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Highlights of the 83rd NNI Workshop on Frailty: Pathophysiology, Phenotype and Patient Care
Nutrition, frailty and prevention of disabilities with aging

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Conference calendar
Nutrition, Frailty and Prevention of Disabilities with Aging

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Summary

Older adults can be categorized into three subgroups to better develop and implement personalized interventions: the “disabled” if needing assistance in the accomplishment of basic activities of daily living (ADL), the “frail” if limitations and impairments are present in the absence of disability, and “robust” if there is no frailty or disability present. However despite evidence linking frailty to poor outcomes, frailty is not a criterion for implementation of clinical interventions in most countries. Since many elderly are not identified as frail, they frequently are treated inappropriately in healthcare settings. Assessment of frailty or pre-frailty in older adults is recommended to preventively act before the irreversible cascade of disability commences. Clinical characteristics of frailty (weakness, low energy, slow walking speed, low physical activity and weight loss) underline the links between nutrition and frailty. Physical frailty is also associated with cognitive frailty. At the Gérontopôle Frailty Clinics, France, nearly 40% of patients referred by their primary care physician to evaluate frailty have significant weight loss (more than 4.5 kg in the past 3 months), 83.9% of patients present with slow gait speed, 53.8% were sedentary, and 57.7% had poor muscle strength. Moreover, 43% had a Mini Nutritional Assessment (MNA®) score less than 23.5 and 9% less than 17, reflecting risk for and malnutrition respectively. Of those with physical frailty, more than 60% have some cognitive impairment. In this paper we review clinical evidence on undernutrition and frailty and the potential for current interventions to help prevent frailty and disability with aging.

List of abbreviations

ADL: Activities of daily living
AFAR: American Federation of Aging Research
AMDA: American Medical Directors Association
BI: Barthel Index
BMI: Body mass index
CGA: Comprehensive Geriatric Assessment
CHS-PCF: Cardiovascular Health Study Phenotypic Classification of Frailty
ELSA: English Longitudinal Study of Ageing
EU: European Union
EUGMS: European Union Geriatric Medicine Society
FFC: Fried Frailty Criteria
FFQ: Food Frequency Questionnaires
Fl: Frailty Index
GEC: Gateway Geriatric Education Center
IADL: Instrumental activities of daily living
IAGG: International Association of Geriatrics and Gerontology
IANA: International Academy of Nutrition and Aging
InCHIANTI: Invecchiare in Chianti
IOM: Institute of Medicine
RCT: Randomized controlled trial
SPPB: Short Physical Performance Battery
SSCWD: Society on Sarcopenia, Cachexia, and Wasting Disorders
WHAS: Women’s Health and Aging Studies

Introduction

Disability that occurs with aging is a clinical issue representing a priority for public health systems. Indeed, besides posing a severe burden on the patient’s quality of life, disability is associated with high healthcare costs.1 Assessment of frailty and pre-frailty in older adults is recommended to preventively act before the irreversible cascade of disability commences.2 Over the past two decades, a growing body of literature has been specifically focused on exploring the “frailty syndrome”. Frail older adults are at increased risk of negative health-related events, including hospitalization, institutionalization and disability. In particular, frailty is usually considered a pre-disability state which, in contrast to disability, is still amenable to interventions and, hence, reversible.1 On the basis of this novel concept, the heterogeneous older population was subsequently categorized into three subgroups to better develop and implement personalized interventions. Older
persons were considered “disabled” if needing assistance in the accomplishment of basic ADL; “frail” if presenting limitations and impairments are present in the absence of disability; and “robust” if no frailty or disability is present.

Frailty has been conceptualized as a geriatric syndrome resulting from decreased physiological reserve and resilience, which may lead to progressive functional decline, vulnerability to stressors, and an elevated risk of adverse outcomes, including death. It is a major cause of dependency, yet research suggests that it may be possible to prevent disability and dependency by targeting frail and pre-frail older adults with simple screening tools and effective and sustained interventions. Frailty has been recognized as an important condition by the Institute of Medicine (IOM) and the European Union (EU). While a consensus conference held in 2011 concluded that frailty has a clear conceptual framework and is useful to consider in clinical settings, its assessment is not typically implemented in clinical practice today. Another consensus conference – including delegates from the International Association of Geriatrics and Gerontology (IAGG), the American Medical Directors Association (AMDA), the American Federation of Aging Research (AFAR), European Union Geriatric Medicine Society (EUGMS), International Academy of Nutrition and Aging (IANA), Society on Sarcopenia, Cachexia, and Wasting Disorders (SSCWD), the EU, and the Gateway Geriatric Education Center (GEC) was convened in October 2012, in Orlando, Florida, USA, to develop a consensus operational approach (the Orlando Task Force). Nutritional supplementation to address weight loss and muscle dysfunction, and intervention for conditions such as sarcopenia, may also represent feasible approaches to treat the underlying conditions of frailty. Because weight loss is an important part of the frailty syndrome, it is obvious that nutritional assessment and intervention will play a major role in frailty assessment and treatment. We will review in this paper the recent data on the links between nutrition and frailty, and how easily frailty management can be incorporated into clinical practice.

The frailty syndrome: A common situation in geriatric medical care

Strong evidence supports the definition of frailty as a syndrome with a distinct etiology that consists of a constellation of signs and symptoms that increase vulnerability to stressors and that, taken together, are better at predicting an adverse outcome than any individual characteristic. Fried and colleagues proposed that the signs and symptoms of frailty result from the dysregulation of multiple molecular and physiological pathways, which lead to sarcopenia, inflammation, decreased heart rate variability, altered clotting processes and hormone levels, insulin resistance, anemia and micronutrient deficiencies. These physiological impairments result in the five clinical characteristics of physical frailty: weakness, low energy, slow walking speed, low physical activity and weight loss. These clinical characteristics are also known as the Fried Frailty Criteria (FFC). The presence of any three of these phenotypes indicates that a person is “frail”; one or two phenotypes indicate “pre-frail”; while the absence of any of these characteristics indicates the person is “robust”.

A systematic review based on 21 cohorts involving 61,500 participants found that, on average, 10.7% of community-dwelling older persons are frail and another 41.6% are pre-frail. Nevertheless, the reported prevalence differed substantially, ranging from 4.0% to 59.1%. The wide range in the results was considerably reduced by arranging the studies according to the frailty definition used. In studies that used a frailty definition according to purely physical phenotype, frailty prevalence range from 4.0% to 17.0%. In studies that used broad definitions (including social and psychological aspects), prevalence varied from 4.2% to 59.1%. While the Fried approach quantifies frailty using five measures, Rockwood and colleagues have developed a Frailty Index (FI) based on the Comprehensive Geriatric Assessment (CGA), which includes up to 70 items. In a study of community-dwelling older adults in Canada, the FI-CGA estimated the prevalence of frailty was 22.7%; higher FI-CGA scores predicted an increased risk of death at 5 years. The mortality risk increased from 22.4% for the one-third of subjects with FI-CGA values less than 0.15, to 59.9% for the one-third with FI-CGA values greater than 0.30. At the limit of the FI-CGA, 5-year mortality was 100%.

Frailty assessed using the FFC has been linked to longer hospital stays and increased mortality in hospitalized patients. Moreover, in their study of disability trajectories of community-dwelling older persons during the last year of life, Gill and colleagues found that frailty (assessed by the FFC) was the most common condition leading to death, followed by organ failure, cancer, other causes, advanced dementia and sudden death. As there is strong evidence linking frailty to poor outcomes, frailty screening and management should be implemented in clinical practice in all countries. Since many people are not identified as frail, they are frequently treated inappropriately in healthcare settings. Regardless of age, a frail person may be unable to withstand aggressive medical treatment that could benefit a non-frail person.

Observational and interventional studies link nutrition and frailty

Frailty can be influenced by a number of factors with poor nutrition identified as an influencing factor on the development of frailty. The Orlando Task Force considered that evidence supported three treatments that appeared to be effective in decreasing the incidence and/or prevalence of frailty:
- Calorie and protein supplementation
- Vitamin D supplementation
- Exercise (resistance and aerobic)

The aim of this paper is to summarize the recent literature on the relationship between nutrition and frailty demonstrated through epidemiological studies, focusing on adiposity measured by body mass index (BMI); intake of calories, macronutrients (eg, protein) and micronutrients (particularly vitamin D); and physical activity. Results from recent meta-analyses, reviews, longitudinal studies and randomized controlled trials (RCTs) are included. Because there is no consensus definition of frailty, the focus is particularly on results of studies that use the clinical definition of the frailty phenotype developed by Fried. The results are also presented of some studies that use physical frailty-related parameters (such as walking speed, handgrip strength, and disabilities in instrumental activities of daily living [IADL]). Note that the specific criteria used to define frailty in each study are described in the accompanying tables. These tables are included at the end of the article, starting on page 10.

Results of observational studies

Table 1 summarizes observational studies that examine the relationship between frailty and undernutrition. Note that these studies were conducted in community-based populations; hence, the typology of the frail older adults is probably not of the same severity as those referred to by primary care physicians as “frail”.

BMI and frailty risk

For the adult population, the BMI cut offs for “underweight”, “overweight”, and “obesity” are established to be 18.5, 25 to 29.9, and 30 kg/m², respectively. For older adults, a BMI of ≤21 kg/m² is considered to be “underweight”. The relationship between BMI and frailty data remains conflicting.

In the Women’s Health and Aging Studies (WHAS) (follow-up of 599 women, aged 70–79 years with BMI greater than 18.5 kg/m²), Blaum and colleagues showed that being overweight was significantly associated with pre-frailty, and obesity was associated with pre-frailty and frailty. In multinomial regression models, obesity was significantly associated with pre-frailty (odds ratio [OR] 2.23; 95% confidence interval [CI] 1.29–3.84) and frailty (OR 3.52; 95% CI 1.34–9.13), even when controlling for covariates.

In the WHAS II study (including 250 subjects aged 76–86 years), results showed that there is no statistically significant difference in BMI between frail, pre-frail and robust.

In the English Longitudinal Study of Ageing (ELSA) that included 3,055 subjects aged 65 years and older, Hubbard and colleagues showed that the association between BMI and frailty was U-shaped. The lowest FI scores (index of accumulated deficits included sensory and functional impairments, self-reported comorbidities, poor or fair self-rated health, low mood or depression and a score in the lowest 10% of a composite measure of global cognitive function) and lowest prevalence of Fried frailty were in those with a BMI of 25 to 29.9 kg/m². For each BMI category, and using either measure of frailty, patients with a high waist circumference were significantly more frail.

