affected during aging: poor mobility and muscle dysfunction are commonly observed among older people and contribute to limitations in performing daily tasks. In this scenario, the concept of sarcopenia has gained increasing importance [123]. The need of a single and universally shared definition of this condition is even more compelling if we consider that sarcopenia has been recently recognized as a muscle disease codified in the current International Classification of Diseases (ICD-10). European and US experts' groups agree on the need of simultaneous evaluation of muscle mass and strength for the definition of sarcopenia [124,125], since the trajectories of their decline during aging do not overlap and muscle strength declines much more rapidly than muscle mass [32]. Low muscle strength depends on several factors beyond loss of muscle mass [32,126] and maintaining or gaining muscle mass has limited value in preventing aging-related decline in muscle strength [127].

According to the updated algorithm proposed by the European Working Group on Sarcopenia in Older People (EWGSOP2) [30], the diagnosis of sarcopenia should be based firstly on the detection of low muscle strength (LMS) and confirmed by the presence of low

muscle mass (LMM), while poor physical performance (e.g. low gait speed) identifies people with severe sarcopenia. The 2018 consensus suggests using grip strength and/or chair stand measure to identify LMS and recommends using specific cut-off points for LMS and appendicular lean muscle mass to promote harmonization among sarcopenia studies.

In consequence of the recent change in the proposed cut-off for muscle mass and strength, data about the prevalence of sarcopenia as defined according to EWGSOP2 in community dwelling older people are lacking. Moreover, which of the components of sarcopenia (strength and muscle mass loss) is associated to adverse outcomes is still unclear. Although previous studies demonstrated that muscle strength is a better predictor of adverse outcomes than muscle mass [34,128,129], the latter is per se an independent predictor of survival and disability among older people [33,130]. On these assumptions, we aimed to investigate among participants in the InCHIANTI Study 1) the prevalence of LMS and LMM according to EWGSOP2 and EWGSOP1 cut-offs and 2) the individual contribution of LMS and LMM as defined by EWGSOP2 and EWGSOP1 criteria towards risk of mortality and incident mobility disability.

METHODS

Data source and sample selection

For this study we selected a sample of people 65 years and older from the InCHIANTI Study. As described elsewhere [66], this is an epidemiological, population-based study designed to investigate the factors contributing to late-life disability. The study protocol was approved by the Italian National Institute of Research and Care on Aging ethical committee. The participants were randomly selected from the inhabitants of two town areas in the Chianti region (Greve in Chianti and Bagno a Ripoli, Tuscany, Italy) and provided written consent to participate. The eligible subjects were firstly interviewed at their homes in order to collect

data about their health status, physical and cognitive performance, and other factors possibly related to loss of independence in late life; then, the interview was followed by a physical examination at the study clinic. The first wave of the study started in 1998 with 1,453 participants who were followed-up with evaluations every three years. As baseline, for this analysis we used data of the second follow-up, when muscle mass was estimated using bioelectrical impedance analysis (BIA). From the original sample, including 1067 subjects at the second follow-up, we selected 844 participants with age ≥ 65 years. For mortality outcome, we excluded 309 patients who did not undergo performance tests or did not perform BIA examination at baseline, leaving 535 participants available for analysis. Disability outcome was evaluated at the InCHIANTI Study third follow-up. For this analysis, we firstly excluded disabled subjects at baseline (N=95), then those who had died before the three-year follow-up (N=18) or with missing data about functional test at follow-up (N=53), therefore, we analyzed a cohort of 369 subjects (*Figure 3.1*: flowchart of the study population selection).

Assessment of muscle mass and muscle strength

For the purpose of this study, we did not include low physical performance for sarcopenia diagnosis, given that incident mobility disability was the outcome of interest. Muscle mass was estimated through BIA using a Quantum/S Bioelectrical Body Composition Analyzer (Akern Srl, Florence, Italy). BIA measures the opposition of body tissues to the flow of a small (less than 1 mA) alternating current by providing two values (resistance and reactance). According to the EWGSOP2's recommendations [30], muscle mass was calculated using the Sergi equation: Appendicular skeletal muscle mass (kg) = -3.964+(0.227* height^2/BIA resistance)+(0.095*weight)+(1.384*gender)+(0.064*BIA reactance), where height is measured in centimeters; BIA resistance and reactance are measured in ohms; weight is measured in kilograms; for gender, men=1 and women=0 [131]. Using the cut points

indicated in the EWGSOP2 consensus, LMM was defined as having appendicular skeletal muscle mass less than 7 kg/m^2 in men and 6 kg/m^2 in women. For the EWGSOP1's definition, LMM was identified as having a skeletal muscle index less than 8.87 kg/m^2 and 6.42 kg/m^2 in men and women, respectively [124,132,133]. Skeletal muscle index was obtained from standardization by squared meters of the absolute skeletal muscle mass, calculated through Janssen and colleagues equation:[134] Skeletal muscle mass (kg) = ([height^2/BIA resistance x 0.401]+[gender x 3.825]+[age x –0.071])+5.102, where height is measured in centimeters; BIA resistance is measured in ohms; for gender, men=1 and women=0; age is measured in years.

Muscle strength was assessed measuring grip strength (GS) and recording the time to complete repeated chair stand test as a proxy for strength of leg muscles [135,136]. GS was measured three times for each hand using a hand-held dynamometer (hydraulic hand BASELINE; Smith and Nephew, Agrate Bianza, Milan, Italy), and the best of the six measurement (usually, the dominant limb) was retained for analyses [137]. LMS was defined as 1) a GS less than 27 kg in men and 16 kg in women and/or time > 15 s for five rises, as proposed in EWGSOP2 consensus and 2) a GS less than sex and BMI-specific cut points, as previously reported in EWGSOP1: *men*: BMI ≤ 24 kg/m^2 GS ≤ 29 kg, BMI 24.1–28 kg/m^2 GS ≤ 30 kg, BMI > 28 kg/m^2 GS ≤ 32 kg; *women*: BMI ≤ 23 kg/m^2 GS ≤ 17 kg, BMI 23.1–26 kg/m^2 GS ≤ 17.3 kg, BMI 26.1–29 kg/m^2 GS ≤ 18 kg, BMI > 29 kg/m^2 GS ≤ 21 kg.

