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A randomized, controlled trial of disability prevention in frail older patients screened in primary care: the FRASI Study. Design and baseline evaluation

Stefania Bandinelli¹, Fulvio Lauretani¹, Vittorio Boscherini², Francesca Gandi¹, Martina Pozzi¹, Anna Maria Corsi¹, Benedetta Bartali³, Raffaello Molino Lova⁴, Jack M. Guralnik⁵, and Luigi Ferrucci⁶

¹Geriatric Rehabilitation Unit, ASF, Tuscany Regional Health Agency, and Laboratory of Clinical Epidemiology, Italian National Institute of Research and Care of Aging (INRCA), Firenze

²Cooperativa Medica Leonardo, Firenze, Italy

³Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA

⁴Don Gnocchi Foundation, Firenze, Italy

⁵Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, MD

⁶Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, MD, USA

Abstract

Background and aims—We describe the enrollment and intervention phases of FRASI (FRailty, Screening and Intervention), a randomized controlled trial aimed at preventing ADL disability in frail older persons screened in primary care.

Methods—Patients, 70–85 years old, non-disabled and non-cognitively impaired, were screened for frailty (score ≤ 9 on the Short Physical Performance Battery, SPPB) during primary care visits. Of 447 eligible persons, 410 came to the study clinic and 251 were randomized into treatment ($n=126$) and control groups ($n=125$). The active group received an intensive medical intervention, and sixteen 90-minute supervised exercise sessions over 8 weeks. The primary outcome was time to ADL disability onset or death in the 12-month period after study enrollment.

Results—The two study arms were similar for demographics, cognitive function, physical function and health status. Compared with a population-based sample selected according to FRASI inclusion criteria except SPPB score, FRASI participants had significantly worse health and functional status. Restricting the comparison to persons with SPPB ≤ 9 , all differences disappeared. The 99 participants (78.6% of 126) who completed the intervention participated in a mean of 15.3 ± 1.6 exercise sessions.

Conclusions—Screening in primary care for non-disabled, older persons with SPPB ≤ 9 yields individuals with substantial morbidity, impairments and functional limitations that can be successfully involved in an intensive medical and exercise intervention. Whether such an intervention effectively prevents new disability remains to be confirmed.

Keywords

Disability; frailty; FRASI; prevention

Introduction

By 2030, approximately 20% of North Americans, 24% of Europeans and 13% of Asians will be more than 65 years old (1). Despite declining age-specific disability rates (2), the aging of the population is expanding the prevalence of disability and increasing the burden on medical and social services (3). Beyond financial considerations, disability jeopardizes the quality of life of older individuals and their families (4,5). Even a small reduction in disability may translate into large health care savings and improvements in the physical, emotional and social health of older persons.

Limited research indicates that prevention of disability is possible, especially when directed at frail individuals (6,7). Previous trials aimed at preventing functional decline in frail older persons reported positive findings but, because they did not exclude persons who were already disabled, prevention of new disability in activities of daily living (ADL) could not be fully demonstrated (8,9). Additionally, while it is widely recognized that care and prevention in older persons requires a comprehensive approach (10), previous trials of disability prevention have almost exclusively focused on exercise (8,9). To address these problems, we designed a randomized controlled trial to test whether a combined, intensive medical and exercise intervention can prevent ADL disability in non-disabled, frail, older persons screened in primary care. The tested intervention was designed so it could be implemented without major structural changes in the Italian health care system. In this manuscript, we describe the design of the FRASI (FRailty Screening and Intervention) trial, including the enrollment phase and participation in the intervention program.

Methods

Study population

The FRASI study protocol was approved by the INRCA Institutional Review Board. Recruitment began in fall 2002 and was completed in spring 2004. Thirty-nine primary care physicians (PCPs) practising in Florence, Italy, identified potential participants by screening 70-85-year-old patients who came to their office for a routine visit. Frailty was operationally defined as a score of 9 or less on the Short Physical Performance Battery (SPPB) (11,12). The SPPB score is derived from performance in three objective tests: walking speed over 4 meters, five timed repeated chair rises, and standing balance. Each test is scored from 0 to 4 based upon extensive normative data, and the three scores are summed to achieve a total score, ranging from 0 to 12 (12=best) (12). Older, non-disabled persons with a SPPB score of 9 are twice as likely to develop ADL disability compared to those with a score of 12; lower scores, below 9, are associated with progressively higher risk of disability (11,13).