A recent paper that included 4,731 patients aged 60 years or older showed that prevalence of frailty was highest among people who were obese (20.8%), followed by overweight (18.4%), normal weight (16.1%) and, lastly, underweight (13.8%). Independent of BMI, daily energy intake was correlated to frailty risk. Daily energy intake was lowest in people who were frail (1,587 Kcal), followed by pre-frail (1,663 Kcal), and highest in people who were not frail (1,587 Kcal). Energy-adjusted macronutrient intakes (protein, carbohydrate, fat) were similar in people with and without frailty. Food insufficiency was self-reported as “sometimes” or “often” not having enough food to eat. Frail and pre-frail individuals were more likely to self-report being food insufficient than robust individuals, and serum albumin, carotenoids and selenium levels were lower in frail adults than non-frail adults.

More recently, Bowen and colleagues used functional limitations and disabilities in IADL and ADL to define frailty. In 11,491 subjects aged 50 years or older followed-up for 8 years, it was shown that the highest BMIs were protective against functional decline. Compared with the robust, normal weight older adults (BMI 18.6–24.9 kg/m²), pre-frail obese (BMI ≥30 kg/m²) have a 16% (p ≤0.001) reduction in the expected functional limitations rate; frail overweight (BMI 25–29 kg/m²) and obese have a 10% (p ≤0.01) and 36% (p ≤0.001) reduction in the expected functional limitations rate, respectively.

Specific nutrients and frailty risk

A recent study has demonstrated the close association between frailty syndrome and nutritional status in older persons. Moreover, several observational studies have shown an association between inadequate intake of specific nutrients and frailty.

Poor intakes of energy, protein, and specific nutrients elevate frailty risk

In the Invecchiare in Chianti (InCHIANTI) study, Bartali and colleagues found that low daily energy intake (≤ 21 kcal/kg) was significantly associated with frailty (OR 1.24; 95% CI 1.02–1.5). This study also analyzed the association between frailty and specific nutrients. After adjusting for energy intake, a low intake of protein, vitamin...
D, vitamin E, vitamin C, and folate, and having a low intake of more than three nutrients, were significantly and independently related to frailty.16

Three studies have shown an association between inadequate protein intake and frailty.19-21 The WHAS study involved 24,417 subjects aged 65 to 79 years who were frailty-free at baseline and followed-up for 3 years.19 Among the 24,417 eligible women, 3,298 (13.5%) developed frailty over 3 years. After adjustment for confounders, results showed that a 20% increase in uncalibrated protein intake (%kcal) was associated with a 12% (95% CI 8–16%) lower risk of frailty, and that a 20% increase in calibrated protein intake was associated with a 32% (95% CI 23–50%) lower risk of frailty. Uncalibrated protein intake values represent an estimated intake based on food frequency questionnaires (FFQ). Calibrated protein intake values represent estimates derived from linear regression equations developed on the basis of FFQ nutrient measures and participant characteristics.19 In the second study, protein intake below 0.7 g/kg/day was observed in 10% of the community-dwelling, frail elderly population, and 35% of institutionalized elderly.20 Dietary protein intake averaged 1.1 ± 0.3 g/kg/day in community-dwelling, 1.0 ± 0.3 g/kg/day in frail, and 0.8 ± 0.3 g/kg/day in institutionalized elderly men. The third study examined the association between protein and amino acid composition and frailty among elderly Japanese. A total of 2,108 subjects aged 65 years and older participated.21 The number of subjects with frailty was 481 (23%). Adjusted ORs for frailty in the first, second, third, fourth and fifth quintiles of total protein intake were 1.00 (reference), 1.02 (0.72–1.45), 0.64 (0.45–0.93), 0.62 (0.43–0.90) and 0.66 (0.46–0.96), respectively (p for trend<0.0001). Subjects categorized to the third, fourth, and fifth quintiles of total protein intake (>69.8 g/day) showed significantly lower ORs than those to the first quintile (all p<0.03). The intake of animal and plant protein and all selected amino acids (leucine, isoleucine, valine, methionine, cysteine, branched-chain amino acids, sulfur amino acids, essential amino acids) were also inversely associated with frailty (p for trend<0.04) with the multivariate adjusted OR in the highest compared to the lowest quintile of 0.73 for animal protein and 0.66 for plant protein, and 0.66–0.74 for amino acids.21

In one recent study, conducted in 194 healthy older persons, amount of protein intake was not associated with frailty but distribution of protein intake was significantly different between frail (15.4% of participants), pre-frail (40.5% of participants) and non-frail participants.22

Finally, two studies showed a preventive association between a Mediterranean-style diet (based on a Mediterranean diet score evaluated by an interview-based FFQ) and frailty.23,24 The Mediterranean-style diet is described in Table 2. In the InCHIANTI study, 690 subjects aged 65 years or older were followed-up over 6 years.23 Subjects who adhered to a Mediterranean-style diet had lower risk of becoming frail than non-adherents, and were less likely be rated as having “low physical activity” or “slow walking speed”. Parameters of “feelings of exhaustion” and “poor muscle strength” were not correlated with the diet.23

**Poor intakes of specific micronutrients elevate frailty risk**

Poor intakes of specific micronutrients, as indicated by low serum levels, are associated with elevated frailty risk. A number of studies have shown that lower serum levels of 25-hydroxyvitamin D (25[OH]D) are associated with a higher prevalence of frailty.25-28

In one report from a group of 1,600 men older than 65 years, low serum levels of 25(OH)D (<20.0 ng/mL) were associated with a higher prevalence of frailty at baseline but did not predict greater risk for developing frailty during the follow-up period of 4.6 years.28

In the InCHIANTI cohort, 1,155 subjects aged 65 and older were followed-up for 6 years. Results showed that pre-frail individuals with 25(OH)D levels <20 ng/mL were 8.9% (95% CI 2.5–15.2%) more likely to die, 3.0% (95% CI 5.6–14.6%) more likely to become frail, and 7.7% (95% CI -3.5–18.7%) less likely to become robust than pre-frail individuals with 25(OH)D levels of >20 ng/mL. Transitions to pre-frailty from robustness or frailty were not associated with 25(OH)D levels. The evidence suggested that pre-frailty is an “at-risk” state from which older adults with high 25(OH)D levels are more likely to recover than to decline, but high 25(OH)D levels were not associated with recovery from frailty.22

More recently, Wong and colleagues conducted a prospective cohort study among 4,203 older men aged 70–88 years.37 At baseline, 676 (16.1%) men were frail, as defined by having three or more deficits (Frail Scale > 3). In multivariate cross-sectional analysis, low vitamin D status, defined by the lowest quartile of 25(OH)D values (<52.9 nmol/L), was associated with increased prevalent frailty in comparison to the highest quartile of 25(OH)D values (>81.6 nmol/L). After a mean period of 5.3 years, the adjusted OR of being frail at follow-up for men with low vitamin D and having zero deficit at baseline (FRAIL scale = 0) was 1.56 (95% CI 1.07–2.27). Low vitamin D also predicted all-cause mortality over a period of up to 9.2 years, independent of baseline frailty and other covariates.

Finally, four observational studies have found an association between frailty and low serum levels of antioxidants (vitamin E, vitamin C and carotenoids),26,30,38,39 vitamin B6 and folate.29,32 In addition, significant correlations were found between high Cu/Zn ratios and deficits in femoral bone mineral density, measures of speed and strength, muscle mass and hematocrit in 144 frail elderly men suggesting that serum Cu levels and the Cu/Zn ratio may serve as useful predictive biomarkers for poor health in the elderly.40
Physical activity and frailty protection

Numerous studies have shown that physical activity and exercise are beneficial in older adults along the full spectrum of health status. The demonstrated benefits of exercise in older adults include increased mobility and strength, enhanced performance of ADL, improved aerobic capacity, function (particularly walking), gait and bone mineral density, decreased falls, and enhanced general well-being.

Decreased muscle strength occurs naturally with aging, a phenomenon known as “sarcopenia”. Sarcopenia is even more pronounced in the frail older adult, and more likely to impact adverse outcomes such as disability.

Studies suggest that even the most frail and elderly adults are likely to benefit from physical activity at almost any level that can be safely tolerated. Regular physical activity has been shown to protect against diverse components of frailty, such as sarcopenia, functional impairment and depression.

Results of interventional studies

A critical next step in decreasing adverse health outcomes of disability is the implementation of feasible interventions among frail and pre-frail older adults.

Nutrients and frailty protection

Table 3 summarizes the results of interventional studies, suggesting that supplementation with specific nutrients can modify frailty risk.

There are few RCTs that evaluate the relationship between nutrient supplementation and frailty protection as measured by improvement in physical functionality.

The effect of vitamin D supplementation (a single dose of calciferol, 300,000 IU) versus placebo on physical performance was studied in 243 frail adults aged 65 years and older. The results did not show a difference between treatment groups, even in those who were vitamin D deficient (< 12 ng/mL) at baseline.

In an RCT on the effect of protein supplementation, Tieland and colleagues showed an improvement of Short Physical Performance Battery (SPPB) in frail older adults randomized to receive 15 g of supplemental protein daily for 24 weeks compared with the placebo group (p=0.02). Another RCT on the effect of a daily supplementation with protein and micronutrients for 12 weeks in 87 frail older adults (usual gait speed <0.6 m/s; MNA® < 24) has been published recently. Results showed that physical functioning increased by 5.9% (1 point) in the intervention group, although no change was observed in the control group. SPPB remained stable in the intervention group, although it decreased by 12.5% (1 point) in controls.

While a few RCTs show promising effects of nutritional supplementation on physical functionality, further long-term studies are needed, with multi-domain intervention in large populations of older adults.

Physical activity and frailty protection

Table 4 summarizes the results of interventional studies suggesting that physical activity can modify frailty risk. Exercise is believed to be the most effective of all interventions proposed to improve functionality in older adults. A systematic review by Theou et al found that exercise has a positive impact on physical determinants (cardiorespiratory function, muscle function, flexibility) and functional ability (including mobility, balance and functional performance) in frail older adults. Multicomponent training interventions, of long duration (≥ 5 months), performed three times per week, for 30–45 minutes per session, generally had superior outcomes than other exercise programs.

More recently, another systematic review has been published on the effect of exercise in frail older adults. The authors concluded that the exercise intervention only slightly affected physical function, mainly by increasing gait speed and Berg Balance Scale score and improving performance in ADL. Nevertheless, they emphasized that participants included in these trials may not represent the average frail, elderly population. It is likely that those who would have benefited from exercise were excluded from the trial due to age or other comorbidities that prevented them from exercising. Furthermore, this review does not clarify what type of exercise is likely to be most beneficial. Similar conclusions were proposed in the systematic review and meta-analyses published by Giné-Garriga. When compared with control interventions, exercise was shown to improve normal gait speed, fast gait speed, and the SPPB. Results are inconclusive for endurance outcomes, and no consistent effect was observed on balance and the ADL functional mobility. The evidence comparing different modalities of exercise remains scarce and heterogeneous.