On this basis, as indicated in the EWGSOP2 algorithm [30], probable sarcopenia is defined as the presence of LMS, and the co-occurrence of LMS and LMM confirms the diagnosis of sarcopenia.

Outcome measures

Vital status was available up to April 2010. Mobility disability was evaluated through a direct measure of physical performance, that is the ability to complete a 400-m walk test

within 15 minutes without sitting and without the help of another person or walker. Therefore, incident mobility disability was defined as loss of ability to walk 400m at three-year follow-up (InCHIANTI third follow-up).

Covariates

At baseline (InCHIANTI second follow-up), data about sociodemographic characteristics (education, marital status) were obtained through interview. Prevalence of specific medical conditions was established through self-reported history, medical records and physical examination. A Mini-Mental State Examination score <24 (corrected for education and age) defined cognitive impairment [80]. Adapted Fried et al's criteria were measured as previously described [63], and frail individuals were identified as those having three or more positive criteria. Physical performance was evaluated through 400m walking test. For each participant, we also recorded the SAFE (Survey of Activities and Fear of Falling in the Elderly) score, which investigated fear of falling during performance of 11 activities [138].

Analytic approach

According to the distribution of LMS and LMM, four groups of people were obtained from the original sample (normal muscle mass and strength, LMM/normal muscle strength, normal muscle mass/LMS, LMM/LMS). The main socio-demographic and clinical characteristics were shown using descriptive statistics. The agreement between EWGSOP2 and 1 definitions of LMM and LMS was evaluated using weighted k coefficient and shown through confusion matrix. To examine the association with mortality and 3-year mobility disability risk, Cox and log-binomial regressions were carried out, respectively.

The proportional hazard assumption of Cox regressions was tested through the inspection of Schoenfeld residuals. Multivariable models were adjusted for age, gender, BMI, marital status, education and comorbidities. Finally, the predictive capacity of LMM, LMS or their combination towards mortality was considered and sensitivity, specificity and positive and

negative predictive values were calculated. All the analyses were performed using R 3.3 for Mac (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The general characteristics of study participants, according to the four groups obtained from the combination of LMM and LMS as defined by EWGSOP2 and EWGSOP1 criteria, are presented in *Table 3.1*. Overall, the mean age was 77 years (SD 5.5) and 53.6% were women. Only 17 individuals (3.2%) were classified as having LMS/LMM based upon EWGSOP2 criteria. This group included people who were older, less likely to be women and married, and had a higher prevalence of comorbidities and frailty compared to the other groups (people with normal mass and strength and those with either LMM or LMS). When using EWGSOP1 criteria, a higher percentage of people were classified as having LMM/normal strength compared to the new criteria (24.7% vs. 8.4%) and LMM/LMS (6.2% vs 3.2%). Conversely, a lower number of people had LMS and normal lean mass according to the EWGSOP1 criteria in respect to EWGSOP2 classification (8.4% vs. 15.5%, respectively).

Table 3.2 displays the agreement between 2010 and 2018 criteria. When EWGSOP2's definition was applied, the percentage of participants whose classification according to EWGSOP1 did not change were 88%, 30% 49% and 24% for normal mass/normal strength, LMM/normal strength, normal mass/LMS and LMM/LMS, respectively, with a low-moderate overall agreement (weighted Cohen kappa 0.43, 95% C.I. 0.23-0.63).

Over a mean follow-up of 37 months, 56 participants died. *Figure 3.2* represents Kaplan-Meier curves for mortality for the groups identified using EWGSOP2 (panel A) and EWGSOP1 (panel B) criteria. Association between sarcopenia components defined by EWGSOP2 and adverse outcomes are reported in *Table 3.3*. Cox proportional hazard models showed that LMM, LMS and their combination conferred a higher risk of mortality in

comparison to the presence of normal mass and strength (LMM: HR 3.95, 95% C.I. 1.8-8.65; LMS: HR 2.59 95% C.I. 1.29-5.23; LMM/LMS: HR 6.01, 95% C.I. 2.56-14.15). The result was confirmed also after adjustment for potential confounders (age, sex, BMI, marital status, education and comorbidities), although hazard ratio [HR] for the group LMM/LMS was no longer significant (LMM: HR 2.69, 95% C.I. 1.04-6.94; LMS: HR 3.18, 95% C.I. 1.44-7.01; LMM/LMS: HR 2.95, 95% C.I. 0.86-10.16). None of the sarcopenia components conferred a higher risk of mobility disability (relative risk [RR] adjusted for age, sex and SAFE score: 1.49, 95% C.I. 0.72-2.79 for LMM; 1.40, 95% CI 0.74-2.48 for LMS; 2.57, 95% CI 0.40-9.06 for LMM/LMS). When exploring the individual contribution of chair rise time and grip strength for adverse outcomes, we obtained inconclusive results given the low number of individuals in each group (8 subjects had LMM and impaired chair rise test and 9 subjects had LMM and reduced grip strength -*Table 3.4*). We also analyzed the association of probable sarcopenia (LMS independent of muscle mass) and sarcopenia (LMS and LMM) with adverse outcomes considering people with normal strength as the reference group (*Table 3.5*). The results showed that only probable sarcopenia is independently associated with mortality (probable sarcopenia: HR 2.42, 95% C.I. 1.21-4.84; sarcopenia: HR 1.96, 95% C.I. 0.63-6.15). Again, neither probable sarcopenia nor sarcopenia were associated with disability (*Table 3.5*).