Self-reported need for help in performing one or more ADL (walking across a small room, bathing, dressing, toileting, transferring), a diagnosis of dementia or a Mini Mental State Examination (MMSE) education-adjusted score of less than 24 (14), any acute medical condition, a recent surgical procedure or a life expectancy of less than 12 months were considered as exclusion criteria.

Primary care physicians (PCPs) received extensive training in the correct administration of the screening test, which required 4-7 minutes for administration and scoring. We had previously demonstrated that this screening protocol is feasible, efficient, and well accepted by PCPs (15).

Of 954 screened patients, 447 (46.9%) were potentially eligible, 410 (91.7% of those eligible) came to the Study Clinic where they received a full description of the study, and 251 (61.2% of those eligible) agreed to participate and signed a participation consent form. Common

reasons for refusal were transport difficulties (n=98), caregivers unwilling to cooperate (n=19) and discomfort with randomized assignment (n=15). Eligible persons who declined to participate did not differ significantly from those who agreed to participate for age, sex and SPPB score.

Assessments

Potential participants were referred to the Day Hospital of the Italian National Institute of Research and Care of Aging (INRCA) in Florence, where a comprehensive evaluation was completed in 6 to 15 days. Assessments were conducted by a team including a geriatrician, two physical therapists, and a dietician using pre-defined, standardized methods.

The assessment included: 1) Ascertainment of major disease (diabetes, hypertension, myocardial infarction, angina, heart failure, pulmonary disease, stroke, Parkinson's disease, cancer, hip and knee osteoarthritis, osteoporosis, back pain, peripheral artery disease, peripheral neuropathy) using pre-determined criteria (16); 2) Careful consideration of treatments not strictly necessary and/or potentially harmful; 3) Collection of self-reported information on medical history, education, sensory deficits, perception of well-being, personal mastery (17), depressive symptoms (18), disability in basic ADL (walking across a small room, bathing, dressing, toileting, transferring) (19), walking ability, physical activity, falls in the last 12 months, fear of falling (20) and incontinence. The same evaluation was performed at the end of the intervention in the active intervention group.

Physical function evaluations included: 1) SPPB; 2) Maximum walking speed under various challenging conditions, including walking within a 15-cm wide course, stepping over obstacles, walking while carrying a large, light object, walking while responding to questions, and walking 400 m (21); 3) Handgrip strength and knee extension strength, measured according to a standard protocol (22); 4) Ankle isometric extension strength, measured by a "REV-9000" (Technogym, Forli, Cesena, Italy) dynamometer; 5) Lower extremity muscle power (23).

Dietary intake was evaluated by the European Prospective Investigation into Cancer (EPIC) and nutrition food frequency questionnaires (24). Motor and sensory conduction velocities were evaluated by standard surface electroneurography on the lower leg. Bone strength and bone mineral density were measured at the lower leg by peripheral Quantitative Computed Tomography (pQCT, XCT 2000, Stratec Medizintechnik, Germany).

After baseline measurement, participants were randomly assigned (by a computer-generated list) to either active intervention (n=126) or control (n=125) groups (Fig. 1).

Intervention group

The medical intervention aimed at the optimization of chronic diseases management and risk profile improvement. To accomplish this goal, members of the evaluation team scheduled follow-up visits (n=86), consulted with specialists (n=31), requested additional testing (n=112), modified treatment regimens and monitored their effectiveness (n=90). Major medical problems commonly encountered in geriatric patients were managed according to pre-established guidelines, in agreement with the participants' PCPs (Table 1). The most frequent interventions were: 1) Discontinuation of unnecessary or potentially detrimental drugs (n=39); 2) Improved control of hypertension (n=24) or diabetes (n=13); 3) Dietary prescription (n=15); 4) Prescription of antidepressants (n=12); 5) Surgery (n=5) and 6) Family counseling (n=5). Participants' health status was intensively monitored during the 3-month intervention period, and optimization of medical treatment was pursued through multiple adjustments of drug regimens and follow-up visits.