Langlois and colleagues have recently published the results of an RCT on exercise-training intervention over 12 weeks in 83 frail older adults aged 61–89 years. Compared with the control groups, the intervention group showed significant improvement in physical capacity (using the modified Physical Performance Test [PPT] and 6-minute walk test), cognitive performance and quality of life. Overall benefits were equivalent between frail and robust individuals.

A study is underway to evaluate the impact of the Nintendo Wii Active program against standard gym-based rehabilitation on reducing falls and fear of falling in moderately frail older adults.

A recent paper reviewed the literature on the utility of exercise training as an intervention for frailty. While further long-term RCTs are still needed, the majority of studies suggest that clinicians should recommend regular physical activity.
activity or exercise training to frail older adults as a means to modify frailty risk and its adverse outcomes. Most trials found benefits associated with resistance exercise training, while an aerobic activity such as walking offers distinct advantages and should also be practiced.

**Efficacy of a multi-domain approach in the management of frailty**

Multi-domain interventions are currently being tested in large programs. This multi-domain approach will aim to treat physical and cognitive frailty using nutrition supplementation in combination with physical and cognitive exercise.

Table 5 summarizes the results of interventional studies suggesting that a multi-domain approach can modify frailty risk.

The combination of exercise and a weight loss diet (a balanced diet providing an energy deficit of 500–750 kcal/d from daily energy requirement) as one arm of an RCT for obese adults aged 65 years or older had greater impact on measures of frailty (strength, balance, gait, scores on the PPT, peak oxygen consumption) than either intervention alone. Feasibility and benefits of interventions combining nutritional supplements and exercise were also previously demonstrated in very frail elderly nursing home residents.

Most studies of multi-domain interventions in frail older adults have evaluated the effect of a combination of nutritional supplementation and physical activity. In one study, 96 frail adults older than 75 years were randomized into one of four groups: physical training program (aerobic, muscle strength, balance), nutritional intervention program (individually targeted advice and group sessions), a combination of these interventions, and a control group. Subjects were evaluated at baseline, immediately after the intervention (which lasted for 12 weeks), and after another 6 months. Significant improvements in lower-extremity muscle strength were observed in both training groups compared with the nutrition group at 12 weeks. There were small significant changes for some of the balance measurements in the training group without nutrition treatment. The nutrition intervention alone did not show any significant improvement in outcomes. In addition, both interventions were not associated with a positive effect on energy intake, resting metabolic rate or fat-free mass. The participants with a low energy intake who managed to increase their energy intake during the study (‘responders’) had a statistically significantly lower BMI (21 vs 24 kg/m²) and a lower fat percentage (23 vs 30%) at baseline than the ‘non-responders’.

Similarly, in another randomized clinical trial of 7 weeks’ duration, it was shown that comprehensively structured, high-intensity regimen comprised of diverse exercise types (ie, functionally-oriented, progressive resistance and standard exercises), preferably combined with nutritional supplementation (200 mL liquid supplying 300 kcal in the form of carbohydrate [49%], lipids [35%] and protein [16%]), demonstrates clear potential for appreciably improving overall status in the frail elderly in terms of individual walking capacity and muscle strength.

Finally, Tieland and colleagues conducted an RCT in 62 frail older adults (mean age of 78 years) randomized into two groups: progressive resistance-type exercise training program (two sessions per week for 24 weeks) and supplemented twice a day with either 15 g protein (total 30 g/day) or protein-free placebo. Results showed that lean body mass (measured by DEXA) increased significantly from baseline (47.2 kg to 48.5 kg) in the protein-supplemented group but did not change in the placebo group (45.7 kg to 45.4 kg). Strength and physical performance (SPPB) improved significantly in both groups (p=0.000) with no interaction of dietary protein supplementation. Dietary protein supplementation offered no functional benefit in this small-scale study that was unlikely powered sufficiently to detect effects of strength and physical performance.

An RCT testing nutritional and physical activity interventions in malnourished frail community-dwelling persons by trained lay buddies is currently in progress. In this study, malnourished frail persons are visited by buddies at home twice a week for about 1 hour during an initial period of 10–12 weeks. Participants allocated to the intervention group (n=40) receive intervention to improve their fluid intake, protein and energy intake, perform strength training and try to increase their baseline activities; the control group (n=40) receive only home visits without any intervention.

Since many factors other than exercise influence the occurrence of frailty, three recent RCTs have explored other components of this clinical syndrome.

Li and colleagues studied the effect of an intervention including both CGA and appropriate intervention by medication adjustment, exercise instruction, nutrition support, physical rehabilitation, social worker consultation, and specialty referral versus a control group in 310 frail older adults (mean age of 79 years) on the FFC and the Barthel Index (BI) of activities of daily living after 6 months of follow-up. Results showed that compared to the control group, the FFC and BI of the intervention group were more likely to improve and less likely to deteriorate but without a significant difference between the mean values for the two groups.

More recently, Fairhall and colleagues implemented a multifactorial, interdisciplinary intervention that targets defined frailty components (home exercise program targeting mobility, and coordinated management of psychological and medical conditions) in 216 frail older adults (mean age of 83 years). At 12 months, 4 m gait speed in the intervention group was faster (by 0.05 m/s) than the control.
Incorporating assessment and management of frailty into clinical practice

Primary care physicians and other healthcare professionals are essential for assessing frailty risk in older adults incorporating frailty management in routine patient care. The first step in the management of frailty is the use of a simple screening test to identify vulnerable individuals. Several different methods of screening for frailty have been developed and validated. The FFC was operationalized into a screening algorithm for use in the Cardiovascular Healthy Study (CHS). Other frailty measures have also been proposed, including the Study of Osteoporotic Fractures (SOF) Index. All of these measures count deficits and quantify the degree of frailty and, thus, the degree of vulnerability to adverse outcomes. Moreover, all of them reflect an aging-associated failure of physiological systems.

Another frailty screening tool that relies on the clinical opinion of the general practitioner was developed in France. In response to the French government’s policy on preventing disability in older persons, a day hospital was established in 2011 at the Gérontopôle of Toulouse (ie, the geriatric center of disability). Geriatric patients are referred to the center of Toulouse for the evaluation of frailty and prevention of disability. Geriatric patients are referred to the center by general practitioners who detect signs and symptoms of frailty and are screened using a simple, quick frailty questionnaire, and undergo an assessment of gait speed. The Frailty Screening Tool asks six questions regarding living alone, weight loss, fatigue, mobility, memory, and slow gait speed. If the physician identifies one of these areas as an area of concern, he/she is asked, “In your own clinical opinion, do you feel that your patient is frail and at an increased risk for further disabilities?” It is this last question that is used to distinguish patients who are frail.

The goal of the Gérontopôle frailty clinics is to identify frailty in the early stages through a multidisciplinary evaluation, attempt to identify the cause or causes (ie, underlying comorbidities or other risk factors), and implement multidisciplinary interventions adapted to each patient’s individual needs. These interventions may include nutrition, physical exercise and/or physical therapy, social support, and education. Patients are followed-up principally by their general practitioner, with additional follow-up through telephone contact and a structured interview with a nurse from the center to assess the efficacy of the interventional plan.

We recently published a description of the first 160 patients referred for frailty by general practitioners to the Gérontopôle Frailty Clinic (Table 6). The mean age of this population is 82.7 years, with the majority aged 75 years and older. Most patients are women (61.9%). Approximately two thirds of patients received some kind of regular help at home. Regarding level of frailty, 65 patients (41.4%) were pre-frail, and 83 (52.9%) were frail.

Nearly 40% had significant weight loss of more than 4.5 kg in the past 3 months. In terms of functional status, 83.9% of patients presented with slow gait speed, 53.8% were sedentary, and 57.7% had poor muscle strength. Only 27.2% of patients had a SPPB score assessing physical performance of 10 or higher. Autonomy in ADL was quite well preserved (mean ADL score 5.6 ± 0.8), as expected. Collectively, these data suggest that the Frailty Clinic patients have not yet developed disability and, thus, stand to benefit from intervention. A marginal loss of autonomy was observed with a mean score IADL sore of 6.0 ± 2.3. Numerous patients presented with vision problems. Finally, it is noteworthy that 9% of the Frailty Clinic population presented in an objective state of protein-energy malnutrition (MNA® ≤ 17), and 34% an early alteration of nutritional status (MNA® 17–23.5); almost all (94.9%) had vitamin D deficiency as measured by low serum levels.

It is important to underline that in frail older adults it is easier to successfully intervene on nutrition than in individuals with an acute or more severe condition who usually have severe anorexia. We have found that risks for undernutrition are also present in pre-frail subjects (Table 7). About one third of patients (33.1%) presented with a Mini Mental State Examination (MMSE) score lower than 25. Dementia (measured by the Clinical Dementia Rating [CDR] scale) was observed in 11.6% of the Frailty Clinic
population, whereas 65.8% of subjects had mild cognitive impairment (CDR equal to 0.5). These data underscore the link between physical and cognitive frailty. Mild cognitive impairment is prevalent in frail older adults and is in some part probably related to poor nutritional status. More data should be collected in terms of the link between risk of cognitive frailty and low nutrient levels (eg, folate, vitamin B12, vitamin D, omega-3 fatty acids) in this population. The Multidomain Alzheimer’s Preventive Trial (MAPT) study is currently underway and may provide additional data in the near future.

In a study of 754 community-dwelling, non-disabled older adults, Gill and colleagues showed that frailty is a dynamic process with frequent transitions. While the overall trend was towards worsening of frailty status, and the likelihood of transitioning from being frail to non-frail was very low, about 10% of pre-frail subjects transitioned to non-frail during each 18-month follow-up period. Early screening to identify pre-frail and frail older adults and an early multi-domain intervention is likely to largely increase this proportion.

Today in most geriatric centers, physicians deal with patients who already have severe disability that is often not reversible. Almost 95% of geriatric care providers are involved in treating already dependent older adults. Continuing to take care of these individuals with severe disabilities is essential. Moreover, proactive care of pre-frail and frail older adults to prevent a rapid rise of disability in our aging population is also important. Frail older adults are more likely to become dependent, but today they are not being readily identified and managed by healthcare systems. To meet this challenge, collaboration between geriatric care providers and general practitioners to provide targeted, strong and sustained intervention is required.

- **Targeted intervention** (specifically pre-frail and frail older adults)

  Simple screening tools are readily available to be used by general practitioners and other front-line healthcare professionals to identify vulnerable individuals. For example, many studies have found that individuals with an MNA® score between 17 and 23.5 are more likely to be frail. In settings where nutritional screening with the MNA® is routine at admission (eg, acute care, long-term care, and home care), a poor MNA® score can be considered as an alert to an individual’s vulnerability, and a prompt for further, more-comprehensive assessment.

- **Strong intervention**

  To have a real impact, the intervention must be strong and tailored to the results of a CGA in pre-frail and frail patients. Specific tools can be used to diagnose potential age-related disease at the first onset of symptoms, where it is still possible to cure the patient. The CGA must also include social, health, economic and psychosocial assessment, as well as the evaluation of the deficit accumulation.