Using the EWGSOP1 cut-offs, people who had LMM, LMS or both showed higher mortality risk compared to the group with normal mass and strength (HR: 2.85, 95% C.I. 1.35-6.06; 4.58, 95% C.I. 2.04-10.24 and 4.63, 95% C.I. 1.96-10.94, respectively). After adjustment for confounders, people with LMS and normal mass showed a four-time greater probability to die in comparison with people with normal strength and mass (HR 4.43 - 95% C.I. 1.85-10.57) (*Table 3.6*). At variance with the LMS/normal mass combination, neither LMM nor LMS/LMM were independently associated with mortality. Furthermore, none of

the sarcopenia components was independently associated with 3-year mobility disability (*Table 3.6*).

The predictive capacity of LMM, LMS and their combination for mortality were similar for EWGSOP1 and 2. Both definitions show low sensitivity and positive predictive values and high specificity and negative predictive values towards mortality (*Table 3.7*). As expected, we obtained the same results when analyzing the predictive capacity of probable sarcopenia and sarcopenia according to EWGSOP2 algorithm (*Table 3.7*).

DISCUSSION

The identification of universally accepted criteria to diagnose sarcopenia is crucial both in clinical practice and in the research field. The new operational definition of sarcopenia, proposed by the European consensus, led to changes in the cut-off points for muscle strength and appendicular lean mass and proposed alternative tools to assess muscle strength (chair rise time). According to the results of our study, the estimated prevalence of sarcopenia, as combination of LMM and LMS, is lower when using EWGSOP2 algorithm compared to EWGSOP1. Irrespective of the definition used, in our cohort the combination of LMS and normal muscle mass was independently associated with a higher risk of mortality (in comparison to the presence of normal mass and strength). Nevertheless, none of the sarcopenia parameters was independently associated with mobility disability.

There are few data concerning the prevalence of sarcopenia according to the revised operational definition firstly published in September 2018 [30,139]. Locquet and collaborators [140] reported that, in a sample of 501 participants of the Sarcopenia and Physical impairment with advancing Age (SarcoPhAge) study, the prevalence of sarcopenia according to EWGSOP2's definition was 7.4% (37 of 501 individuals), that is higher than ours (3.2%, 17 of 535 individuals). This discrepancy may be due primarily to different

population selection. While we used data from community-dwelling older inhabitants, the SarcoPhAge study enrolled outpatients from different departments [141], including individuals with a higher percentage of comorbidities and frailty compared to the InCHIANTI cohort. Thus, it is not surprising that, despite the small percentage of sarcopenic patients in the SarcoPhAge sample, the prevalence we found in our cohort was even lower. Moreover, literature data published very recently confirms that the estimated prevalence of sarcopenia according to the new algorithm is low [142,143].

Our results showed a low-moderate agreement between the EWGSOP1 and EWGSOP2 definitions for identification of LMS and LMM (Cohen kappa: 0.43). Phu and collaborators published similar results for severe sarcopenia (defined as concomitant presence of poor handgrip strength, low lean mass and low gait speed) [144], although data cannot be directly compared to ours, due to different study design and objectives. The lack of agreement between the two definitions may be explained both by the revised cut-off points for LMS and LMM and by the alternate assessment of low strength according to EWGSOP2. Interestingly, applying the new criteria, we obtained a lower percentage of people with low lean mass but a greater prevalence of low muscle strength, probably because the assessment of strength is based on the evaluation of both grip strength and chair rise time.

According to our results, LMM and LMS alone, diagnosed according to EWGSOP2 criteria, conferred a higher mortality risk (HR 2.69, 95% C.I. 1.04-6.94; HR 3.18, 95% C.I. 1.44-7.01, respectively), while the combination LMM/LMS was not independently associated (HR 2.95, 95% C.I. 0.86-10.16). In addition, probable sarcopenia according to EWGSOP2 (that is the presence of LMS independent of muscle mass) but not sarcopenia conferred a higher mortality risk (see *Table 3.3*). These results are similar to those described by Locquet et al [140] and Petermann-Rocha et al [145], reporting no significant association between sarcopenia defined by EWGSOP2 and mortality. Moreover, using FNIH criteria for weakness

and low lean mass, McLean and collaborators obtained inconsistent results with regards to mortality risk patterns [146]. We cannot rule out that this apparently counterintuitive finding may be explained by the low number of people in the LMM/LMS group as previously discussed; nevertheless, it is also plausible that low lean mass reflects the burden of age and comorbidities rather than being an independent predictor of mortality, while LMS is *per se* a risk factor for adverse outcomes.

According to our results, the predictive value of EWGSOP2 algorithm towards mortality is similar to that obtained applying the old criteria, resulting in low sensitivity and positive predictive values and high negative predictive values. Therefore, both definitions seem to well discriminate people who would not die rather than identify the individuals at higher mortality risk.

Independently of the definition, in our cohort sarcopenia components were not associated with incident mobility disability. Although our data are influenced by the low prevalence of low muscle mass and weakness in this sample, they are valuable given that literature data regarding association of EWGSOP2 definition of sarcopenia and mobility disability are lacking. Moreover, the relevance of our findings lies in the definition of the outcome, since the inability to walk 400 m is a direct, not self-reported, measure of mobility disability, leading to major health effects in vulnerable older people. A previous analysis of the InCHIANTI Study [132] reported that the combination of LMS and LMM, defined according to EWGSOP1 thresholds, was associated with functional impairment, but the outcome was incident or worsening IADL disability, instead of inability of walking 400m, as in our study. In the study by McLean and collaborators [146], low grip strength and low lean mass-to-BMI ratio were associated with mobility disability (4-m gait speed ≤ 0.8 m/s). However, the sample was larger (6,280 individuals) than our cohort, different definitions of the predictors and of the outcome were used and no corrections for confounders were applied. Finally, it

should be mentioned that other studies reported that, when examining the individual components of sarcopenia, the presence of low strength predicts the incidence of disability and falls better than the consensus algorithm [129,133], suggesting that the assessment of strength may be preferable, less expensive and time-consuming compared to sarcopenia algorithms to predict functional deterioration.