The exercise component of the intervention was not initiated until the research team deemed the participant clinically stable, which took 13 ± 3 days (range 10-21) on average, following the initial evaluation. The intervention consisted of 16, 90-minute sessions conducted twice a week for a total of 8 weeks. Each session started with a 15-minute warm-up consisting of aerobic activities, including walking across the gymnasium, deep breathing, and callisthenic exercises involving the major joints. The warm-up phase was aimed at raising body temperature, increasing muscle blood flow, and improving the elastic properties of muscles, tendons and joint structures. The warm-up phase was followed by the core intervention, which included three components, each lasting approximately 20 minutes: 1. Stretching; 2. Strength training, and 3. Balance training.

In the stretching program, participants were asked to maintain each position in which specific muscle groups were gently stretched for 10 seconds, and then tension on the same muscle was maximized for 20 more seconds. Stretching training was applied to the following muscle groups: neck flexors, neck rotators, lateral trunk flexors, trunk extensors, shoulder flexors, shoulder extensors, elbow extensors, hip flexors, quadriceps, hamstrings, and ankle flexors.

Strength training consisted of exercises performed against resistance, obtained by applying weight-loaded straps to limb sections that were lifted against gravity during the exercise. Weight was progressively increased over the first two weeks to determine thresholds for 8-repetition maximum (RM). The same weight was then used until the participant was able to accomplish 12 repetitions. Then, the weight was increased, the intensity set back to 8RM, and the cycle repeated. During each training session, patients performed three sets of 8-12 repetitions. The time preset for each repetition was 3-5 seconds for concentric contractions and 6-10 seconds for eccentric contractions. When hip flexors, hip extensors, knee flexors and knee extensors were trained, the loaded strap was on the ankles, and for hip abductor training it was on the thighs. For ankle flexors and extensors, an elastic band was applied to the ankle joints. In addition, participants performed strength training exercises (5 repetitions) involving trunk extensor and flexor muscles, the erector spinae muscles, abdominal muscles, and dorsal flexor muscles.

For balance training, participants were asked to maintain balance in progressively more difficult positions, including: performing a maximal functional reach, maintaining balance while sitting on a large ball, maintaining balance on a narrow base of support (side-by-side, one foot over a ball, semi-tandem, tandem, single foot stand), on various surfaces (with shoes, barefoot, on a thick carpet), and with reduced sensory inputs (eyes closed, hyper-extended neck, etc.) (25). Participants were also asked to walk in conditions mimicking normal life situations associated with risk of falls, including rapid change in direction (forward, backward, laterally, crossed steps, turning 180°), changing speed (usual pace, fast pace), changing support (with shoes, barefoot, on a carpet), changing pattern (free, tandem, on toes, rising on toes), walking while overcoming obstacles and avoiding unexpected perturbations, stopping suddenly, and picking up objects from the ground. A final 15-minute cool-down session included the same aerobic exercises performed in the initial warm-up session.

A report including recommendations for pharmacological and non-pharmacological treatment and instructions to continue exercise at home was given to participants at the end of the intervention and discussed with their PCPs.

Strategies to enhance adherence to the intervention

Because of the characteristics of FRASI participants, maximizing intervention adherence was critical for the success of the project. The FRASI research team monitored participants' health status and, when an acute condition or decompensation of a previously existing chronic condition was suspected, referred the participant to the study geriatrician. To maximize

participation in the intervention program, members of the research team provided positive feedback to the participants and their relatives, and transport was available free of charge to all participants. The study coordinator contacted participants who had not attended one or more session without explanation, and discussed possible strategies for adherence improvement.

Control group

After the initial evaluation, the PCPs of control participants received a detailed report of the main findings, including recommendations for treatment and health-related behaviors (diet, physical activity, giving up smoking) tailored to participants' specific problems. After the initial evaluation, the PCPs performed three monthly follow-up visits and made all choices concerning the need for treatment modification, other interventions, and other possible evaluations. No further formal evaluation was foreseen before the final follow-up visit, which was planned to occur 12 months after study enrollment.