- **Sustained intervention**

  The growing aging population necessitates having long-term and sustained intervention. A combination of physical exercise, cognitive exercise, nutrition intervention, and social services will be needed for the management of age-related diseases. The potential to develop more standardized multi-domain interventions is an important topic for further research. It is necessary to find a balance between very strong interventions that will be appropriate for a select few frail older adults, and interventions that are too mild to have a real impact on the broad population.

**Key points for application to clinical practice**

- Poor nutrition has been identified as factor influencing the development of frailty.
- Consideration of BMI alone is not an appropriate nutrition screening method in older adults
- Poor MNA® score is an alert to an individual’s vulnerability, and a prompt for further, more-comprehensive assessment
- Frail older adults are a good target for nutritional assessment and intervention
- Multi-domain intervention (combining physical exercise, nutrition intervention, cognitive exercise, and social services) is an important topic for future research on frailty
Table 1. Results of observational studies on the relationship between poor nutrition and frailty risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Nutritional assessment</th>
<th>Frailty criteria</th>
<th>Participants:</th>
<th>Results</th>
</tr>
</thead>
</table>
| Blaum<sup>12</sup> | cross-sectional analysis | BMI                     | FFC              | n=599 women, aged 70–79 with BMI ≥ 18.5 kg/m² | - Being overweight was significantly associated with prefrailty, and obesity was associated with prefrailty and frailty
- In multinomial regression models, obesity was significantly associated with prefrailty (OR 2.23, 95%CI 1.29–3.84) and frailty (OR 3.52, 95% CI 1.34–9.13), even when controlling for covariates |
| Hubbard<sup>14</sup> | cross-sectional analysis | BMI                     | FFC, Index of accumulated deficits (FI) and Sensory impairments | n=3,055, aged ≥ 65 years | - The association between BMI and frailty showed a U-shaped curve. This relationship was consistent across different frailty measures. The lowest FI scores and lowest prevalence of Fried frailty were in those with BMI 25–29.9 kg/m²
- At each BMI category, and using either measure of frailty, those with a high waist circumference were significantly more frail |
| Frisoli<sup>13</sup> | cross-sectional analysis | BMI and body composition (DEXA) | FFC              | n=250, aged 76–86 years | - There is no statistically significant difference between frail prefrail and robust in BMI
- In an adjusted logistic regression model, severe osteopenia/osteoporosis (OR 2.1; 95% CI 0.68–6.6; p=0.196) and sarcopenia (OR 3.1; 95% CI 0.88–11.1; p=0.077) were individually associated with frailty, though not statistically significant
- The likelihood of being frail was substantially higher in the presence of these two syndromes (OR 6.4; 95% CI 1.1–36.8, p=0.037) |
| Bowen<sup>16</sup> | longitudinal study Follow-up: 8 years | BMI                     | Functional limitations and disabilities in IADL and ADL | n=11,491, aged ≥ 50 years | - Compared with the nonfrail normal weight, prefrail obese have a 16% (p<0.001) reduction in the expected functional limitations rate and frail overweight and obese have a 10% (p<0.01) and 36% (p<0.001) reduction in the expected functional limitations rate, respectively
- In addition, frail obese have a 27% (p<0.05) reduction in the expected ADL disability rate |
### Smit

**Study:** Third National Health and Nutrition Examination Survey  
**Nutritional assessment:** intake assessed by 24 h dietary recall. Food insufficiency was self-reported as ‘sometimes’ or ‘often’ not having enough food to eat.  
**Frailty status:** meeting ≥ two (frail) or meeting one (pre-frail) of the following four-item criteria: slow walking; muscular weakness; exhaustion; and low physical activity  
**Participants:** 4,731 older adults, aged ≥ 60 years  
- Prevalence of frailty was highest among people who were obese (20.8%), followed by overweight (18.4%), normal weight (16.1%) and lowest among people who were underweight (13.8%)  
- Independent of BMI, daily energy intake was lowest in people who were frail, followed by pre-frail and highest in people who were not frail (1,587 [se 31], 1,663 [se 19] and 1,738 [se 20] kcal, respectively, p<0.01)  
- Energy-adjusted macronutrient intakes were similar in people with and without frailty. Frail (adjusted OR [AOR] 4.7; 95% CI 1.7–12.7) and pre-frail (AOR 2.1; 95% CI 0.8–5.8) people were more likely to report being food insufficient than non-frail people  
- Serum albumin, carotenoids and selenium levels were lower in frail adults than nonfrail adults

### Beasley

**Study:** WHAS  
**Method:** longitudinal study  
**Follow-up:** 3 years  
**Nutritional assessment:** baseline protein intake by FFQ. Calibrated estimates of energy and protein intake were corrected for measurement error using regression calibration equations estimated from objective measures of total energy expenditure (doubly labeled water) and dietary protein (24-hour urinary nitrogen)  
**Frailty status:** at least three of the following components: low physical function (measured using the Rand-36 questionnaire); exhaustion; low physical activity; and unintentioned weight loss  
**Participants:** n=24,417 free of frailty, aged 65–79 years  
- 3,298 women (13.5%) developed frailty over 3 years  
- After adjustment for confounders, a 20% increase in uncalibrated protein intake (%kcal) was associated with a 12% (95% CI 8–16%) lower risk of frailty, and a 20% increase in calibrated protein intake was associated with a 32% (95% CI 23–50%) lower risk of frailty

### Bollwein

**Study:** InCHIANTI  
**Method:** longitudinal study  
**Follow-up:** 6 years  
**Nutritional assessment:** interview-based FFQ. A MED score (maximum 9 points) was used to evaluate dietary quality  
**Frailty criteria:** FFC  
**Participants:** n=690, aged ≥ 65 years  
- Higher adherence (score ≥6) to a MED was associated with lower odds of developing frailty (OR 0.30 [95% CI 0.14–0.66]) compared with those with lower adherence (score <3)  
- A higher adherence to a MED at baseline was also associated with a lower risk of low physical activity (OR 0.62; 95% CI 0.40–0.96) and low walking speed (OR 0.48; 95% CI 0.27–0.86) but not with feelings of exhaustion and poor muscle strength

### Talegawkar

**Study:** InCHIANTI  
**Method:** longitudinal study  
**Follow-up:** 6 years  
**Nutritional assessment:** interview-based FFQ. A MED score (maximum 9 points) was used to evaluate dietary quality  
**Frailty criteria:** FFC  
**Participants:** n=690, aged ≥ 65 years  
- Dietary protein intake averaged 1.1 ± 0.3 g/kg/day in community-dwelling, 1.0 ± 0.3 g/kg/day in the frail, and 0.8 ± 0.3 g/kg/day in institutionalized elderly men. Similar protein intakes were found in women  
- 10% of the community-dwelling and frail elderly and 35% of the institutionalized elderly people showed a protein intake below the estimated average requirement (0.7 g/kg/day)

### tiel and

**Study:** InCHIANTI  
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- 10% of the community-dwelling and frail elderly and 35% of the institutionalized elderly people showed a protein intake below the estimated average requirement (0.7 g/kg/day)
**Kobayashi21**

**Method:** cross-sectional analyses

**Nutritional assessment:** intakes of total, animal and plant protein, and eight selected amino acids (leucine, isoleucine, valine, methionine, cysteine, branched chain amino acids, sulfur amino acids, essential amino acids) estimated from a validated brief type self-administered diet history questionnaire

**Frailty status:** presence of three or more of the following four components: slowness and weakness (two points); exhaustion; low physical activity; and unintentional weight loss

**Participants:** 2,108, aged ≥ 65 years

- The number of subjects with frailty was 481 (23%).
- Adjusted ORs for frailty in the first, second, third, fourth and fifth quintiles of total protein intake were 1.00 (reference), 1.02 (0.72–1.45), 0.64 (0.45–0.93), 0.62 (0.43–0.90) and 0.66 (0.46–0.96), respectively (p for trend=0.0001).
- Subjects categorized to the third, fourth, and fifth quintiles of total protein intake (>69.8 g/day) showed significantly lower ORs than those to the first quintile (all p<0.03).
- The intake of animal and plant protein and all selected amino acids were also inversely associated with frailty (p for trend <0.04) with the multivariate adjusted OR in the highest compared to the lowest quintile of 0.73 for animal protein and 0.66 for plant protein, and 0.66–0.74 for amino acids

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**Bollwein17**

**Method:** cross-sectional analyses

**Nutritional assessment:** amount of protein intake and its distribution over the day assessed using FFQ. Unevenness of protein distribution was calculated as coefficient of variation (CV)

**Frailty status:** Fried criteria

**Participants:** 194 community-dwelling seniors (≥ 75 years)

- 15.4% of the participants were frail, 40.5% pre-frail
- Median daily protein intake was 77.5 (38.5–131.5) g, 1.07 (0.58–2.27) g/kg body weight and 15.9 (11.2–21.8) % of energy intake without significant differences between the frailty groups
- The risk of frailty did not differ significantly between participants in the higher compared to the lowest quartile of protein intake
- Frail participants consumed significantly less protein in the morning (11.9 vs 14.9 vs 17.4%, p=0.007), but more at noon (61.4% vs 60.8% vs 55.3%, p=0.0024) than pre-frail and non-frail
- The median (min-max) CV of protein distribution was highest in frail (0.76 (0.18–1.33) compared to pre-frail (0.007–1.29) and non-frail (0.68 (0.15–1.24) subjects (p=0.024)

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**Macro- and micronutrients**

**Bartali18**

**Study:** InCHIANTI

**Nutritional assessment:** daily intake of energy and nutrients assessed by the EPIC questionnaire. Low intake was defined using the value corresponding to the lowest sex-specific intake quintile of energy and specific nutrients

**Frailty status:** having at least two of the following criteria: low muscle strength; feeling of exhaustion; low walking speed; and reduced physical activity