Some limitations of this study should be pointed out. Since data were collected from a population of central Italy, our findings may not be translated to other communities. Secondly, regarding the association between EWGSOP2 LMM/LMS and mortality, we obtained a poor power (66%) for detecting the observed risk estimate as statistically significant; similarly, power calculations for all the comparisons with mobility disability, ranged from 21 to 66%. Accordingly, these results should be interpreted with caution. Moreover, we did not stratify the analyses according to gender since this may further reduce the power. Finally, the choice of excluding physical performance from sarcopenia diagnostic pathway (as explained in the methods section) may have limited the generalizability of our findings.

Despite these limitations, our study has some strengths. Our population of over 65 community-dwelling people is representative of the real world of old outpatients. Moreover, we analyzed the association of sarcopenia with "hard" outcomes, death and ability to walk 400m. Finally, when analyzing association with the outcomes, we took into account potential confounders, since several factors apart from muscle strength and mass may be responsible for adverse outcomes in an elderly population.

In conclusion, we obtained a low-to-moderate agreement between old and new criteria for identification of LMM and LMS, due to changed cut-off points and to alternative assessments of muscle strength. The EWGSOP2 algorithm and cut-offs lead to a reduction in the estimated prevalence of sarcopenia defined as combination of LMM and LMS, but this may

not translate into a better identification of people at higher risk of adverse outcomes. This finding may be clinically relevant, given that a number of individuals at risk of adverse outcomes could be classified as non-sarcopenic according to EWGSOP2; however, they confirm the pivotal role of muscle strength in sarcopenia diagnostic pathway as suggested in the new algorithm. It is plausible that other factors, instead of low muscle mass itself, could be responsible for reduced grip strength and worse prognosis in our cohort of old individuals. Other studies are needed to confirm these findings and further research is advisable with the aim to identify which factors apart from low lean mass may contribute to reduced strength and may represent the target for interventions.

TABLES AND FIGURES

Table 3.1. Selected demographic and clinical characteristics of the four groups obtained from the distribution of LMM and LMS according to EWGSOP2 (table 3.1a) and EWGSOP1 (table 3.1b)

Table 3.1a

	Normal MM and MS	LMM/ Normal MS	Normal MM/LMS	LMM/LMS
	390	45	83	17
Age (years), mean(SD)	76.1 (5.1)	78.2 (5.1)	79.1 (5.8)	82.7 (8)
Sex (Female), %	200 (51.3%)	28 (62.2%)	53 (63.9%)	6 (35.3%)
BMI (Kg/m2), mean(SD)	27.9 (3.5)	21.8 (2.1)	28.6 (3.6)	22.1 (3.1)
Education (years), mean(SD)	6.1 (3.4)	6.8 (3.7)	5.7 (3.5)	5.1 (4.2)
Marital status (married), %	254 (65.1%)	31 (68.9%)	45 (54.2%)	6 (35.3%)
Hypertension, %	255 (65.4%)	32 (71.1%)	62 (74.7%)	12 (70.6%)
Diabetes Mellitus, %	49 (12.6%)	6 (13.3%)	12 (14.5%)	3 (17.6%)
Chronic Lung disease, %	65 (16.7%)	9 (20%)	22 (26.5%)	5 (29.4%)
CHF,%	79 (20.3%)	12 (26.7%)	21 (25.3%)	8 (47.1%)
Cardio-vascular disease,%	56 (14.4%)	5 (11.1%)	4 (4.8%)	5 (29.4%)
Cerebro-vascular disease,%	18 (4.6%)	4 (8.9%)	4 (4.8%)	1 (5.9%)
Peripheral artery disease,%	47 (12.1%)	3 (6.7%)	10 (12%)	7 (41.2%)
Chronic Kidney disease,%	117 (30.5%)	30 (66.7%)	30 (37.5%)	12 (70.6%)
Parkinson disease,%	20 (5.1%)	2 (4.4%)	9 (10.8%)	3 (17.6%)
MMSE, mean(SD)	26.1 (3.6)	25.1 (3.7)	25 (3.5)	22 (6.9)
Cognitive impairment,%	69 (17.8%)	11 (24.4%)	29 (35.4%)	9 (52.9%)
Comorbidity number, median(IQR)	2 (1-3)	3 (2-4)	3 (2-4)	4 (3-6)
Grip Strength (Kg), mean(SD)	34.3 (10.5)	29.5 (9.2)	25.5 (8.7)	23.4 (7.7)
Chair rise ability (5 times), %	371 (100%)	42 (100%)	75 (97.4%)	14 (100%)
Chair rise time, mean(sec)	10.9 (2)	11.1 (1.8)	17.6 (4.7)	14.4 (3)
Appendicular Skeletal Muscle Mass Index (Kg/m^2), mean(SD)	7.5 (0.8)	6 (0.6)	7.2 (0.8)	6.2 (0.5)
Frailty, %	20 (5.1%)	1 (2.2%)	20 (24.1%)	7 (41.2%)
Deaths, %	18 (4.6%)	10 (22.2%)	19 (22.9%)	9 (52.9%)

MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength; BMI: body mass index; CHF: cardiac heart failure; MMSE: Mini-Mental State Examination

