Identification of five frailty profiles in community-dwelling individuals aged 50–75: A latent class analysis of the SUCCEED survey data

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Highlights

- Frailty is a commonly used approach to the health status of older people.
 - Frailty increases the likelihood of adverse health outcomes.
 - Frailty profiles have been identified among relatively young seniors.
 - Frailty could be detected in young seniors to prevent adverse health outcomes.
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Identification of five frailty profiles in community-dwelling individuals aged 50 to 75: a latent class analysis of the SUCCEED survey data

Running title: Frailty profiles of community-dwelling individuals

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Abstract

Objectives: We sought to identify frailty profiles in individuals aged 50 to 75 by considering frailty as an unobservable latent variable in a latent class analysis (LCA).

Study design: 589 prospectively enrolled community-dwelling individuals aged 50-75 (median: 61.7 years) had undergone a standardized, multidomain assessment in 2010-2015. Adverse health outcomes (non-accidental falls, fractures, unplanned hospitalizations, and death) that had occurred since the assessment were recorded in 2016-2017.

Main outcome measures: The LCA used nine indicators (unintentional weight loss, relative slowness, weakness, impaired balance, osteoporosis, impaired cognitive functions, executive dysfunction, depression, and hearing impairment) and three covariates (age, gender, and consultation for health complaints). The resulting profiles were characterized by the Fried phenotype and adverse health outcomes.

Results: We identified five profiles: “fit” (LC1, 29.7% of the participants; median age: 59 years); “weight loss, relative slowness, and osteoporosis” (LC2, 33.2%; 63 years); “weakness and osteopenia” (LC3, 21.9%; 60 years); “impaired physical and executive functions” (LC4, 11%; 67 years); and “impaired balance, cognitive functions, and depression” (LC5, 4.3%; 70 years). Almost all members of LC3 and LC4 were female, and were more likely than members of other profiles to have a frail or pre-frail Fried phenotype. Non-accidental falls were significantly more frequent in LC4. LC5 (almost all males) had the highest number of comorbidities and cardiovascular risk factors but none was frail.

Conclusions: Our data-driven approach covered most geriatric assessment domains and identified five frailty profiles. With a view to tailoring interventions and prevention, frailty needs to be detected among young seniors.

Keywords: ageing, frailty profiles, multidomain geriatric assessment, data-driven approach

1. INTRODUCTION

Frailty is commonly used to assess the health status of older people. It is a multidimensional syndrome in which decreased physiological reserve capacity leads to impaired stress adaptation mechanisms. Frailty corresponds to a deceptive, precarious state of equilibrium that can decompensate when a stressful event occurs (e.g. when a close friend dies or a relative moves away) and increases the likelihood of adverse health outcomes such as falls, disability, hospitalization and death [1]. It is a progressive but reversible condition

that begins with a preclinical stage; hence, early detection of frailty and the application of preventive measures might slow the loss of autonomy.

Various operational definitions of frailty have been proposed. The two most widely used tools are based on different conceptual frameworks. Firstly, Fried's measure of physical frailty defines three phenotypes (robust, pre-frail and frail) according to the presence or absence of shrinking, weakness, exhaustion, slowness, and/or a low activity level [1]. Secondly, the cumulative deficit model is based on a multidimensional geriatric assessment that yields a frailty index reflecting the proportion of predefined deficits in a given individual [2]. Both operationalisations are predictive of mortality and other adverse health outcomes [1,2]. These theory-driven tools were built by considering that each frailty domain is independent. In contrast, a few studies used a holistic data-driven approach to identify frailty or health profiles [3-6]. However, these studies generally included individuals aged 65 and over, even though a quarter of individuals display at least one frailty criterion at the age of 50 [7].

We therefore sought to identify frailty profiles on the basis of frailty parameters recorded in a multidomain geriatric assessment of a population aged 50 to 75. Although these individuals tend not to consult a geriatrician, they might gain benefit from a geriatric assessment for preventive purposes (i.e. to prevent future adverse events). Our hypothesis was that a population of younger seniors comprises several frailty profiles. By considering frailty as a latent variable, we conducted a hypothesis-free latent class analysis (LCA) to identify frailty profiles among community-dwelling individuals aged 50 to 75.

2. METHODS

2.1. Study design, population and data source

We used data from the SUCCEED survey of community-dwelling volunteers aged 50 years or over consecutively attending an outpatient clinic in a geriatric teaching hospital (1925

beds, of which 178 are short-stay beds) in the Paris area (France) [8]. Individuals underwent a comprehensive, multidimensional clinical evaluation of cognition, mood, balance, mobility, muscle strength, nutrition, comorbidities, incontinence, hearing, and bone density. For the present analysis, we selected individuals aged 50 to 75 recruited between 2010 and 2015 (Figure 1). They were contacted by phone in 2016-2017 for information on adverse health outcomes since the first assessment.

All study participants received written information about the use of their personal medical data for the study, and provided oral consent. In compliance with French legislation, written informed consent was not required for this observational study. The French National Data Protection Commission authorized the study (#1789613v0).