Outcomes

The primary outcome of FRASI was time to the onset of the combined outcome either for new ADL disability, or death, during the 12-month period after study enrollment. Disability is defined as self-reported need for help in performing one or more ADL (walking across a small room, bathing, dressing, toileting, transferring). We included death, because frail older persons have high mortality rates, and possible differences in mortality between the two groups could have substantially influenced the interpretation of study results. Secondary outcomes were changes in SPPB score and time to walk 400 m, which are both reliable proxy measures of disability, with good predictive validity for multiple adverse outcomes (13,26). Tests used to establish the main outcomes were administered by physical therapists who were blind to group assignment and who had no additional contact with participants. Death or development of ADL disabilities were monitored by monthly phone interviews with participants or, in their absence, with family members or PCPs. A final evaluation of functional status was performed in the context of the final 12-month follow-up visit.

Sample size justification

We sought to enroll and maintain in the study at least 200 participants. Given participants' characteristics, we estimated that 30% of controls would either develop ADL disabilities or die over the 12-month follow-up (13). Assuming 100 participants in each of the intervention and control groups, the power to detect a 33% difference in the one-year rate of new disabilities (30% rate in the control group versus 20% rate in the treatment group) was close to 80%. This large size effect was equivalent to having to treat 10 frail older persons to prevent one ADL "disability event", and took into account the fact that the intervention included both medical and exercise components.

Statistical analysis

Continuous variables were summarized as means $\pm$ standard deviations (SD) and categorical variables as percentages. Baseline characteristics of participants in the two groups were compared by unpaired Student's *t*-test and Pearson's Chi-square test, as appropriate. To understand how the FRASI study population differed from the general population, participant baseline characteristics were compared with those assessed in an age-matched random sample of the general population using the same standard protocol. This reference sample was selected from the InCHIANTI study, an epidemiological study on risk factors for mobility disability performed in a representative Italian cohort (21).

Results

Participants in the two groups were similar for demographics, body mass index, physical activity, energy intake, bone mineral density (BMD), cognitive function (MMSE score), muscle and lower extremity function, depressive symptoms, self-report of falls, and drugs taken regularly over the previous 12 months. The prevalence of major chronic conditions and comorbidity distribution was also similar (Table 2).

In Table 3, the characteristics of the FRASI study population are compared with two population samples of InCHIANTI study participants selected according to the main FRASI inclusion criteria (age 70-85 years, no ADL disability, MMSE $\geq$ 24). The first sample (n=408) included the full range of SPPB scores, whereas the second (n=118) was restricted to participants with SPPB scores of 9 or less. Compared with the full-range SPPB score group, and after adjusting for age and sex, the FRASI study participants were significantly less physically active, had lower BMD, lower extremity muscle strength and power, poorer lower extremity function, more depressive symptoms, and were more likely to report a history of falls in the previous 12 months. Additionally, FRASI participants had significantly higher chronic morbidity and were taking significantly more drugs. We found no difference in the dietary intake of energy (Table 3). When the comparison group was restricted to the subgroup of 118 InCHIANTI participants with SPPB scores of 9 or less, none of the evaluated characteristics was different between groups (Table 3).

Of the 126 participants randomized in the active treatment group, 99 (78.6%) completed the intervention and participated on average in 15.3 $\pm$ 1.6 sessions, and 86 participated in all sessions. Of the 27 participants who dropped out, 23 left within the first 4 weeks. Causes of drop-out were family problems (n=8, 29.6%), fear of trauma (n=2, 7.4%), loss of interest (n=4, 14.8%), medical problems (n=12, 44.4%) and transport problems (n=1, 3.7%).

Discussion

In this first part of the FRASI trial, we found that busy PCPs were able to screen frail, older persons during routine work using a simple standard protocol. Older persons identified by this strategy had substantial morbidity and functional limitations, similar to those of community-dwelling persons with the same characteristics. Because of intensive medical observation, free transport and constant encouragement, almost 80% of participants in the active group successfully completed the 8-week intervention, which is a far higher percentage than that reported in other studies (6).

Our study builds on recent literature, showing that supervised exercise improves physical performance in older volunteers (9) and prevents functional decline in persons who already have mild disability (7,8). However, because of three unique design features, FRASI has the potential to provide novel information concerning the effectiveness of the geriatric approach to care in the prevention of disability. First, in FRASI, the optimization of medical care and supervised exercise are envisioned as two inseparable, synergic elements of a successful intervention. This is consistent with the concept that impairment in the musculo-skeletal and energy production systems and increased susceptibility to disease are both involved in the causal pathway leading to disability in older persons (27). This view is also supported by the substantial morbidity that we found in FRASI participants, compared with the general population. Second, participants were non-disabled, frail, older patients, systematically screened in primary care. This type of recruitment substantially reduces the potential bias that is always implicit in studying volunteers, and greatly improves the external validity of the findings. Third, the intervention was constrained to an initial period of 2-3 months, whereas

the disability outcome was assessed for up to 12 months - an approach which makes the implementation of this intervention quite feasible and, probably, cost-effective.