Table 3.1b

	Normal MM and MS	LMM/ Normal MS	Normal MM/ LMS	LMM/LMS
	325	132	45	33
Age(years), mean(SD)	75.5(4.9)	78.7(5.5)	78.1(4.7)	83.4(6.2)
Sex(Female),%	164(50.5%)	84(63.6%)	23(51.1%)	16(48.5%)
BMI(Kg/m2), mean(SD)	28.2(3.7)	24.6(3.5)	28.4(4.1)	25.8(4.3)
Education(years), mean(SD)	6.1(3.3)	6.3(3.8)	6.6(4.1)	4.6(1.9)
Marital status(married),%	221(68%)	76(57.6%)	24(53.3%)	15(45.5%)
Hypertension,%	217(66.8%)	91(68.9%)	30(66.7%)	23(69.7%)
Diabetes Mellitus,%	42(12.9%)	20(15.2%)	4(8.9%)	4(12.1%)
Chronic Lung disease,%	53(16.3%)	29(22%)	10(22.2%)	9(27.3%)
CHF,%	64(19.7%)	33(25%)	11(24.4%)	12(36.4%)
Cardiovascular disease,%	42(12.9%)	17(12.9%)	5(11.1%)	6(18.2%)
Cerebrovascular disease,%	17(5.2%)	6(4.5%)	2(4.4%)	2(6.1%)
Peripheral artery disease,%	35(10.8%)	17(12.9%)	6(13.3%)	9(27.3%)
Chronic Kidney disease,%	92(28.6%)	67(51.5%)	12(27.9%)	18(60%)
Parkinson disease,%	17(5.2%)	6(4.5%)	5(11.1%)	6(18.2%)
MMSE, mean(SD)	26.2(3.6)	25.4(4.1)	24.9(3.3)	23.5(4.4)
Cognitive impairment,%	58(17.9%)	30(22.9%)	16(36.4%)	14(42.4%)
Comorbidity number, median(IQR)	2(2)	3(2)	3(3)	3(3)
Grip Strength(Kg), mean(SD)	35.7(10.4)	29.7(8.6)	22.2(5.8)	20.7(6.1)
Skeletal Muscle Index(Kg/m^2), mean(SD)	8.6(1.5)	6.7(1.3)	8.5(1.6)	6.9(1.4)
Frailty,%	13(4%)	10(7.6%)	13(28.9%)	12(36.4%)
Deaths,%	12(3.7%)	16(12.1%)	15(33.3%)	13(39.4%)

MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength; BMI: body mass index; CHF: cardiac heart failure; MMSE: Mini-Mental State Examination

Table 3.2. Agreement between EWGSOP1 and 2 definitions for LMS and LMM (row percentages)

		EWGSOP2		
	Normal MM and MS	**LMM/Normal MS**	**Normal MM/LMS**	**LMM/LMS**
EWGSOP1				
Normal MM and MS	285 (88%)	4 (1%)	36 (11%)	0 (0%)
LMM/Normal MS	73 (55%)	39 (30%)	15 (11%)	5 (4%)
Normal MM/LMS	19 (42%)	0 (0%)	22 (49%)	4 (9%)
LMM/LMS	13 (39%)	2 (6%)	10 (30%)	8 (24%)

MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength

Table 3.3. Risk of mortality and 3-year incident mobility disability for individuals with LMM, LMS and their combination according to EWGSOP2 definition

	Normal MM and MS	LMM/Normal MS	Normal MM/LMS	LMM/LMS
Mortality				
Sample,N	390	45	83	17
Events, N	18	10	19	9
Unadjusted HR(95% CI)	Ref	3.95 (1.8-8.65)	2.59 (1.29-5.23)	6.01 (2.56-14.15)
Age and Sex-Adjusted HR (95% CI)	Ref	3.78 (1.72-8.3)	2.33 (1.13-4.82)	3.33 (1.18-9.38)
Model A[a] HR (95% CI)	Ref	2.69 (1.04-6.94)	3.18 (1.44-7.01)	2.95 (0.86-10.16)
Disability				
Sample,N	296	30	40	3
Events,N	58	10	15	2
Unadjusted RR(95% CI)	Ref	1.7 (0.82-3.18)	1.91 (1.05-3.28)	3.4 (0.56-10.88)
Model B[b] RR(95% CI)	Ref	1.49 (0.72-2.79)	1.40 (0.74-2.48)	2.57 (0.40-9.06)

[a]*Adjusted for age, sex, BMI, marital status, education and comorbidities*
[b] *Adjusted for age, sex and SAFE score*
MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength; HR:Hazard ratio; RR:Relative Risk

Table 3.4. Risk of mortality and 3-year incident mobility disability for individuals with LMM and LMS, defined according to increased chair rise time and reduced grip strength as reported in the EWGSOP2.

	Normal MM and MS	LMM/LMScr	LMM/LMSgs
Mortality			
Sample,N	390	8	9
Events, N	18	3	6
Unadjusted HR(95% CI)	Ref	16.15 (4.41-59.01)	3.66 (1.15-11.58)
Age and Sex-Adjusted HR (95% CI)	Ref	7.20 (1.80-28.78)	1.39 (0.31-6.17)
Model A[a] HR (95% CI)	Ref	4.53 (0.68-30.15)	7.62 (1.21-48.81)
Disability			
Sample,N	296	2	1
Events,N	58	1	1
Unadjusted RR(95% CI)	Ref	2.55 (0.14-11.56)	5.10 (0.28-23.12)
Model B [b] RR(95% CI)	Ref	1.16 (0.06-6.83)	6.81 (0.38-32.28)

[a]*Adjusted for age, sex, BMI, marital status, education and comorbidities*
[b] *Adjusted for age, sex and SAFE score*
MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength; LMScr, low muscle strength defined by increased chair rise time; LMSgs, low muscle strength defined by reduced grip strength.
HR:Hazard ratio; RR:Relative Risk