2.2. Data collection

Baseline parameters were collected prospectively using a self-administered questionnaire. This was followed by an interview, physical measurements, and performance tests conducted by trained nurses, and then a standardized clinical evaluation by a geriatrician. Hypertension was defined as a mean systolic blood pressure (based on three measurements) ≥ 140 mmHg, a mean diastolic blood pressure ≥ 90 mmHg, or antihypertensive treatment. Exhaustion was defined as a “yes” answer to the question: “Did you feel any significant or unusual fatigue over the previous year?”. Participants were asked about unintentional weight loss over the previous year, and the Mini Nutritional Assessment Short-Form score was recorded (risk of malnutrition: $<12/14$, i.e., <12 out of 14).

Mobility and muscle strength were assessed via a daily pedometer count for a week (low activity: <7500 steps/day) [9], gait speed over 10 meters (slowness: <1 m/s [10], relative slowness: $<$ median speed), dynamometer-measured maximum dominant-hand grip strength (JAMAR®, Sammons Preston, Bolingbrook, IL, USA; weakness: <30 kg in men and <20 kg

in women) [11], and the completion time in a five-time sit-to-stand test [12]. The appendicular lean mass index was estimated by dual-energy X-ray absorptiometry (GE Healthcare, Lunar, Prodigy) [13]; sarcopenia was defined as a combination of low muscle mass ($<7.23 \text{ kg/m}^2$ in men, <5.67 in women) with weakness or slowness [13]. Osteopenia and osteoporosis were defined according to the bone mineral density T-score (osteopenia: between -2.5 and -1; osteoporosis, ≤ -2.5). Balance was assessed using the one-leg standing test ($<5 \text{ s}$) [14], resistance to sternal push, and ankle dorsiflexion ($<20^\circ$ was taken as the cut-off for clinical incipient ankylosis). A tuning fork was used to evaluate deep sensitivity. Global cognitive performance was evaluated using the Mini-Mental State Examination score adjusted for age and years of schooling [15]. The five-word screening test was used to assess episodic memory ($<10/10$) [16], the seven-point clock-drawing test was used to assess executive and visuospatial functions ($<7/7$) [17] and Frontal Assessment Battery ($<16/18$) [18] was used to assess frontal lobe functions (which include executive functions). Ten-meter walking test times during concurrent motor and cognitive tasks were recorded. We used the Geriatric Depression Scale to explore mood (risk of depression: $\geq 11/30$ or $\geq 5/15$) [19]. A finger friction test was used to assess possible hearing impairments.

To address the Fried phenotype (according to the Cardiovascular Health Study (CHS) criteria) [1], we considered shrinking ($>4.5 \text{ kg}$ in the last year), weakness, exhaustion, slowness, and a low level of physical activity (<7500 steps per day, and no regular physical activity).

During the 2016-2017 phone interviews, we recorded non-accidental falls (i.e., those not related to sports, DIY or domestic accidents), fractures (hip, spine, and wrist), unplanned hospitalization, and death.

2.3. Illustrative variables and outcomes

To characterize the frailty profiles, we considered the following factors as being potentially associated with latent class (LC) membership: lifestyle, comorbidities, non-accidental falls in the past year, and the Fried phenotype. For prospective validation, we considered a composite outcome that comprised any of the following events since the first assessment: non-accidental falls, fractures, unplanned hospitalizations, and death.

2.4. Statistical analysis

Quantitative and qualitative variables were respectively described as the median [interquartile range] and number (%).

2.4.1. Selection of indicators for the latent class analysis

We first considered 25 potentially relevant frailty markers used in the SUCCEED survey to assess nutrition, mobility, muscle strength, balance, bone density, cognition, mood, hearing, and incontinence. To select the indicators, we first considered the proportion of missing data and the prevalence. Next, we performed a multiple correspondence analysis to assess links between variables, summarize them as a smaller number of factors, and check that each item contributed significantly to the relevant domain. To characterize the clusters and predict class membership, we considered three active covariates: age, gender, and the reason for attending the outpatient clinic (preventive action or a health complaint).

2.4.2. Latent class analysis

We iteratively fitted models comprising up to 8 classes, and selected the model with the best statistical properties. Our one-step approach involved the simultaneous estimation of the LC model of interest and a multinomial logistic regression in which the LCs were related to the active covariates listed above. To deal with missing data, we used the procedure

implemented in Latent GOLD software (V 5.0, Statistical Innovations, Belmont, MA) with a missing-at-random hypothesis. The local dependency between two indicators (bone mineral density and relative slowness) was accounted for by adding a direct effect [20].

2.4.3. Characterization of the profiles identified

To characterize the identified LCs, all individuals were assigned to their most likely class. The distribution of illustrative variables and outcomes was compared across LCs by using the Chi2, Fisher's test, Kruskal-Wallis test or a logistic regression to adjust for the length of follow-up. Post-hoc pairwise comparisons were performed when p was ≤ 0.10 .

All statistical analyses were performed with STATA software (V 14.1, StataCorp, College Station, TX). P values of two-sided test ≤ 0.05 were considered statistically significant. P values from multiple pairwise comparisons were corrected using the false discovery rate method [21].

3. RESULTS

3.1 Study participants

Of the 625 individuals in the database, the 589 aged ≤ 75 years (median age: 61.7 years [57.1-65.8]) were analyzed. After a median follow-up of 3 years (2-4), outcomes were available for 469 individuals (79.6%) (Figure 1).