**Participants:** n=802, aged ≥ 65 years

- Daily energy intake ≤ 21 kcal/kg was significantly associated with frailty (OR 1.24; 95% CI 1.02–1.5)
- After adjusting for energy intake, a low intake of protein (OR 1.98; 95% CI 1.38–3.31); vitamins D (OR 2.35; 95% CI 1.48–3.73), E (OR 2.06; 95% CI 1.28–3.33), C (OR 2.15; 95% CI 1.34–3.45), and folate (OR 1.84; 95% CI 1.14–2.98); and having a low intake of more than three nutrients (OR 2.12; 95% CI 1.29–3.50) were significantly and independently related to frailty
<table>
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<th>Micronutrients</th>
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| **Cesari**<sup>33</sup> | **Study**: InCHIANTI  
**Method**: cross-sectional analyses  
**Nutritional assessment**: plasma vitamin E levels  
**Frailty status**: physical performance tests (knee extension strength; performance of the lower extremities assessed with the use of 3 tests: walking speed, ability to stand from a chair, and ability to maintain balance)  
**Participants**: n= 827, aged ≥ 65 years  
- In adjusted analyses, plasma alpha-tocopherol was significantly correlated with knee extension (beta = 0.566, p=0.003) and the summary physical performance score (beta = 0.044, p=0.008). Plasma gamma-tocopherol was associated only with knee extension strength (beta = 0.327, p=0.04).  
- Of the daily dietary intake measures, vitamin C and beta-carotene were significantly correlated with knee extension strength, and vitamin C was significantly associated with physical performance (beta = 0.029, p=0.04) |
| **Ble**<sup>34</sup> | **Study**: InCHIANTI  
**Method**: cross-sectional analyses  
**Nutritional assessment**: daily dietary intakes of vitamin C, vitamin E, beta-carotene, and retinol assessed by The EPIC questionnaire; Plasma alpha- and gamma-tocopherol concentrations  
**Physical functions**: physical performance tests (knee extension strength; performance of the lower extremities assessed with the use of thee tests: walking speed, ability to stand from a chair, and ability to maintain balance)  
**Participants**: n=986, aged ≥ 65 years  
- Age and gender adjusted levels of vitamin E decreased gradually from the nonfrail to the frail group (p for trend=0.015)  
- In the logistic model adjusted for multiple potential confounders, participants in the highest vitamin E tertile were less likely to be frail than were participants in the lowest vitamin E tertile (OR 0.30; 95% CI 0.10–0.91) |
| **Michelon**<sup>29</sup> | **Study**: WHAS  
**Method**: cross-sectional study  
**Nutritional assessment**: micronutrient serum concentrations  
**Frailty criteria**: FFC  
**Participants**: n=754, aged 70–80 years  
- Among nonfrail, prefrail, and frail women, respectively, geometric mean serum concentrations were 1.842, 1.593, and 1.376 µmol/L for total carotenoids (p<0.001); 2.66, 2.51, and 2.43 µmol/L for retinol (p=0.04); 50.9, 47.4, and 43.8 nmol/L for 25(OH)D (p=0.019); 43.0, 35.8, and 30.9 nmol/L for vitamin B6 (p=0.0002); and 10.2, 9.3, and 8.7 ng/mL for folate (p=0.03)  
- Frail women were more likely to have at least two or more micronutrient deficiencies (p=0.05)  
- The age-adjusted OR for being frail were significantly higher for those participants whose micronutrient concentrations were in the lowest quartile compared to the top three quartiles for total carotenoids, alpha-tocopherol, 25(OH)D and vitamin B6  
- The association between nutrients and frailty was strongest for beta-carotene, lutein/zeaxanthin, and total carotenoids (ORs 1.82–2.45, p=0.05), after adjusting for age, sociodemographic status, smoking status, and BMI |
<table>
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<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Nutritional assessment</th>
<th>Frailty assessment</th>
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<tr>
<td>Semba30</td>
<td>WHAS prospective study</td>
<td>n=766, aged ≥ 65 years</td>
<td>Micronutrient serum concentrations</td>
<td>FFC</td>
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<tr>
<td>Boxer25</td>
<td>Cross-sectional study</td>
<td>n=60 patients with a left ventricular ejection fraction of ≤ 40%</td>
<td>Serum 25(OH)D</td>
<td>The 6-minute walk distance and FFC</td>
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<tr>
<td>Shardell32</td>
<td>InCHIANTI study</td>
<td>n=1,005, aged ≥ 65 years</td>
<td>Serum 25(OH)D</td>
<td>FFC</td>
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<tr>
<td>Wilhelm35</td>
<td>NHANES III</td>
<td>n=5,048, aged ≥ 60 years</td>
<td>Serum 25(OH)D</td>
<td>FFC</td>
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- Of 463 nonfrail women at baseline who had at least one follow-up visit, 205 (31.9%) became frail, with an overall incidence rate of 19.1 per 100 person-years
- Compared with women in the upper three quartiles, women in the lowest quartile of serum carotenoids (hazard ratio [HR] 1.39; 95% CI 1.01–1.92), alpha-tocopherol (HR 1.39; 95% CI 1.02–1.92), and 25(OH)D (HR 1.34; 95% CI 0.94–1.90) had an increased risk of becoming frail
- The number of nutritional deficiencies (HR 1.10; 95% CI 1.01–1.20) was associated with an increased risk of becoming frail, after adjusting for age, smoking status, and chronic pulmonary disease
- Adjusting for potential confounders, we found that women in the lowest quartile of serum carotenoids had a higher risk of becoming frail (HR 1.54; 95% CI 1.11–2.13)

- Longer 6-minute walk distance was correlated with higher 25(OH)D level
- Higher frailty phenotype score (more frail) was correlated with lower 25(OH)D levels (p<0.05)
- Linear regression with the 6-minute walk distance as the dependent variable and independent variables of age, sex, percentage of free testosterone, DHEAS, 25(OH)D, intact PTH, hsCRP, IL6, cortisol/DHEAS ratio, and NTpro-BNP, revealed 25(OH)D to be significant (coefficient of determination=53.5%)
- Ordinal logistic regression with the frailty phenotype and hormonal levels revealed that 25(OH)D also predicted frailty status.

- Independent of covariates, men with 25(OH)D <50 nmol/L had greater odds of frailty than those with 25(OH)D ≥50 nmol/L (OR 4.94; 95% CI 1.80–13.61). In women, the adjusted OR for frailty was 1.43 (95% CI 0.58–3.56). The 25(OH)D ORs differed between men and women (p=0.041)

- 25(OH) D deficiency (defined as a serum concentration <15 ng/mL), was associated with a 3.7-fold increase in the odds of frailty amongst white subjects and a 4-fold increase in the odds of frailty amongst non-white subjects
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<tr>
<th>Study</th>
<th>Method</th>
<th>Nutritional assessment</th>
<th>Frailty assessment</th>
<th>Participants</th>
<th>Findings</th>
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<tr>
<td>Chang26</td>
<td>Observational study</td>
<td>serum 25(OH)D</td>
<td>FFC and Edmonton Frail Scale</td>
<td>n=215, aged 65–79 years</td>
<td>- Frail subjects had lower 25(OH)D levels based on the FFI (p&lt;0.009) and the EFS (p&lt;0.004) &lt;br&gt; - The associations between insufficient 25(OH)D status and both frailty scales were significant &lt;br&gt; - After adjustment, the OR of 25(OH)D insufficiency comparing subjects with pre-frailty and frailty to those with robust was 3.14 (95% CI 1.43–6.91) and 10.74 (95% CI 2.60–44.31), respectively, using the FFI</td>
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<tr>
<td>Ensrud28</td>
<td>Cross-sectional and longitudinal analyses of a prospective cohort study</td>
<td>serum 25(OH)D</td>
<td>FFC and Edmonton Frail Scale</td>
<td>n=6,307, aged ≥ 69 years</td>
<td>- At baseline, there was a U-shaped association between 25(OH)D level and odds of frailty with the lowest risk among women with levels 20.0–29.9 ng/mL (reference group). Compared with this group, the odds of frailty were higher among those with levels &lt; 15.0 ng/mL (multivariable odds ratio [MOR] 1.47, 95% CI 1.19–1.82), those with levels 15.0–19.9 ng/mL (MOR 1.24, 95% CI 0.99–1.54), and those with levels ≥ 30 ng/mL (MOR 1.32, 95% CI 1.06–1.63) &lt;br&gt; - Among 4,551 nonfrail women at baseline, the odds of frailty (vs robust/intermediate) at follow-up appeared higher among those with levels 15.0–19.9 ng/mL (MOR 1.21, 95% CI 0.99–1.49), but the CI overlapped 1.0</td>
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<tr>
<td>Ensrud29</td>
<td>Prospective cohort study</td>
<td>serum 25(OH)D</td>
<td>FFC</td>
<td>n=1,600, aged ≥ 65 years</td>
<td>- After adjusting for multiple potential confounders, men with 25(OH)D levels ≤ 20.0 ng/mL had 1.5 times higher odds (MOR 1.47; 95% CI 1.07–2.02) of greater frailty status at baseline than men with 25(OH)D levels of 30.0 ng/mL or greater (reference group), whereas frailty status was similar in men with 25(OH)D levels from 20.0 to 29.9 ng/mL and those with levels of 30.0 ng/mL or greater (MOR 1.02; 95% CI 0.78–1.32) &lt;br&gt; - However, in 1,267 men not classified as frail at baseline, there was no association between lower baseline 25(OH)D level and odds of greater frailty status at the 4.6-year follow-up</td>
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<tr>
<td>Shardell33</td>
<td>InCHIANTI cohort study</td>
<td>serum 25(OH)D</td>
<td>FFC</td>
<td>n=1,155, aged ≥ 65 years</td>
<td>- The median (interquartile range) 25(OH)D concentration was 16.0 ng/mL (10.4–25.6 ng/mL; multiply by 2.496 to convert to nmol/L) &lt;br&gt; - Prefrail participants with 25(OH)D levels ≤ 20 ng/mL were 3.0% (95% CI -5.6–14.8%) more likely to become frail, and 7.7% (95% CI -3.5–18.7%) less likely to become robust than prefrail participants with 25(OH)D levels of &gt; 20 ng/mL &lt;br&gt; - In prefrail participants, each 5-ng/mL decrement of continuous 25(OH)D was associated with a 1.13 higher odds of incident frailty (95% CI 0.90–1.39) than with recovery of robustness &lt;br&gt; - Transitions from robustness or frailty were not associated with 25(OH)D levels</td>
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<tr>
<td>Study</td>
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<td>Nutritional assessment:</td>
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</table>
| Smit34                 | Study: NHANES III             | serum 25(OH)D                                           | n=4,731, aged ≥ 60 years                         | - Serum 25(OH)D concentrations were lowest in participants with frailty, intermediate in participants with pre-frailty and highest in participants without frailty.  
- The odds of frailty in the lowest quartile of serum 25(OH)D was 1.94 times the odds in the highest quartile (95% CI 1.09–3.44) |
| Tajar35                | Study: European Male Ageing Study (EMAS) | serum 25(OH)D                                           | n=1,504, aged 60–79 years                        | - 5.0% of subjects were classified as frail and 36.6% as prefrail. Lower levels of 25(OH)D were associated with being prefrail (per 1 SD decrease: reporting odds ratio [ROR] 1.45; 95% CI 1.26–1.67) and frail (ROR 1.89; 95% CI 1.30–2.76), after adjusting for age, center and health and lifestyle confounders (robust group = base category).  
- FI and FFC found similar results |
| Hirani36               | Study: Concord Health and Ageing in Men Project | serum 25(OH)D and 1,25(OH)D                              | 1,659 community-dwellers                         | - Frailty was present in 9.2% of the sample.  
- Low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were independently associated with frailty and with four of the five components of frailty (except weight loss). |
| Wong37                 | Method: prospective cohort study | 25(OH)D                                                 | n=4,203 older men, aged 70–88 years             | - At baseline, 676 (16.1%) men were frail, as defined by having ≥3 deficits (FRAIL scale ≥ 3).  
- In multivariate cross-sectional analysis, low vitamin D status, defined by the lowest quartile of 25(OH)D values (<52.9 nmol/L), was associated with increased prevalent frailty (OR 1.96; 95% CI 1.52–2.52) in comparison to the highest quartile of 25(OH)D values (>81.6 nmol/L).  
- After a mean period of 5.3 years, the adjusted OR of being frail at follow-up for men with low vitamin D and having zero deficit at baseline (FRAIL scale = 0) was 1.56 (95% CI 1.07–2.27).  
- Low vitamin D also predicted all-cause mortality over a period of up to 9.2 years (HR 1.20; 95% CI 1.02–1.42), independent of baseline frailty and other covariates |