Table 3.5. Risk of mortality and 3-year incident mobility disability for probable sarcopenia and sarcopenia according to EWGSOP2 algorithm

	Normal MS	Probable Sarcopenia	Sarcopenia
Mortality			
Sample,N	435	100	17
Events,N	28	28	9
Unadjusted HR (95% CI)	Ref	2.29 (1.28-4.11)	4.32 (1.93-9.69)
Age and Sex-Adjusted HR (95% CI)	Ref	1.74 (0.92-3.30)	2.30 (0.85-6.18)
Model A[a] HR(95% CI)	Ref	2.42 (1.21-4.84)	1.96 (0.63-6.15)
Disability			
Sample, N	326	43	3
Events, N	68	17	2
Unadjusted RR(95% CI)	Ref	1.89 (1.08-3.15)	3.20 (0.52-10.17)
Model B [b] RR(95% CI)	Ref	1.39 (0.76-2.39)	2.43 (0.38-8.53)

[a]*Adjusted for age, sex, BMI, marital status, education and comorbidities*
[b] *Adjusted for age, sex and SAFE score*
MS: muscle strength; HR:Hazard ratio; RR:Relative Risk

Table 3.6. Risk of mortality and 3-year incident mobility disability for individuals with LMM, LMS and their combination according to EWGSOP1 definition

	Normal MM and MS	LMM/Normal MS	Normal MM/ LMS	LMM/LMS
Mortality				
Sample,N	325	132	45	33
Events,N	12	16	15	13
Unadjusted HR(95% CI)	Ref	2.85 (1.35-6.06)	4.58 (2.04-10.24)	4.63 (1.96-10.94)
Age and Sex-Adjusted HR (95% CI)	Ref	2.35 (1.09-5.06)	4.4 (1.95-9.92)	2.52 (0.97-6.58)
Model A[a] HR(95% CI)	Ref	1.52 (0.66-3.51)	4.43 (1.85-10.57)	1.29 (0.41-4.03)
Disability				
Sample,N	250	88	17	14
Events,N	47	22	6	10
Unadjusted RR(95% CI)	Ref	1.33 (0.79-2.18)	1.88 (0.72-4.06)	3.8 (1.81-7.2)
Model B [b] RR(95% CI)	Ref	1.02 (0.6-1.68)	1.79 (0.68-3.93)	2.16 (0.99-4.29)

[a]*Adjusted for age, sex, BMI, marital status, education and comorbidities*
[b] *Adjusted for age, sex and SAFE score*
MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength
HR:Hazard ratio; RR:Relative Risk

Table 3.7. Predictive value of LMM, LMS and their combination for mortality

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
			EWGSOP2	
Normal MM and MS	Ref	Ref	Ref	Ref
LMM/Normal MS	0.33	0.89	0.12	0.97
Normal MM/ LMS	0.44	0.84	0.13	0.97
LMM/LMS	0.38	0.98	0.46	0.97
Normal MS	Ref	Ref	Ref	Ref
Probable sarcopenia	0.48	0.84	0.18	0.96
Sarcopenia	0.29	0.98	0.46	0.96
			EWGSOP1	
Normal MM and MS	Ref	Ref	Ref	Ref
LMM/Normal MS	0.5	0.71	0.08	0.97
Normal MM/ LMS	0.43	0.89	0.17	0.97
LMM/LMS	0.47	0.93	0.28	0.97

MM: muscle mass; MS: muscle strength; LMM: low muscle mass; LMS: low muscle strength

Figure 3.1. Flowchart of the study population selection.