The baseline characteristics of the study population are summarized in Table 1. Half of the population had one comorbidity and over a quarter had at least one of the following frailty factors: urinary incontinence, weakness, limited ankle dorsiflexion, osteopenia, executive dysfunction or exhaustion. Slowness and shrinking were more scarce ($< 5\%$).

The nine selected indicators are described in Tables 2 and 3.

3.2. Determination of frailty profiles

A five-class solution showed the best fit; it had a non-significant bootstrap p value, the lowest adjusted Akaike information criterion and sample-size-adjusted Bayesian information criterion values, a significant improvement in fit compared to the four-class solution, and no improvement in fit for a six-class solution (Table 4). The classification quality was good (entropy = 0.72).

The conditional probabilities of indicators and covariates for each of the five LCs (interpreted as the probability of each item being present in class members) are summarized in Table 3. Of the 589 participants, 29.7% belonged to latent class 1 (LC1), with 33.2% in LC2, 21.9% in LC3, 11% in LC4, and 4.3% in LC5. Members of LC1 had lower probabilities of almost all indicators, and so this class was designated as “fit”. LC2 was chiefly characterized by high probabilities of weight loss relative to all the other classes and by high probabilities of relative slowness, osteoporosis, depressive mood and hearing impairment; hence, it was designated as “weight loss, relative slowness and osteoporosis”. LC3 was characterized by high probabilities of weakness and osteopenia, as so was designated as “weakness and osteopenia”. LC4 was characterized by high probabilities of relative slowness, weakness, osteoporosis, impaired balance, and executive dysfunction; we designated this class as “impaired physical and executive functions”. Lastly, LC5 was characterized by high probabilities of relative slowness, impaired balance, impaired global cognitive performance, executive dysfunction and depressive mood, and was designated as “impaired balance, cognitive functions and mood”. Age and gender were significantly associated with class membership ($p < 0.001$), as was the reason for consultation ($p = 0.004$). Members of LC1 were predominantly male (probability=0.680), with a median age of 59 [55-63]. Almost all members of LC3 and LC4 were female (0.952 and 0.995, median age: 60[56-63] and 67[63-70], respectively), and almost all the members of LC5 were male (0.992, median age: 70[67-72]). Lastly, most of the

members of LC2 were female (0.787, median age: 63[58-66]). Over one third of the participants in LC4 and LC5 had consulted for a complaint.

3.3. Characteristics of the frailty profiles

The classes differed significantly with regard to the Fried phenotype distribution and the proportions of members living alone, having retired, and presenting with comorbidities or sarcopenia (Table 4). The comorbidity distributions in LC1 and LC2 were similar, with the exception of hypertension (more prevalent in LC1). The members of LC3 and LC4 were more likely to have sarcopenia, and a frail Fried phenotype than members of all the other classes. Lastly, members of LC5 had a greater comorbidity burden and greater prevalences of hypertension, diabetes, and dyslipidaemia, even though the latter condition was not significant. The Fried phenotype distribution in LC5 was similar to that observed for LC1 and LC2.

The median follow-up time was similar for all classes ($p=0.24$). Overall, adverse health outcomes were reported by 21% of the individuals. The incidence of adverse health outcomes (particularly falls) was higher in LC4 than in LC1 and LC2. Two members of LC2 died from acute decompensated heart failure.

4. DISCUSSION

Our data-driven analysis of a population of community-dwelling young seniors (median age: 61.7) identified five frailty profiles, namely “fit” (LC1, 29.7% of the participants), “weight loss, relative slowness, and osteoporosis” (LC2, 33.2%), “weakness and osteopenia” (LC3, 21.9%), “impaired physical and executive functions” (LC4, 11%), and “impaired balance, cognitive functions and mood” (LC5, 4.3%). LC1 and LC2 contained the highest proportion of robust Fried phenotype (>47%), while LC3 and LC4 contained the

lowest proportions (<2%). LC5 had the highest number of comorbidities and cardiovascular risk factors, but none of the members was frail. After a median follow-up of 3 years, the incidence of non-accidental falls was significantly higher in LC4 than in LC1 and LC2.

4.1. Comparison with the literature data

To the best of our knowledge, this is the first study to have defined clusters of community-dwelling individuals aged from 50 to 75 by analysing a large number of frailty parameters. Previous studies using similar approaches generally included older (over-65) participants [3,6,22,23] with disabilities [3,6] or considered comorbidities as indicators [3,5,23]. In line with the literature data, we observed a class of “fit” individuals (LC1) who were predominantly male and younger (median age: 59) than members of other classes [3,5,23]. LC2, LC3, and LC4 were characterized by physical impairment and female predominance (>0.79) which is consistent with the known higher prevalence of physical frailty among women than men [1]. Although almost none of the LC3 or LC4 members had a robust Fried phenotype, almost half of the LC2 members did; this might be because the physical indicators observed in LC2 members differed from the CHS criteria [1].

The association between hearing impairment, slowness and depressive symptoms in LC2 is consistent with a previous report [24].