ADL: Activities of Daily Living; BMI: Body mass index; CI: confidence interval; DEXA: Dual-energy X-ray absorptiometry; DHEAS: Dehydroepiandrosterone sulfate; EPIC: European Prospective Investigation into Cancer and Nutrition; FFC: Fried Frailty Criteria; FFQ: Food Frequency Questionnaire; FI: Frailty Index; hsCRP: high-sensitivity C-reactive protein; HR: hazard ratio; IADL: Instrumental Activities of Daily Living; InCHIANTI: Invecchiare in Chianti (aging in the Chianti area); MED: Mediterranean diet; NHANES III: Third National Health and Nutrition Survey; NTproBNP: N-terminal pro b-type natriuretic peptide; 25(OH)D: 25-hydroxyvitamin D; OR: odds ratio; PTH: parathyroid hormone; WHAS: Women’s Health and Aging Studies
Table 2. The Mediterranean-style diet

<table>
<thead>
<tr>
<th>Food groups</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meats and sweets</td>
<td>Less often</td>
</tr>
<tr>
<td>Poultry, eggs, cheese and yogurt</td>
<td>Moderate portions, daily to weekly</td>
</tr>
<tr>
<td>Fish and seafood</td>
<td>Often, at least twice a week</td>
</tr>
<tr>
<td>Fruits, vegetables, grains (mostly whole), olive oil, beans, nuts, legumes, seeds, herbs and spices</td>
<td>Base every meal on these foods</td>
</tr>
</tbody>
</table>

Table 3. Randomized controlled trials to evaluate the efficacy of nutrient supplementation to modify frailty risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Intervention</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latham</td>
<td>Physical health according to the short-form health survey assessed at 3 months and falls assessed over 6 months (Assessments took place in the participants’ homes)</td>
<td>Single dose of vitamin D (calciferol, 300,000 IU) or placebo tablets and 10 weeks of high-intensity home-based quadriceps resistance exercise or frequency-matched visits 6 months</td>
<td>n=243 frail* older people, aged ≥ 65 years (*Frailty criteria: according to simple clinical measures of frailty as described by Winograd et al (participants were screened during their hospitalization in geriatric rehabilitation units))</td>
<td>There was no effect of either intervention on physical health or falls, but patients in the exercise group were at increased risk of musculoskeletal injury (risk ratio 3.6; 95% CI 1.5–8.0). Vitamin D supplementation did not improve physical performance, even in those who were vitamin D deficient (&lt;12 ng/mL) at baseline</td>
</tr>
<tr>
<td>Tieland</td>
<td>Skeletal muscle mass (DEXA), muscle fiber size (muscle biopsy), strength (1-RM), and physical performance (SPPB) were assessed at baseline, and at 12 and 24 weeks</td>
<td>Daily protein supplementation (15 g protein at breakfast and lunch) or placebo</td>
<td>n=65 frail older people</td>
<td>Skeletal muscle mass did not change in the protein- (from 45.8 ± 1.7 to 45.8 ± 1.7 kg) or placebo-supplemented group (from 46.7 ± 1.7 to 46.6 ± 1.7 kg) following 24 weeks of intervention (p&gt;0.05). Muscle strength increased significantly in both groups (p&lt;0.01), with leg extension strength tending to increase to a greater extent in the protein (57 ± 5 to 68 ± 5 kg) compared with the placebo group (57 ± 5 to 63 ± 5 kg) (treatment × time interaction effect: p=0.059). Physical performance improved significantly from 8.9 ± 0.6 to 10.0 ± 0.6 points in the protein group and did not change in the placebo group (from 7.8 ± 0.6 to 7.9 ± 0.6 points) (treatment × time interaction effect: p&lt;0.02)</td>
</tr>
<tr>
<td>Kim</td>
<td>Change of the Physical Functioning and SPPB</td>
<td>Protein-energy supplementation (two 200-mL cans of commercial liquid formula [additional 400 kcal of energy, 25 g of protein, 9.4 g of essential amino acids, 400 mL of water] per day) or placebo</td>
<td>n=87 frail* older people (*Frailty criteria: usual gait speed &lt; 0.6 m/s and MNA® &lt; 24)</td>
<td>Physical Functioning increased by 5.9% (1 point) in the intervention group, although no change was observed in the control group (p=0.052). SPPB remained stable in the intervention group, although it decreased by 12.5% (1 point) in controls (p=0.039)</td>
</tr>
</tbody>
</table>

BI: Barthel Index; DEXA: Dual-energy X-ray absorptiometry; FFM: Fat Free Mass; MNA®: Mini Nutritional Assessment; SPPB: Short Physical Performance Battery
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Intervention</th>
<th>Participants</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen51</td>
<td>Outcomes: physical fitness (body composition, cardiovascular-respiratory functions, body flexibility, muscle power and endurance, balance, and agility) assessed at baseline, 12 and 24 weeks</td>
<td>Intervention: Two groups:  - senior-tailored silver yoga for transitional frail older group (yoga exercises three times per week, 70 minutes per session) (n=38)  - control group (n=31) 24 weeks</td>
<td>Participants: n=69 frail elderly living in assisted-care facilities</td>
<td>- 55 participants completed the pretest and post-test study  - Physical fitness indicators of participants in the silver yoga group had improved significantly, and they had better physical fitness than participants in the control group (all p values p&lt;0.05)</td>
</tr>
<tr>
<td>Hagedorn52</td>
<td>Outcomes: strength, physical endurance, balance and falls efficacy scale scoring assessed at baseline and after end of training</td>
<td>Intervention: Two groups: Both groups received progressive resistance muscle strength training and physical fitness training. Additionally, one group received traditional balance training and the other group received computer feedback balance training. 12 weeks</td>
<td>Participants: n=27 frail elderly, mean age 81.3 ± 6.9 years (outpatients referred to a geriatric falls and balance clinic)  &quot;Frailty criteria: Dynamic Gait Index Score &lt; 19&quot;</td>
<td>- In the combined group, significant mean improvement was observed in knee extension (19%), ankle dorsiflexion (16%), sitting to standing (16%), and in the 6-minute walk test (8%)  - In the traditional balance training group, the static balance in the Modified Clinical Test of Sensory Interaction and Balance standing on a foam mat with closed eyes showed a significant increase (80%)  - No increase occurred in the computer balance training group. However, the computer feedback training group showed a marked improvement that was up to 400% in the training specific performance</td>
</tr>
<tr>
<td>Giné-Garriga53</td>
<td>Outcomes: measures of physical frailty, function, strength, balance, and gait speed assessed at baseline, 12 and 36 weeks</td>
<td>Intervention: Two groups: - functional circuit-training program (FCT) (n=26)  - control group (CG; health education meetings once a week) (n=21) 12 weeks</td>
<td>Participants: n=51 frail community-dwelling adults (31 F, 20 M), mean age 84.0 ± 2.9 years</td>
<td>- Physical frailty measures in FCT showed significant (p &lt; 0.05) improvements relative to those in CG (BI at Weeks 0 and 36: 73.4 ± 2.3 and 77.0 ± 2.4; for the FCT and 70.8 ± 2.5; and 66.7 ± 2.7 for the CG)</td>
</tr>
<tr>
<td>Langlois54</td>
<td>Outcomes: physical capacity (modified PPT, grip strength, physical endurance (6-minute walk test), mobility (Timed Up and Go Test) and gait speed; cognitive performance; quality of life assessed at baseline and 12 weeks</td>
<td>Intervention: Two groups:  - exercise-training group (3 times a week for 12 weeks)  - control group (waiting list) 12 weeks</td>
<td>Participants: n=83 frail elderly, age 61–89 years  &quot;Frailty criteria: FFC+ score of ≤28/36 on the modified PPT + geriatrician’s judgment after assessing the 70 possible deficits of the FI&quot;</td>
<td>- Compared with controls, the intervention group showed significant improvement in physical capacity on modified PPT and 6-minute walk test, cognitive performance (executive functions, processing speed, and working memory) and quality of life (global quality of life, leisure activities, physical capacity, social/family relationships, and physical health)  - Benefits were overall equivalent between frail and non-frail participants</td>
</tr>
</tbody>
</table>