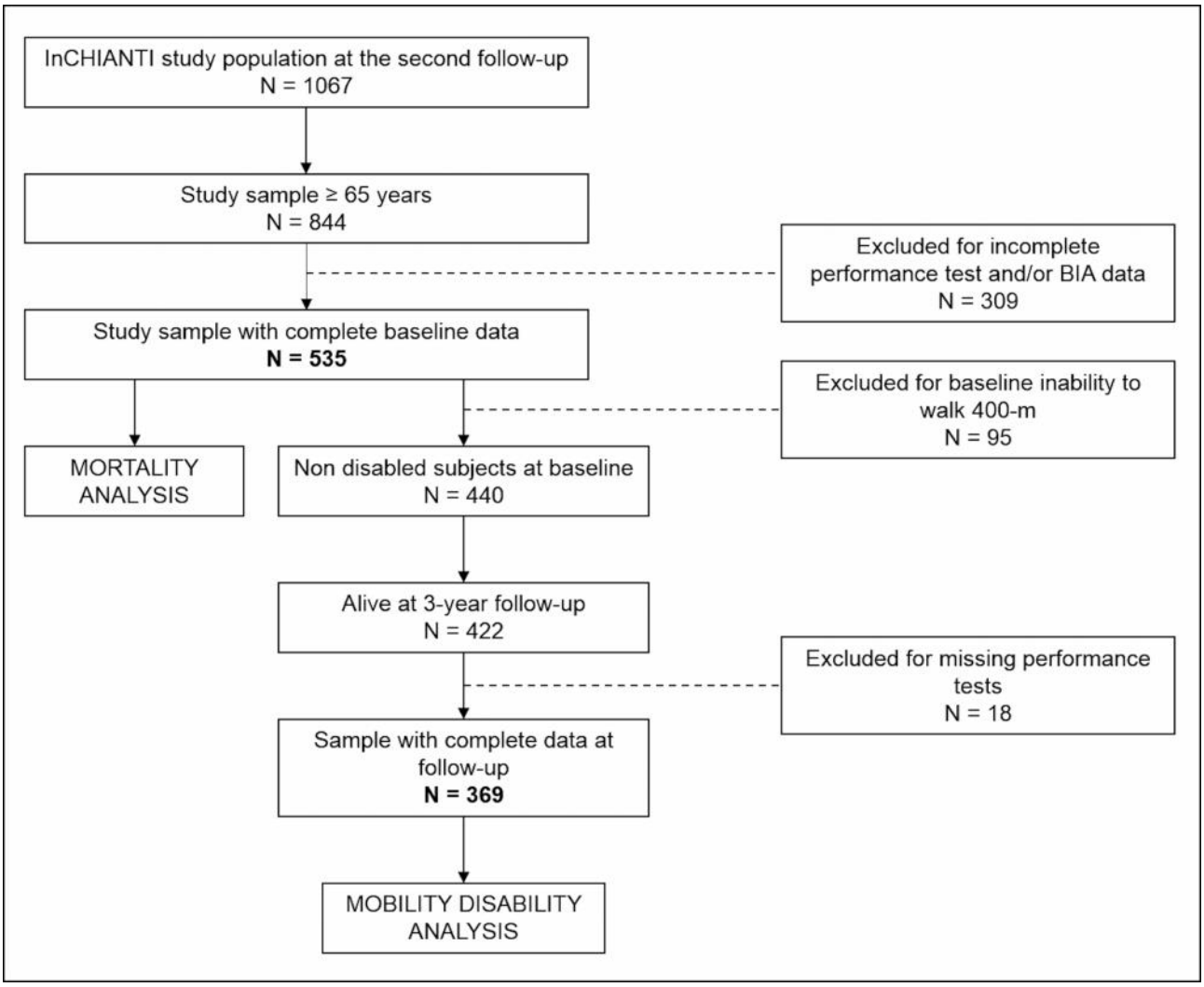
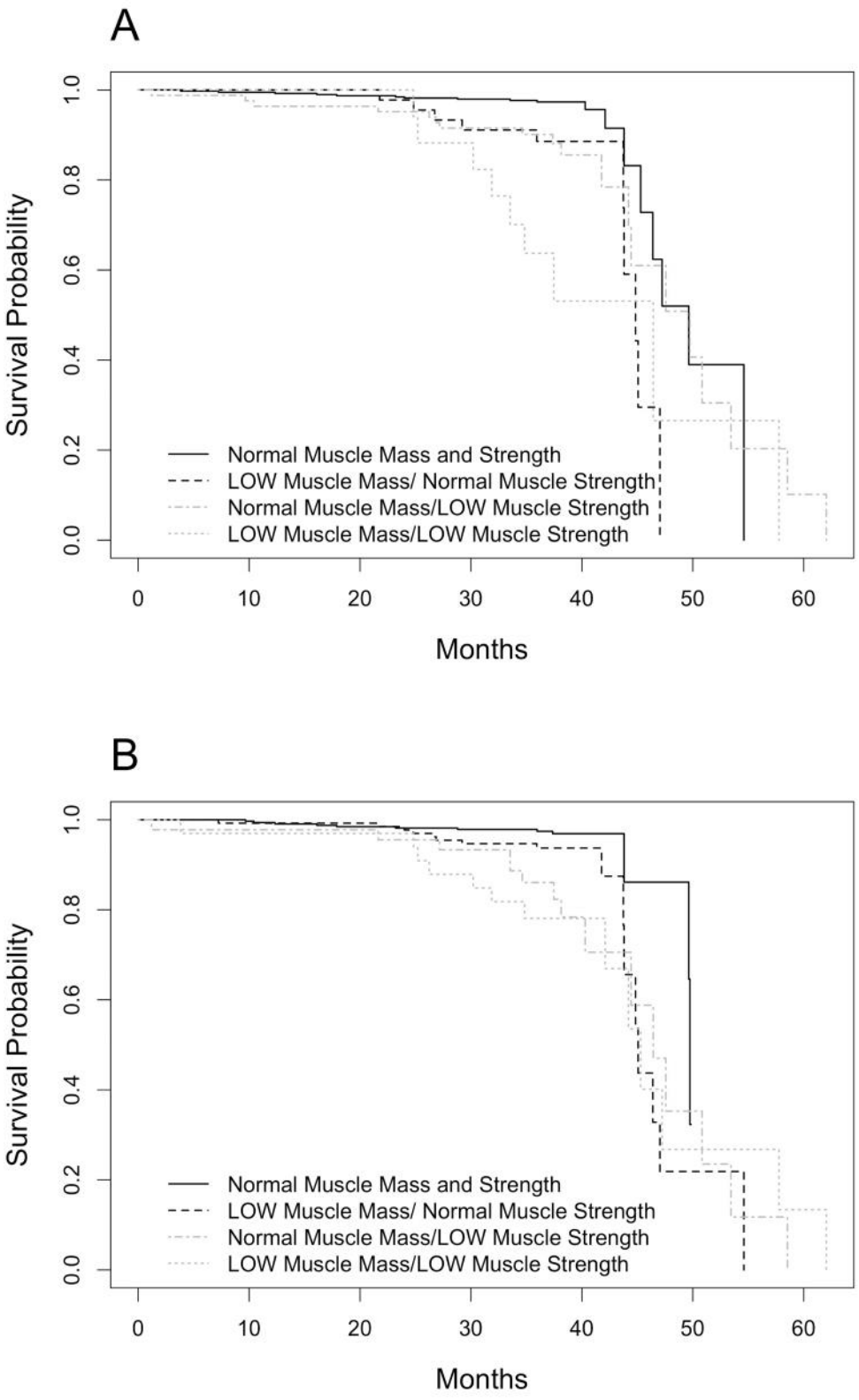