Both LC3 and LC4 were characterized by weakness and osteopenia. LC4 was also characterized by high probabilities of relative slowness, osteoporosis, executive dysfunction, and balance impairment. Considering the two classes' similar proportions of females (>94%) and the younger age of LC3 members (median age: 60, versus 67 for LC4), we hypothesize that LC3 represents a frailty stage preceding LC4 - especially since weakness has been associated with the subsequent development of slowness and cognitive decline [25,26]. However, this hypothesis will have to be investigated in longitudinal studies. In LC4, we

observed impairments in both physical and executive functions, as reported in many epidemiological studies of older adults [26,27]. However, these studies did not report a major gender effect. Although the serum C-reactive protein level is associated with frailty and mediates the relationship between muscle strength and cognitive function among women (but not men) [27,28], we cannot conclude that this is why LC4 has such a high proportion of females.

In line with previous findings, we observed a cluster (LC5) that aggregated executive dysfunction, depressive symptoms, relative slowness, and high prevalence of cardiovascular risk factors [22]. Hence, LC5 might correspond to a vascular ageing phenotype, which is more prevalent in men. Whereas the members of LC5 were the oldest and had the highest number of comorbidities, none had a frail Fried phenotype. This profile emphasizes the complexity of the relationships between comorbidities and frailty [29] but might be ascribable to the small number of individuals in LC5; furthermore, selection bias cannot be totally ruled out.

Sexual dimorphism in frailty and cognitive impairment has been reported; several underlying mechanisms have been proposed including “inflammaging” and endocrine changes prior to and following andropause and menopause [28,30]. These sex-specific pathways to frailty may partly explain our gender-specific profiles. However, the putative relationships between our classification and biomarkers have yet to be investigated.

4.2. Clinical implication

It is noteworthy that even though few members of LC2 and LC3 had consulted for a health complaint ($\leq 11\%$), most already had frailty parameters. Recent literature data have emphasized the impact of multidomain interventions (physical activity and nutrition-

especially Mediterranean diet) on reducing physical frailty [26,27]. Furthermore, the results of a small number of observational and interventional studies suggest that physical exercise has cognitive benefits [26,27,31]. Therefore, screening for frailty would be valuable even in relatively young, asymptomatic subjects-especially since the rate of falls in LC3 was twice that in LC1.

4.3. Strengths and weaknesses

The main strength of our study is the development of a classification for individuals aged 50 to 75 that integrates prospectively collected indicators from almost all domains of geriatric assessment, using validated scales. The second strength is our use of the Fried phenotype and the subsequent occurrence of adverse outcomes to characterize frailty clusters. However, our operationalization of the CHS criteria was restricted by the low prevalence of several criteria among relatively young seniors. Similarly, we were not able to use the most common indicator of altered balance.

The one-step clustering method used here is known to minimize classification error [32]; the use of the bootstrap method and several parsimony indices increased the reliability of our five-class analysis. Even though our overall sample size ($n=589$) was acceptable [32], some of the cells in the LCA were small, and LC5 had few members. However, it has been suggested that using a large number of indicators (≥ 12) and including covariates may compensate for a small sample size and thus prevent bias and convergence problems [33]. Other study limitations relate to the study's single-centre design (limiting external validity), the recording of adverse health outcomes via phone interviews (possibly inducing measurement bias), and the small number of events (likely to result in a lack of power). Hence, our analyses should be replicated (and thus external validated) in a larger sample.

5. CONCLUSION

Using a data-driven approach to analyse frailty parameters, we identified five frailty profiles among relatively young seniors (50-75 years). Our results highlight the importance of detecting frailty among young seniors in order to tailor interventions for preventing adverse health outcomes.

Our analysis would be usefully complemented by a latent transition analysis, which could account for the progressive nature of frailty. In this respect, it would be interesting to determine (i) whether individuals with an LC3 profile progress to the more severe LC4 profile, and (ii) how the health trajectories of relatively fit individuals change over time.

The relationships between our clusters and biomarkers should be also investigated, in order to better understand the pathophysiological mechanisms (including putative sex-specific pathways).

Contributors

Lauriane Segaux performed the data analyses, contributed to data interpretation and drafted the manuscript.

Nadia Oubaya contributed to data analysis, interpretation and drafting the manuscript.

Amaury Broussier contributed to data collection, interpretation, and revision of the manuscript.

Marjolaine Baude contributed to data collection, interpretation, and revision of the manuscript.

Florence Canoui-Poittrine contributed to data analysis, interpretation and revision of the manuscript.

Henri Naga contributed to data collection, interpretation, and revision of the manuscript.

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Christophe Chailloleau contributed to data collection, interpretation, and revision of the manuscript.

Isabelle Fromentin contributed to data collection, interpretation, and revision of the manuscript.

Jean-Philippe David conceived the study, and contributed to data analysis and interpretation, and drafting the manuscript.

Sylvie Bastuji-Garin conceived the study, and contributed to data analysis and interpretation, and drafting the manuscript.

All authors saw and approved the final version.

Sylvie Bastuji-Garin takes responsibility for the integrity of data analysis

Conflict of interest

None of the authors reports any conflict of interest.