BI: Barthel Index; FFC: Fried Frailty Criteria; FI: Frailty Index; PPT: Physical Performance Test
Table 5. Randomized controlled trials to evaluate the efficacy of multi-domain interventions to modify frailty risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Intervention</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonnefoy62</td>
<td>FFM determined by labelled water and muscle power measured by a leg-extensor machine at baseline and at 9 months</td>
<td>Progressive exercise program compared with memory training and nutritional supplements compared with placebo</td>
<td>n= 57 very frail older people living in nursing homes, aged ≥ 72 years</td>
<td>At 9 months, the compliance was 63% for exercise sessions, and 54% for nutritional supplements - In patients with dietary supplements, muscle power increased by 57% at 3 months (p=0.03), and showed only a tendency at 9 months. Although FFM increased by 2.7% at 9 months, the difference was not significant (p=0.10) - Exercise did not improve muscle power at 9 months, but improved functional tests (five-time-chair rise, p=0.01)</td>
</tr>
<tr>
<td>Rydwik63</td>
<td>Physical performance (muscle strength, balance, mobility and ADL) and nutritional aspects (such as energy intake, body weight and FFM) assessed at baseline and, 3 and 9 months after study entry</td>
<td>Four groups: -physical training 2 x 45 minutes per week (aerobic, muscle strength, balance) -individual nutritional advice and group sessions on nutrition - combined nutritional and physical intervention</td>
<td>n=96 frail* elderly people; ≥ 75 years (40% men)</td>
<td>The intention-to-treat analysis indicated significant improvements in lower-extremity muscle strength in both training groups compared with the nutrition group at 12 weeks - There were small significant changes for some of the balance measurements in the training group without nutrition treatment - The nutrition intervention did not show any significant results</td>
</tr>
<tr>
<td>Lammes64</td>
<td>Energy intake (4-day food diary); RMR (indirect calorimetry) and body composition (anthropometry) performed at baseline, and 3 and 9 months after study entry</td>
<td>Four groups: -physical training 2 x 45 minutes per week -individual nutritional advice and group sessions on nutrition - combined nutritional and physical intervention</td>
<td>n= 96 frail* elderly people; ≥ 75 years (40% men)</td>
<td>The training group showed a significantly increased RMR at 3 months. There were no observed differences within or between the four groups. There was no correlation over time between energy intake, RMR and FFM - The participants with a low energy intake who managed to increase their energy intake during the study (‘responders’) had a statistically lower BMI (21 vs 24 kg/m²) and a lower fat percentage (23 vs 30%) at baseline than the ‘non-responders’</td>
</tr>
<tr>
<td>Zak65</td>
<td>Strength with regard to four muscle groups, ie, hip and knee extensors and flexors assessed at 80% (1 RM) weekly, and balance and mobility assessed at baseline and at the end of the study</td>
<td>Four groups: -group I: progressive resistance exercises (PRE) + functionally-oriented exercises (FOE) + nutritional supplementation (NS) -group II: PRE + FOE + placebo -group III: standard exercises (SE) + FOE + NS -group IV: SE + FOE + placebo. Each group pursued a 45-minute exercise session five times weekly 7 weeks</td>
<td>n=80 frail* elderly (F 71, M 20), mean age 79 years, community dwellers or nursing home residents</td>
<td>Significant differences in muscle strength were noted both in Group I and II (p=0.01; p=0.04; respectively), although this did not translate directly into perceptible improvement in individual mobility - Notable improvements in individual mobility were reported in Group III and IV (p=0.002), although without positive impact on individual muscle strength</td>
</tr>
<tr>
<td>Li68</td>
<td>Outcomes: FFC and BI assessed at baseline and 6 months</td>
<td>Intervention: Two groups: - intervention group by CGA and appropriate intervention by medication adjustment, exercise instruction, nutrition support, physical rehabilitation, social worker consultation, and specialty referral (n=152) - placebo group (n=158) 6 months</td>
<td>Participants: n=310 pre-frail or frail* elderly; mean age 78.8 ± 8.4 years *Frailty criteria: FFC</td>
<td>- Compared to the control group, the intervention group tended to have a better outcome, with an OR 1.19 (95% CI 0.48–3.04; p=0.71), and 3.29 (95% CI 0.65–16.64, p=0.15) respectively, and were less likely to deteriorate with an OR 0.78 (95% CI 0.34–1.79; p=0.57) and 0.94 (95%CI 0.42–2.12, p=0.88), respectively. - There were no significant differences between the two groups</td>
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</tr>
<tr>
<td>Fairhall69</td>
<td>Outcomes: Disability in the mobility domain using the International Classification of Functioning, Disability and Health framework: Activity (execution of mobility tasks) using the 4-metre walk and self-report measures; participation (involvement in life situations) using the Life Space Assessment and the Goal Attainment Scale at baseline, and at 3 and 12 months</td>
<td>Intervention: Two groups: - a multi-factorial interdisciplinary treatment program intended to target frailty (home exercise program targeting mobility, and coordinated management of psychological and medical conditions) - a comparison group receiving the usual health care and support services 12 months</td>
<td>Participants: n=241 frail* community-dwelling older people, mean age of 83.3 ± 5.9 *Frailty criteria: CHS-PCF</td>
<td>- Study was completed for 216 participants (90%) - At 12 months, the intervention group had significantly better scores than the control group on the Goal Attainment Scale (OR 2.1; 95% CI 1.3–3.3; p=0.004) and Life Space Assessment (4.68 points; 95% CI 1.4–9.9; p=0.005) - There was no difference between groups on the global measure of participation or satisfaction with ability to get out of the house - At the activity level, the intervention group walked 0.05 m/s faster over 4 m (95% CI 0.0004–0.1; p=0.048) than the control group, and scored higher on the Activity Measure for Post Acute Care (p&lt;0.001)</td>
</tr>
<tr>
<td>Tieland66</td>
<td>Outcomes: Lean body mass (DEXA), strength (1-RM), and physical performance (SPPB) assessed at baseline, and after 12 and 24 weeks of intervention</td>
<td>Intervention: Two groups: - progressive resistance type exercise training program (two sessions per week for 24 weeks) and supplemented twice daily with either protein (2 * 15 g) - placebo group 24 weeks</td>
<td>Participants: n=62 frail elderly subjects, average age 78 ± 1 years</td>
<td>- Lean body mass increased from 47.2 kg (95% CI 43.5–50.9) to 48.5 kg (95% CI 44.8–52.1) in the protein group and did not change in the placebo group (from 45.7 kg [95% CI, 42.1–49.2] to 45.4 kg [95% CI 41.8–48.9]) following the intervention (p value for treatment × time interaction =0.0006) - Strength and physical performance improved significantly in both groups (p = 0.000) with no interaction effect of dietary protein supplementation</td>
</tr>
<tr>
<td>Chan72</td>
<td>Primary outcome: Improvement of the CHS-PCF by at least one category from baseline assessment. Subjects were followed-up at 3, 6 and 12 months</td>
<td>Intervention: Two intervention groups: - intervention group with exercise and nutrition (EN*, n = 55) or problem solving therapy (PST, n = 57) - control group (non-EN, n = 62 or non-PST, n = 60). *EN group subjects received nutrition consultation and a thrice-weekly exercise-training program while PST group subjects received six sessions in 3 months. 12 months</td>
<td>Participants: n=117 frail* older adults; mean age 71.4 ± 3.7 years (59% females) *Frailty criteria: score of 3–6 on the CCSHA-CFS-TV and score ≥ 1 on the CHS-PCF</td>
<td>- EN group subjects had a higher improvement rate on the primary outcome than non-EN group subjects (45% vs 27%, adjusted p=0.008) at 3 months, but not 6 or 12 months - They also had greater increase of serum 25(0H) vitamin D level (4.9 ± 7.7 vs 1.2 ± 5.4; p=0.0006) and lower percentage of osteopenia (74% vs 89%; p=0.042) at 12 months - PST group subjects had better improvement (2.7 ± 6.1 vs 0.2 ± 6.7; p=0.0035, 6-month) and less deterioration (-3.5 ± 9.7 vs -7.1 ± 8.7; p=-0.0036, 12-month) of dominant leg-extension power than non-PST subjects</td>
</tr>
<tr>
<td>Cameron²³</td>
<td>Primary outcome: Frailty assessed by the Cardiovascular Health Study criteria, and mobility assessed by SPPB at 3 and 12 months after study entry</td>
<td>Intervention: Two groups: -a multi-factorial interdisciplinary treatment program intended to target frailty (home exercise program targeting mobility, and coordinated management of psychological and medical conditions), - a comparison group receiving the usual health care and support services 12 months</td>
<td>Participants: n=241 frail* older people, aged ≥ 72 years</td>
<td>- Study was completed for 216 participants (90%) - In the intention to treat analysis, the between group difference in frailty was 14.7% at 12 months (95% CI 2.4–27%; p=0.02) The score of the SPPB was stable in the intervention group and had declined in the control group with the mean difference between groups being 1.44 (95% CI 0.80–2.07; p&lt;0.001) at 12 months - There were no major differences between the groups with respect to secondary outcomes including disability, depressive symptoms and health-related quality of life</td>
</tr>
<tr>
<td>Fairhall²⁰</td>
<td>Primary outcome: Risk factors for falls measured using the PPA and mobility measures at baseline and 12 months</td>
<td>Intervention: Two groups: -a multi-factorial interdisciplinary treatment program intended to target frailty (home exercise program targeting mobility, and coordinated management of psychological and medical conditions), - a comparison group receiving the usual health care and support services 12 months</td>
<td>Participants: n=241 frail* older people, aged ≥ 72 years</td>
<td>- Study was completed for 216 participants (90%) - After 12 months, the intervention group had significantly better performance than the control group, after controlling for baseline values, in the PPA components of the quadriceps strength (between-group difference 1.84 kg; 95% CI 0.17–3.51; p=0.03) and body sway (-90.63 mm, 95% CI -168.6 – -12.6; p=0.02), SPPB (1.58; 95% CI 1.02–2.14; p&lt;0.001) and 4 m walk (0.06 m/s; 95% CI 0.01–0.10; p=0.02) with a trend toward a better total PPA score (-0.40; 95% CI -0.83 – -0.04; p=0.07) but no difference in fall rates (incidence rate ratio 1.12; 95% CI 0.78–1.63; p=0.53)</td>
</tr>
</tbody>
</table>

*Frailty criteria: CHS-PCF

ADL: Activities of Daily Living; BI: Barthel Index; BMI: body mass index; CCSHA-CFS-TV: Chinese Canadian Study of Health and Aging Clinical Frailty Scale Telephone Version; CGA: Comprehensive Geriatric Assessment; CHS-PCF: Cardiovascular Health Study Phenotypic Classification of Frailty; CI: confidence interval; DEXA: Dual-energy X-ray absorptiometry; FFC: Fried Frailty Criteria; FFM: fat-free mass; OR: odds ratio; PPA: Physical Profile Assessment; PFT: Physical Performance Test; RM: repetition maximum; RMR: resting metabolic rate; SPPB: Short Physical Performance Battery
Table 6. Characteristics of the first 160 patients evaluated during the first 6 months of operation of the program