Figure 3.2. Kaplan-Meier curves for mortality in the different groups obtained from the combination of low muscle mass (LMM) and low muscle strength (LMS) as defined by EWGSOP2 (panel A) and EWGSOP1 (panel B) criteria



CHAPTER 5. CONCLUSIONS

Frailty and sarcopenia are common, but not yet recognized geriatric syndromes that have an impact on the health status of older adults. The lack of a widely accepted operationalization of these conditions delays the implementation of effective preventive and therapeutic strategies. An appropriate operational definition should be universally accepted, easy to use in clinical practice and with good discriminative properties. Moreover, the algorithm for diagnosis of sarcopenia has been recently revised by the European Working Group on Sarcopenia in Elderly People (EWGSOP2)[30]. In this thesis, composed of three sequential studies, we analyzed in an Italian cohort of community-dwelling older people the predictive ability of frailty towards incident adverse events and the changes in sarcopenia diagnosis in light of the EWGSOP2 criteria [147–149].

Given that previous studies from our and other groups demonstrated that FP has a poor predictive ability and discriminative capacity for death and incident disability [63–65], in the study presented in *Chapter 2*, we used a multidimensional approach to detect frailty, combining physical, psychological and social indicators: however, this approach results in a still inadequate ability to identify the persons at risk of future adverse events. In the second study (*Chapter 3*), we verified that, when considering as an outcome the pattern of disability in an extended list of tasks, instead of loss of one or more Katz's activities of daily living, the ability of the FP to identify people at risk of functional decline modestly improved, therefore the prognostic capacity of frailty assessment instruments depends also on the definition of the outcome.

The results of these two studies suggest that, although a substantial correlation between frailty and adverse events has been demonstrated in epidemiological studies, researchers and clinicians should take into account the predictive ability of frailty assessment instruments in order to improve the capacity to discriminate the older persons in the need of preventive

actions. It is worth mentioning that the discriminative capacity of frailty tools may depend on the validity of each instrument in the setting of interest (e.g. general population or hospitalized patients) and on the ultimate purpose to be fulfilled (e.g. screening or risk assessment) [150,151].

Similarly, a universally accepted definition of sarcopenia may facilitate the identification of people with physical frailty. Nowadays, the agreement on the variables to be included in sarcopenia diagnosis and corresponding cut-off points is not yet achieved. The revised criteria proposed by the European consensus (EWGSOP2) defined sarcopenia using muscle mass and muscle strength, indicating sex-specific cut offs based on the latest evidence from epidemiological studies [30]. Using the new criteria, the estimated prevalence of sarcopenia seems to be lower compared to the first definition [140,143], but a number of subjects at risk of adverse outcomes could be classified as non-sarcopenic according to EWGSOP2 (see *Chapter 4*). The presence of sarcopenia showed low sensitivity and positive predictive value towards mortality, therefore the EWGSOP definition seems to well discriminate people who would not die rather than identify the individuals that are at increased risk. This issue should be kept in mind when using the algorithm for sarcopenia diagnosis in order to identify people that deserve specific interventions: people labelled as sarcopenic may not be those at increased risk of adverse events, thus appropriate treatments may be not useful nor cost-effective.

The study presented in *Chapter 4* confirms that muscle strength is strongly associated with adverse outcomes, irrespective of muscle mass, as previously demonstrated [133,152,153]. This result is important in light of the fact that physical function impairment (e.g., low muscle strength) represents a common trait of frailty and sarcopenia and is a diagnostic criterion for both conditions [35,36,154]. Skeletal muscle decline may represent one of the pathogenetic explanations of physical frailty, therefore being an objective and measurable target for

interventions against disability in older adults. Further studies are warranted to identify which factors apart from low lean mass may contribute to reduced strength and may represent the target for interventions.

Future directions

Specific research should continue in the field in order to improve the capacity to discriminate the older persons in the need of preventive actions. The lack of an adequate instrument to diagnose frailty and sarcopenia affects the ability to promptly recognize subjects at risk of becoming disabled or die, to plan personalized interventions and, ultimately, to provide the best care to our older patients. In this scenario, geriatricians are called to act as first players in the implementation of screening and management of frailty at various levels. The first step should be identifying which tool is better to use in each setting to detect frailty: each instrument should be easy to use, have clear cut-offs for diagnosis and prove an accurate discriminative capacity. Although at present time there is no robust evidence to support yet routine frailty diagnosis as a means to improve clinical care and cost-effectiveness in older populations [155,156], it is plausible that the refinement in frailty and assessment may facilitate the screening in specific settings.

This thesis was focused on the prognostic ability of physical frailty and sarcopenia, nevertheless, the new concept of cognitive frailty has been emphasized in recent years[157]. This can be defined as the simultaneous presence of both physical frailty and cognitive decline and has been associated with increased incidence of functional disability, poor quality of life, and mortality[158–160]. To note, in the study presented in *Chapter 2* the applied multidimensional approach to frailty was designed to include both physical and cognitive deficits and the predictive capacity of the construct was not improved. Further investigation is needed to confirm these data.

Moreover, the present work analysed data collected from general population, but hospitalized older people for an acute illness represent a distinct community, where predictive ability of frailty assessment instruments may be peculiar. Therefore, in the last months we have started collecting data about hospitalized elderly patients at Campus Bio-Medico Teaching Hospital. At admission, all patients undergone a multidimensional geriatric assessment including various frailty tools, in order to identify which instrument (or set of instruments) better predict in-hospital and 30-day mortality, re-hospitalization and institutionalization.

Finally, future research in the field of frailty will be integrated by advances in the identification of resilience, a concept that is very close to frailty. It has been described as the ability to adapt when a traumatic life event occurs [6] but a consensus on the exact definition of this concept is still lacking [161]. It is plausible that adding a measure of resilience to the assessment of frailty would improve predictive accuracy and inform clinical decision making.

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