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Ethical approval

All study participants received written information about the use of their personal medical data for the study, and provided oral consent. In compliance with French legislation, written informed consent was not required for this observational study. The French National Data Protection Commission authorized the study (#1789613v0)

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The data sets generated are not currently publicly available.

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Table 1. Characteristics of the 589 community-dwelling individuals aged 50 to 75 included in the cross-sectional analysis.

Characteristics	N (%)
Age, years, median [IQR]	61.7 [57.1-65.8]
Females	397 (67.4)
No regular physical activity (missing data n/%: 62/10.5) ^a	220 (41.8)
Years of full-time education, median [IQR] (18/3.1)	13 [11-15]
Retired (5/0.9)	298 (51.0)
Living alone (1/0.2)	174 (29.6)
Comorbidities	
Number of comorbidities, median [range]	1 [0-6]
Hypertension ^b (4/0.7)	152 (26.0)
Diabetes (6/1.0)	32 (5.5)
Dyslipidemia (7/1.2)	197 (33.9)
Obesity (body mass index ≥ 30) (1/0.2)	82 (14.0)
Cardiovascular disease ^c (6/1.0)	25 (4.3)
Other cardiac diseases ^d (7/1.2)	34 (5.8)
Depression (4/0.7)	79 (13.5)
Cancer (6/1.0)	29 (5.0)
Thyroid disorders (7/1.2)	51 (8.8)
Other comorbidities ^e	59 (10.0)

Notes. The data are quoted as the number (%), unless otherwise stated. (/) indicates the number and % of missing data.

Abbreviations: IQR: interquartile range; MNA: Mini Nutritional Assessment; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; CHS: Cardiovascular Health Study

(I) variables considered as potential indicators for the latent class analysis

^aRegular physical activity included walking, recreational sports and other physical activities and/or number of steps/day > 7500

^bHypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or drug treatment for hypertension

^c Cardiovascular disease included stroke (n=6), transient ischemic attack (n=6), and coronary heart disease (n=8)

^d Other cardiac diseases included chronic heart failure (n=5), valvulopathy (n=9), and cardiac rhythm disorders (n=20)

^eOther comorbidities included: obstructive sleep apnea syndrome (n=28), obsessive compulsive disorder (n=3), bipolar disorder (n=4), anorexia (n=1); polymyalgia rheumatica (n=1); Parkinson's disease (n=2); age-related macular degeneration (n=4); HIV (n=2), chronic hepatitis B/C (n=4), sickle-cell anaemia (n=3), ulcerative colitis (n=1), asthma (n=19), chronic obstructive pulmonary disease (n=4), and chronic bronchitis (n=7)

Table 1. (continued)

Characteristics	N (%)
Chronic pain (84/14.3)	151 (29.9)
Nutrition	
Unintentional weight loss in the past year, regardless of the amount lost (45/7.6) (I)	76 (14.0)
Shrinking (unintentional weight loss in the past year >4.5kg) (45/7.6) (I)	23 (4.1)
Risk of malnutrition/malnutrition (MNA Short-Form <12) (5/0.9) (I)	36 (6.2)
Mobility and muscle strength	
Steps/day, median [IQR] (120/20.4)	7700 [5500-100000]
Number of steps/day < 7500 (120/20.4) (I)	228 (48.6)
Gait speed m/s, median [IQR] (1/0.2) (I)	1.43 [1.25-1.64]
Slowness (gait speed <1 m/s) (1/0.2) (I)	13 (2.2)
Appendicular lean mass index <7.23 (males) or <5.67 (females) (I)	70 (11.9)
Completion time in a five-time sit-to-stand test $\geq$ 11.19 (13/2.2) (I)	48 (8.3)
Weakness (grip strength <30 kg (males), <20 kg (females)) (3/0.5) (I)	183 (31.2)
Sarcopenia ^a (1/0.2) (I)	26 (4.4)
Balance	
Impaired deep sensitivity (86/14.6) (I)	29 (5.8)
One-leg standing test <5 s (7/1.2) (I)	48 (8.3)
Failure in a sternal push test (15/2.6) (I)	29 (5.1)
Ankle dorsiflexion <20° (17/2.9) (I)	167 (29.2)
Bone mineral density (31/5.3) (I)	
Normal (T-score > -1)	262 (47.0)
Osteopenia (T-score between -1 and -2.5)	219 (39.3)
Osteoporosis (T-score $\leq$ -2.5)	77 (13.8)
Cognition	
MMSE score, median [IQR] (19/3.2)	29 [28-30]
MMSE score $\leq$ lowest quartile after adjustment for age and educational level (19/3.2) (I)	95 (16.7)
Five-word test score <10 (2/0.3) (I)	13 (2.2)
Seven-point clock-drawing test <7 (8/1.4) (I)	147 (25.3)
Frontal Assessment Battery score <16 (6/1.0) (I)	92 (15.8)
Time to walk 10 meters in a dual task, s, median [IQR]	
Motor dual task (I)	7 [6.3-8]
Cognitive dual task (I)	7.6 [6.9-9]
Mood	
Depressive symptoms (GDS score $\geq$ 11/30 or 5/15) (74/12.6) (I)	85 (16.5)

Self-reported exhaustion (98/16.6) (I)	146 (29.7)
Self-reported urinary incontinence (9/1.5) (I)	148 (25.5)
Hearing impairment (30/5.1) (I)	100 (17.9)
Non-accidental fall(s) in the past year (7/1.2)	45 (7.7)
Fried physical frailty phenotype (modified CHS criteria)^b	
Robust	192 (32.6)
Pre-frail	369 (62.7)
Frail	28 (4.8)

Notes. The data are quoted as the number (%), unless otherwise stated. (I) indicates the number and % of missing data.