Some limitations in the design of FRASI should be acknowledged. We conducted full functional assessments soon after the intervention, but no parallel interim assessment was performed in controls. Performing full assessments but not providing recommendations to participants' physicians was considered unethical, and doing so would have reduced the differences between the two study groups. While we encouraged discharged participants to keep exercising at home and provided them with a structure program, subsequent decisions concerning treatment and health behaviors were left to participants' physicians. Maintaining contact with participants would have required implementing a surveillance system, which currently does not exist in the Italian healthcare system.

We demonstrated that, through close collaboration between PCPs and geriatricians, a program of screening and intensive multifactorial intervention can be implemented without major efforts in the current healthcare system. Whether such a program prevents new disability in frail older persons remains to be confirmed. In the case of a positive result, the FRASI model may be widely implemented and become the standard approach to care and prevention in frail older persons.

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Fig. 1. Flow diagram of study participation. When this manuscript was submitted, the 12-month follow-up had not been completed.

Table 1
Examples of standard approaches to medical problems implemented in the FRASI trial

Problem	Diagnostic	Treatment
Depression	CES-D Score > 20 and psychiatric consultation	Behavioral + antidepressive medication
Anemia	WHO criteria + Ferritin, Iron, B12, Folate, CRP	Iron+B12+Folate, Erythropoietin in refractory cases
Peripheral artery disease	Ankle-arm index <0.90, vascular surgeon consultation	Medical and/or surgical treatment. Aggressive control of risk factors
Osteoporosis	pQCT	Modified guidelines of U.S. National Osteoporosis Foundation (28)
Undernutrition	Dietary interview, EPIC questionnaire	Dietary intervention
Foot problems	Self-report of foot pain + podiatric consultation	Prosthesis and/or podiatric surgery

Table 2
Characteristics of randomized FRASI participants

	Treatment group (n=126) (Mean±SD; n, %)	Control Group (n=125) (Mean±SD; n, %)	p [#]
Age (years)	76.4±3.6	76.4±3.4	0.82
Sex (% , male)	34 (27.0%)	40 (32.0%)	0.38
Marital status			
never married	10 (7.9%)	9 (7.2%)	0.86
married	72 (57.1%)	67 (53.6%)	
widowed	43 (34.1%)	47 (37.6%)	
divorced	1 (0.8%)	2 (1.6%)	
Education (years)	6.1±3.5	5.8±2.7	0.37
BMI (Kg/m ²)	27.7±3.7	28.0±4.4	0.57
Physical activity [*]			
low	33 (26.2%)	31 (24.8%)	0.80
moderate	93 (73.8%)	94 (75.8%)	
high	0 (0.0%)	0 (0.0%)	
Energy intake (Kcal)	1961±488	1896±527	0.32
Bone mineral density (mg/cm ³) ^{**}	233.5±47.3	231.4±47.7	0.72
MMSE Score	27.0±2.1	27.0±2.1	0.95
Knee extension strength (Kg)	12.1±3.4	11.9±3.3	0.62
Muscle power (W)	66.7±40.4	66.3±35.0	0.94
SPPB score	7.8±1.6	7.9±1.6	0.73
Depressive symptoms (CES-D)	17.0±10.6	18.0±9.6	0.43
History of falls in past year	43 (34%)	39 (31%)	0.78
No. of drugs taken	3.0±2.0	3.3±2.2	0.25
Diabetes	19 (15.1%)	18 (15.2%)	0.84
Hypertension	92 (73.0%)	90 (72%)	0.86
Coronary heart disease	15 (11.9%)	18 (14.4%)	0.56
Stroke	13 (10.3%)	10 (8.0%)	0.52
Congestive heart failure	7 (5.6%)	13 (10.4%)	0.16
Anemia	18 (14.3%)	19 (15.2%)	0.88
Chronic pulmonary disease	17 (13.5%)	20 (16.0%)	0.57
Cancer	7 (5.6%)	14 (11.2%)	0.11
No. of Diseases	1.4±1.0	1.5±1.0	0.40

* Physical activity defined as: Low=mostly sitting or lying down; Moderate=walking least 1-2 hours per day; High=walking more than 2 hours per day.