Abbreviations: IQR: interquartile range; MNA: Mini Nutritional Assessment; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; CHS: Cardiovascular Health Study

(I) variables considered as potential indicators for the latent class analysis

^aSarcopenia was defined as low muscle mass (appendicular lean mass index <7.23 (males) or <5.67 (females)) combined with weakness (grip strength <30 kg (males), <20 kg (females)) or slowness (gait speed<1m/s)

^b The modified CHS criteria were shrinking, self-reported exhaustion, weakness, slowness, and low physical activity (<7500 steps/day and no regular physical activity). Individuals with ≥3 criteria are considered to be frail, those with 1-2 criteria are considered to be pre-frail, and those with no criteria are considered to be robust.

Table 2. Selection of indicators for the latent class analysis.

Potential indicators	Selection criteria	Indicator selected
Nutrition		
Risk of malnutrition/malnutrition (MNA Short-Form<12)	Complex indicator which includes dimensions other than nutrition (neurology, medication, etc.)	Unintentional weight loss, regardless of amount lost
Unintentional weight loss in the past year >4.5 kg	Low proportion of events (4.1%)	
Unintentional weight loss in the past year, regardless of amount lost		
Mobility and muscle strength		
Number of steps/day < 7500	Too many missing data (20.4%)	Relative slowness
Slowness (gait speed <1 m/s)	Low proportion of events (2.2%)	
Relative slowness (gait speed < median value 1.43 m/s)		
Sarcopenia ^a	Low proportion of events (4.4%)	
Contribution to the first axis of the muscle strength MCA		
Appendicular lean mass index <7.23 (males) or <5.67 (females)	Weak contribution (0.004)	Weakness
Completion time in a five-time sit-to-stand test ≥11.19	Similar contributions for these two indicators (#0.40). Weakness is more frequently referenced in the literature, and so was selected.	
Weakness (grip strength <30 kg (males), <20 kg (females))		
Contribution to the first axis of the balance MCA		
Impaired deep sensitivity	Weak (0.11)	Ankle dorsiflexion <20°
One-leg standing test <5 s	Weak (0.12)	
Failure in a sternal push test	Weak (0.17)	
Ankle dorsiflexion <20°	High (0.39)	
Bone mineral density (osteoporosis and osteopenia)		Bone mineral density

Cognition

Five-word test score <10	Small proportion of events (2.2%)	
Time to walk 10 meters during a dual task		
Motor dual task	Highly correlated with slow walking speed (Rho= -0.40, p<0.001)	
Cognitive dual task	Highly correlated with slow walking speed (Rho= -0.39, p<0.001)	
MMSE score $\leq$ lowest quartile after adjustment for age and educational level	The only test for global cognition	MMSE score $\leq$ lowest quartile
Seven-point clock-drawing test <7	Less consensual than the frontal assessment battery	Frontal Assessment Battery score <16
Frontal Assessment Battery <16		
Mood		
Depressive symptoms (GDS score $\geq$ 11/30 or 5/15)		GDS $\geq$ 11/30 or 5/15
Exhaustion	Too many missing data (16.6%)	-
Self-reported urinary incontinence	Highly correlated with female gender (Rho=0.30, p<0.001)	-
Hearing loss		Hearing loss

Abbreviations: MCA: multiple comparison analysis; MNA: Mini Nutritional Assessment; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale

^aSarcopenia was defined as low muscle mass (appendicular lean mass index <7.23 (males) or <5.67 (females)) combined with weakness (grip strength <30 kg (males), <20 kg (females)) or slow walking speed (gait speed <1m/s)

Table 3. Indicators estimates for the five-class solution among 589 community-dwelling individuals aged 50 to 75 (one-step approach).

		LC1	LC2	LC3	LC4	LC5	
	Prevalence of indicators (%)	"Fit"	"Weight loss, relative slowness, osteoporosis"	"Weakness- osteopenia"	"Impaired physical and executive functions"	" Impaired balance, cognitive functions, and mood"	<i>P</i> value ^a
Cluster size		0.297	0.332	0.219	0.110	0.043	
Indicators							
Unintentional weight loss ^b	14.0	0.126	0.211	0.115	0.071	0.001	
Relative slowness (<1.43 m/s)	43.7	0.241	0.576	0.325	0.756	0.490	
Weakness (grip strength <30 kg (males) or <20 kg (females))	31.2	0.023	0.014	0.872	0.988	0.045	
Ankle dorsiflexion <20°	29.2	0.273	0.258	0.159	0.443	0.989	
Bone mineral density							
T-score > -1	47.0	0.910	0.262	0.355	0.100	0.512	
Osteopenia (T-score between -1 and -2.5)	39.3	0.089	0.539	0.521	0.511	0.427	
Osteoporosis (T-score ≤ -2.5)	13.8	0.001	0.199	0.124	0.389	0.062	
MMSE score ≤ lowest quartile after adjustment for age and educational level	16.7	0.191	0.219	0.073	0.099	0.242	
Abnormal FAB score (<16)	15.8	0.143	0.153	0.060	0.350	0.303	
Depressive symptoms (GDS score ≥11/30 or 5/15)	16.5						
		0.105	0.231	0.101	0.190	0.312	
Hearing impairment	17.9	0.191	0.262	0.051	0.208	0.026	
Covariates							
Sex							<0.001
Male	32.6	0.680	0.213	0.048	0.005	0.992	
Female	67.4	0.320	0.787	0.952	0.995	0.008	
Age, years							<0.001
≤55	13.6	0.223	0.098	0.164	0.011	0.000	
56-60	28.0	0.379	0.274	0.316	0.061	0.018	

61-65	28.2	0.239	0.281	0.369	0.304	0.084	
66-70	22.6	0.133	0.292	0.124	0.415	0.393	
71-75	7.6	0.025	0.056	0.028	0.209	0.505	
Consultation for a health complaint	13.3	0.062	0.110	0.074	0.367	0.417	0.004

Abbreviations: LC: latent class; FAB: Frontal Assessment Battery; GDS: Geriatric Depression Scale; MMSE: Mini Mental State Examination

Conditional probabilities of indicators and covariates (i.e. the probability of each item being present in class members) with a high level (relative to the prevalence in the overall population and in the other classes) are given in bold type

^a p value in Wald's test

^b Regardless of the amount

Table 4. Goodness-of-fit indices for latent class models comprising one to eight classes.

Number of classes	BIC(LL)	AIC3(LL)	SABIC(LL)	Entropy	Goodness of fit Chi2 ^a	BLRT ^a
1	5851.645	5814.483	5816.724			
2	5706.339	5625.257	5630.147	0.67	0.05	<0.001
3	5736.928	5611.926	5619.465	0.60	0.20	<0.001
4	5747.356	5578.435	5588.623	0.68	0.19	<0.001
5	5786.624	5573.783	5586.620	0.72	0.22	0.002
6	5839.481	5582.721	5598.207	0.69	0.28	0.10
7	5888.986	5588.306	5606.441	0.72	0.26	0.05
8	5946.968	5602.369	5623.153	0.75	0.25	0.37

Abbreviations: BIC: Bayesian information criterion; LL: log likelihood; AIC3: adjusted Akaike information criterion; SABIC: sample-size-adjusted Bayesian information criterion; BLRT: bootstrap likelihood ratio test

(bivariate residuals, $p > 0.05$)

^a Goodness of fit and the BLRT were calculated or performed using a bootstrap procedure with $n=500$ iterations

Table 5. Comparison of illustrative variables and outcomes in the five latent classes identified within a population of community-dwelling individuals aged 50 to 75 (N=589).

	LC1	LC2	LC3	LC4	LC5		<i>P</i> values for pairwise comparisons ^{ab}									
				"Impaired physical and executive functions"	"Impaired balance, cognitive functions, and mood"	Overall <i>P</i> value ^a	LC1 versus				LC2 versus			LC3 versus		LC4 versus
	"Fit"	"Weight loss, relative slowness, osteoporosis"	"Weakness - osteopenia"				LC2	LC3	LC4	LC5	LC3	LC4	LC5	LC4	LC5	LC5
Cross-sectional analysis																
<i>Lifestyle and habits</i>																
Age in years, median [IQR]	59 [55-63]	63 [58-66]	60 [57-63]	67 [63-70]	70 [67-72]	<0.001	<0.001	0.13	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.04
University degree	73 (42.7)	61 (30.4)	36 (31.3)	20 (33.9)	11 (44.0)	0.097	0.14	0.27	0.492	0.886	0.886	0.836	0.492	0.886	0.492	0.628
Living alone	36 (20.9)	72 (34.6)	39 (33.3)	25 (39.1)	2 (7.4)	0.002	0.03	0.03	0.03	0.21	0.82	0.56	0.03	0.55	0.03	0.03
Retired	56 (32.8)	113 (54.9)	53 (45.7)	55 (85.9)	21 (77.8)	<0.001	<0.001	0.04	<0.001	<0.001	0.13	<0.001	0.04	<0.001	0.01	0.32
No regular physical activities ^c	63 (40.4)	72 (39.6)	45 (42.1)	27 (46.6)	13 (54.2)	0.64										
Comorbidities																
Number of comorbidities, median [range]	1 [0-5]	1 [0-4]	1 [0-6]	1 [0-5]	2 [0-5]	<0.001	0.73	0.11	0.003	<0.001	0.16	0.004	<0.001	0.10	<0.001	0.01
Hypertension ^d (4/0.7)	53 (31.2)	42 (20.3)	24 (20.5)	18 (28.1)	15 (55.6)	0.001	0.03	0.08	0.75	0.03	0.94	0.25	<0.001	0.30	<0.001	0.03
Diabetes (6/1.0)	8 (4.7)	5 (2.4)	9 (7.8)	3 (4.7)	7 (25.9)	<0.001	0.37	0.37	0.90	<0.001	0.06	0.37	<0.001	0.55	0.02	0.02
Dyslipidaemia (7/1.2)	50 (29.4)	69 (33.7)	37 (31.9)	27 (42.2)	14 (51.9)	0.11										
Obesity (body mass index ≥30) (1/0.2)	21 (12.3)	26 (12.5)	17 (14.4)	10 (15.6)	8 (29.6)	0.16										
Cardiovascular diseases (6/1.0)	6 (3.5)	9 (4.4)	5 (4.3)	3 (4.7)	2 (7.4)	0.84										
Other cardiac diseases ^f (7/1.2)	6 (3.5)	10 (4.9)	7 (6.0)	7 (10.9)	4 (14.8)	0.06	0.61	0.45	0.12	0.12	0.62	0.19	0.12	0.39	0.21	0.61
Cancer (6/1.0)	1 (0.6)	10 (4.9)	11 (9.5)	5 (7.8)	2 (7.4)	0.05	0.10	0.04	0.06	0.08	0.22	0.53	0.85	0.94	0.94	0.94
Thyroid disorders (7/1.2)	7 (4.1)	16 (7.8)	18 (15.5)	10 (15.6)	0 (0.0)	0.005	0.22	0.02	0.02	0.59	0.11	0.15	0.26	0.95	0.18	0.18
Other comorbidities ^g	16 (9.3)	22 (10.6)	12 (10.2)	4 (6.3)	5 (18.5)	0.49										
Sarcopenia	1 (0.6)	1 (0.5)	15 (12.7)	9 (14.3)	0 (0.0)	<0.001	0.87	0.003	0.003	0.81	<0.001	<0.001	0.81	0.81	0.25	0.25
Non-accidental falls in the previous year	7 (4.1)	18 (8.7)	9 (7.7)	8 (12.7)	3 (11.1)	0.20										
Fried physical frailty phenotype (modified CHS criteria) ^h						<0.001										
Robust	82 (47.7)	98 (47.1)	0 (0.0)	1 (1.6)	11 (40.7)		0.91	<0.001	<0.001	0.61	<0.001	<0.001	0.61	0.42	0.002	<0.001