** Calculated by pQCT performed on distal tibia.

[#] From Chi-Square or Student's *t*-test.

Table 3
Characteristics of FRASI study population compared with all InCHIANTI study participants 70-85 years old, and a sub-group of same participants selected for FRASI inclusion criteria

	InCHIANTI (n=408) (Mean±SD; n, %)	InCHIANTI Frail (n=118) (Mean±SD; n, %)	FRASI (n=251) (Mean±SD; n, %)	p ^{&}	p [@]
Age (years)	75.0±4.0	76.9±4.1	76.4±3.5	<0.0001	0.29
Sex (%; male)	197 (48.3%)	29 (24.6%)	74 (29.5%)	<0.0001	0.33
Marital status					
never married	28 (6.7%)	7 (5.9%)	19 (7.6%)	0.11	0.10
married	264 (64.7%)	54 (45.8%)	139 (55.4%)		
widowed	113 (27.7%)	57 (48.3%)	90 (35.9%)		
divorced	3 (0.7%)		3 (1.2%)		
Education (years)	6.0±3.6	5.5±3.5	5.9±3.2	0.81	0.26
BMI (Kg/m ²)	27.4±4.0	27.9±4.3	26.8±4.1	0.21	0.85
Physical activity					
low	53 (13.0%)	30 (25.4%)	64 (25.5%)	<0.0001	0.99
moderate	331 (81.3%)	88 (74.6%)	187 (74.5%)		
high	23 (5.7%)				
Intake of energy (Kcal)	1955±512	1822±473	1928±507	0.52	0.06
BMD (mg/cm ³)	258.2±51.4	239.3±48.8	232.4±47.5	<0.0001	0.20
MMSE Score	26.8±1.7	26.4±1.7	27.0±2.1	0.08	0.004
Knee extension strength (Kg)	16.2±5.6	12.7±4.1	12.0±3.4	<0.0001	0.07
Muscle power (W)	107.7±57.9	67.4±42.0	66.5±37.7	<0.0001	0.84
SPPB score	10.7±2.0	8.2±2.1	7.8±1.6	<0.0001	0.08
CES-D Score	12.1±8.3	16.3±9.4	17.5±10.1	<0.0001	0.28
Falls in past year	83 (20.3%)	34 (28.8%)	82 (32.7%)	<0.001	0.46
No. of drugs	2.3±2.0	2.9±2.1	3.2±2.1	<0.0001	0.31
Diabetes	42 (10.3%)	14 (11.8%)	37 (14.7%)	0.09	0.46
Hypertension	268 (65.7%)	92 (78.0%)	182 (72.5%)	0.07	0.26
Coronary heart disease	52 (12.8%)	13 (11.0%)	33 (13.2%)	0.88	0.56
Stroke	21 (5.2%)	8 (10.3%)	23 (9.2%)	0.045	0.44
Congestive heart failure	15 (3.7%)	8 (6.8%)	20 (7.8%)	0.017	0.69
Anemia	34 (8.3%)	13 (11.0%)	37 (14.7%)	0.023	0.36

	InCHIANTI [*] (n=408) (Mean±SD; n, %)	InCHIANTI Frail ^{**} (n=118) (Mean±SD; n, %)	FRASI (n=251) (Mean±SD; n, %)	p ^{&}	p [@]
Chronic pulmonary disease	35 (8.6%)	13 (11.0%)	37 (14.7%)	0.014	0.21
Cancer	25 (6.1%)	12 (10.2%)	21 (8.4)	0.27	0.57
No. of diseases	1.2±0.9	1.4±1.0	1.5±1.0	0.001	0.70

^{*} InCHIANTI participants 70-85 years old, selected according to FRASI inclusion criteria;

^{**} Same as above, but with SPPB ≤9.

[&] *p* for comparison of FRASI vs all InCHIANTI participants.

[@] *p* for comparison of FRASI vs frail InCHIANTI participants.