Pre-frail	88 (51.2)	108 (51.9)	103 (87.3)	54 (84.4)	16 (59.3)											
Frail	2 (1.2)	2 (1.0)	15 (12.7)	9 (14.1)	0 (0.0)											
Follow-up (n=469)																
Follow-up, years [IQR]	3 [2-5]	3 [2-4]	3 [3-4]	4 [3-5]	3 [3-5]	0.24										
Composite outcome ⁱ	23 (16.6)	29 (18.4)	24 (23.3)	17 (38.6)	2 (16.7)	0.05	0.86	0.41	0.03	0.95	0.60	0.045	0.98	0.26	0.86	0.41
Fracture (hip, wrist or spine)	1 (0.7)	0 (0.0)	3 (2.9)	1 (2.3)	0 (0.0)	0.43										
Non-accidental falls	14 (9.9)	21 (13.2)	18 (17.3)	14 (33.3)	1 (8.3)	0.01	0.55	0.22	0.01	0.90	0.55	0.03	0.88	0.15	0.69	0.28
Unplanned hospitalization	9 (6.4)	12 (7.5)	11 (10.6)	4 (9.3)	1 (8.3)	0.80										

Note. The data are quoted as the number (%), unless specified otherwise.

Abbreviations: LC: latent class; IQR: interquartile range; CHS: Cardiovascular Health Study

^a *P* value in a chi-squared test, Fisher's test, a Kruskal-Wallis test or a logistic regression adjusted for the length of follow-up (outcomes)

^b the *p* value was corrected using the false-discovery rate method for multiple comparisons

^c Regular physical activity included walking, recreational sports and other physical activities and/or number of steps/day >7500

^d Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or treatment for hypertension

^e Cardiovascular diseases included stroke (n=6), transient ischemic attack (n=6), and coronary heart disease (n=8)

^f Other cardiac diseases included heart failure (n=5), valvulopathy (n=9), and cardiac rhythm disorders (n=20)

^g Other comorbidities included: obstructive sleep apnoea syndrome (n=28), obsessive compulsive disorder (n=3), bipolar disorder (n=4), anorexia (n=1); polymyalgia rheumatica (n=1); Parkinson's disease (n=2); age-related macular degeneration (n=4); HIV (n=2), chronic hepatitis B/C (n=4), sickle-cell anaemia (n=3), ulcerative colitis (n=1), asthma (n=19), chronic obstructive pulmonary disease (n=4), and chronic bronchitis (n=7)

^h The items considered were unintentional weight loss >4.5 kg in the past year, self-reported exhaustion, weakness, slowness, and low physical activity (<7500 steps/day and no regular physical activity). Individuals with ≥ 3 criteria are considered to be frail, those with 1-2 criteria are considered to be pre-frail, and those with no criteria are considered to be robust; none of the participants met more than three criteria.

ⁱ The composite outcome included hip, spine, or wrist fractures, non-accidental falls, unplanned hospitalizations, and death (n=2 deaths in LC2). Analyses were adjusted for the length of follow-up.

Figure 1. Flow Chart of the SUCCEED survey population.