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99 (61.9)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (38.1)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>14 (8.7)</td>
</tr>
<tr>
<td>75–84</td>
<td>92 (57.5)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>54 (33.7)</td>
</tr>
<tr>
<td><strong>Education, n=158</strong></td>
<td></td>
</tr>
<tr>
<td>Higher education</td>
<td>44 (27.8)</td>
</tr>
<tr>
<td>Senior high school</td>
<td>30 (20.9)</td>
</tr>
<tr>
<td>Junior high school</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Primary school</td>
<td>64 (40.5)</td>
</tr>
<tr>
<td>No school attendance</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>15 (9.4)</td>
</tr>
<tr>
<td>Divorced</td>
<td>11 (6.9)</td>
</tr>
<tr>
<td>Married</td>
<td>67 (41.9)</td>
</tr>
<tr>
<td>Separated</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Widowed</td>
<td>63 (39.4)</td>
</tr>
<tr>
<td>Living with partner</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td><strong>Living environment</strong></td>
<td></td>
</tr>
<tr>
<td>Assisted living facility</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Nursing home for dependent elderly</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>At home (communal home)</td>
<td>61 (38.1)</td>
</tr>
<tr>
<td>At home (individual home)</td>
<td>88 (55.0)</td>
</tr>
<tr>
<td><strong>Help at home, n=106</strong></td>
<td></td>
</tr>
<tr>
<td>Home help</td>
<td>55 (51.9)</td>
</tr>
<tr>
<td>Visiting nurse</td>
<td>12 (11.3)</td>
</tr>
<tr>
<td>Physical therapist</td>
<td>7 (6.6)</td>
</tr>
<tr>
<td>Old age allowance</td>
<td>15 (14.1)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (16.0)</td>
</tr>
<tr>
<td><strong>Frailty status (FFC), n=158</strong></td>
<td></td>
</tr>
<tr>
<td>Non-frail</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>65 (41.4)</td>
</tr>
<tr>
<td>Frail</td>
<td>83 (52.9)</td>
</tr>
<tr>
<td><strong>Frailty criteria (FFC)</strong></td>
<td></td>
</tr>
<tr>
<td>Recent weight loss, n=158</td>
<td>52 (32.9)</td>
</tr>
<tr>
<td>Feeling of exhaustion, n=157</td>
<td>49 (31.2)</td>
</tr>
<tr>
<td>Decreased muscle strength, n=156</td>
<td>90 (57.7)</td>
</tr>
<tr>
<td>Slow gait speed, n=155</td>
<td>130 (83.9)</td>
</tr>
<tr>
<td>Sedentary, n=158</td>
<td>85 (53.8)</td>
</tr>
<tr>
<td><strong>MMSE score, n=154</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>25.4 ± 4.2 (range: 12–30)</td>
</tr>
<tr>
<td>20–24</td>
<td>19 (12.3)</td>
</tr>
<tr>
<td>25–27</td>
<td>32 (20.8)</td>
</tr>
<tr>
<td>≥28</td>
<td>41 (26.6)</td>
</tr>
<tr>
<td><strong>CDR score, n=155</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 (22.6)</td>
</tr>
<tr>
<td>0.5</td>
<td>102 (65.8)</td>
</tr>
<tr>
<td>1</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>2</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td><strong>MIS score (8), n=157</strong></td>
<td></td>
</tr>
<tr>
<td>6.4 ± 1.9 (0–8)</td>
<td></td>
</tr>
<tr>
<td><strong>MIS-D score (8), n=155</strong></td>
<td></td>
</tr>
<tr>
<td>5.5 ± 2.6 (0–8)</td>
<td></td>
</tr>
<tr>
<td><strong>AD-8 score (8), n=157</strong></td>
<td></td>
</tr>
<tr>
<td>3.3 ± 2.3 (0–8)</td>
<td></td>
</tr>
<tr>
<td><strong>ADL score (6), n=159</strong></td>
<td></td>
</tr>
<tr>
<td>5.6 ± 0.8 (1–6)</td>
<td></td>
</tr>
<tr>
<td><strong>IADL score (8), n=159</strong></td>
<td></td>
</tr>
<tr>
<td>6.0 ± 2.3 (0–8)</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Characteristics of the pre-frail and frail patients evaluated during the first 6 months of operation of the program

<table>
<thead>
<tr>
<th></th>
<th>Pre-frail (n=65)</th>
<th>Frail (n=85)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>81.4 ± 6.5</td>
<td>84.1 ± 5.5</td>
<td>0.012</td>
</tr>
<tr>
<td>Gender (%women)</td>
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ADL: Activities Daily Living, CDR: Clinical Dementia Rating, FFC: Frailty Fried Criteria; HHIES: Hearing Handicap Inventory for the Elderly - Screening version; IADL: Instrumental Activities Daily Living; MMSE: Mini Mental State Examination; MIS: Memory Impairment Screen; MIS-D: Memory Impairment Screen Differed; MNA®: Mini Nutritional Assessment; SPPB: Short Physical Performance Battery.
Bibliography


Frailty in the elderly population is a growing problem globally and the quest for a better understanding of this condition was the topic of a landmark meeting in Barcelona, Spain, which took place on 14–15 March 2014, and was chaired by Professors Roger A. Fielding, Cornel Sieber and Bruno Vellas. At this event, experts from around the world met to share their cutting edge research on the central aspects of frailty pathophysiology, phenotype and patient care, and to define the way forward.

“Important breakthroughs have been made in discovering the biological basis of frailty, and from these discoveries new future treatments can be developed”, said meeting Co-Chairman, Professor Roger A. Fielding, Director of The Nutrition, Exercise Physiology and Sarcopenia Laboratory at Tufts University, USA. Inflammation, oxidative stress, mitochondrial dysfunction and cell senescence lie at the core of dysregulation in frailty. It is these areas that present great potential for innovations to support the current multi-modal interventions for frailty of nutrition, exercise and pharmacotherapy. Several lines of evidence have shown that there is a distinct phenotype for frailty. In addition, there are cognitive aspects which have similar biological origins to physical frailty and these can co-exist in some patients. In the future, international teams of researchers will collaborate on topics for investigation, with the aim of further improving patient outcomes while remaining cost-effective.

European initiatives underway to address the problem of frailty
An estimated 17.5% of the EU population (over 500 million in 27 countries), are older than 65 years of age and this percentage will increase over the coming years as the population ages.

Professor Jean-Pierre Michel, Geneva Medical School, Switzerland, and Chairman of the European Union Geriatric Medicine Society (EUGMS) Board, described evidence collected in the population screened by general practitioners and referred for care in the Toulouse Gerontopôle Frailty Clinic.

“A Europe-wide longitudinal study has shown that frailty can be reversed. This was one of the key findings of the Survey of Health, Ageing and Retirement in Europe (SHARE), which included over 85,000 individuals”

Around 40% of 1,108 community-dwelling adults were found to be pre-frail and 55% frail. These results were based on frailty evaluation using a screening questionnaire: the Gerontopôle Frailty Screening Scale. Observations revealed that 62% of patients were recommended a nutritional intervention and over 55% were recommended a physical intervention.

Professor Michel explained the far-reaching effects of these results: “This model prompted several organizations in France to act on frailty; for example, the French National Health Authority, the French National Society of Geriatrics and the French Academy of Medicine, all of which are now involved in frailty education and offer advice on its management”. EUGMS initiatives include several activities relating to sarcopenia as well as to frailty, including the recently published PROT-AGE evidence-based recommendations for optimal dietary protein intake in older people. Other expert consensus papers are due to be published this year, including the importance of nutrition, such as protein-enriched diets, on these conditions and a working group to validate the Gerontopôle questionnaire.
across Europe. Finally, the European Union has several research initiatives. The European Innovation Partnerships (EIPs), a new approach to EU research and innovation, and the MID-FRAIL study are examples. The MID-FRAIL study is a Phase IIb open, randomized, clinical trial to evaluate the effectiveness of a multi-modal intervention (optimizing medical management, resistance-based exercise program and educational/nutritional intervention) in 1,704 frail or pre-frail subjects (aged >70 years) with type 2 diabetes to prevent functional decline and maintain or improve quality of life and its associated costs.

**Fraility is a syndrome with several underlying mechanisms**

Age-related biological decline is connected to frailty. However, not all elderly people are frail. Ultimately, it is hoped that a better understanding of the internal physiologic and molecular changes will lead to identification of a biomarker to the frailty phenotype, in order to facilitate early detection and track progression of the condition. **Professor Jeremy Walston** from Johns Hopkins University, USA, identified several possible physiologic and molecular mechanisms by which frailty may be induced, such as inflammation and insulin resistance. Recently, important progress has been made in understanding the relationship of the dysregulated stress response systems in relation to frailty, with chronic activation of stress hormones such as cortisol driving further changes.

“In the future we need to be able to identify and target ‘vulnerability’ pathways to try and slow functional impairment – a decline that appears to be linked to chronic disease states and adverse health outcomes in older adults”

Recent research focused on aging at the cellular level has identified approaches that can prevent or markedly delay frailty as well as well as other conditions such as Alzheimer’s disease, diabetes and cancer. Cellular senescence has been found to be one possible pathway to frailty development, as this appears to be a driver of aging and age-related conditions. **Professor Nathan K. LeBrasseur** from the Robert and Arlene Kogod Center on Aging at the Mayo Clinic, USA, showed in a mouse model of accelerated aging that preventing or delaying frailty can be achieved by removing senescent cells – or inhibiting the senescence-associated secretory phenotype (SASP).

In addition, animal data from the Mayo Clinic show that chronic consumption of a fast food diet significantly increases both the abundance of senescent cells in middle-aged mice and the expression of SASP components in fat tissue. However, physical activity dramatically prevented the effects of fast food on senescence and the SASP. Many questions remain, and research into various aspects of senescence is ongoing.

“**In order to slow the aging process, lifestyle factors such as diet and exercise can be important**”

As well as inflammation and senescence, there is also the autophagy theory of aging related to aberrant mitochondrial fission and fusion. According to **Professor Christiaan Leuwenburgh** from the Institute on Aging at the University of Florida, USA, aging cells have a reduced turnover of cellular components (ie, reduced ‘garbage disposal’) with intracellular accumulation of altered macromolecules and organelles (ie, accumulation of ‘garbage’). This highlights the importance of changes at a cellular level in the development of frailty. Other factors include telomere changes, as well as mitochondrial DNA instability, mutations and deletions, such as in sirtuin-3 (SIRT3) which normally scavenges reactive oxygen species and can lead to elevated oxidative stress and a variety of adverse outcomes on the aging process.

**Physical frailty is linked to psychological and cognitive frailty**

**Professor L. Jaime Fitten** of the Department of Psychiatry and Biobehavioral Sciences at UCLA, USA, described what is commonly observed in clinical practice: an association between psychological frailty (PsyF) and physical frailty. Patients with both types have a poorer prognosis. PsyF is part of the clinical frailty syndrome that considers cognition, mood and motivation, but very little about it is currently described. PsyF represents one of several possible aging trajectories, and may be worsened by chronic brain disease; however, disease and normal aging do not damage the same networks or to the same degree. More research in this area is needed to answer the outstanding questions regarding PsyF.

Physical performance indicated by gait measures is a strong independent predictor of future cognitive decline and dementia risk. Furthermore, multiple lifestyle factors (such as insufficient nutrient intake, low levels of physical activity) and biological mechanisms (such as inflammation and impaired insulin sensitivity) are closely involved in the development of frailty, therefore offering numerous targets for intervention by healthcare professionals. Longitudinal studies suggest a link between physical and cognitive frailty. As such, individuals with physical frailty may also have deficits in executive function – termed ‘cognitive frailty’. This term has recently been defined by an international consensus group (from the International Academy on Nutrition and Aging [IANA] and the International Association of Gerontology and Geriatrics [IAGG]) as ‘a heterogeneous clinical manifestation characterized by the simultaneous...
presence of physical frailty and cognitive impairment, in the absence of Alzheimer’s Disease or other dementia. Research by Professor Marco Pahor and his team from the University of Florida Institute on Aging has shown that diet alone was able to significantly reduce interleukin-6 (IL-6), a marker of age-related chronic low-grade systemic inflammation.

“The study demonstrated how a behavioral program designed to change eating habits and lower weight by 5% in obese older adults can significantly improve mediators of frailty risk”

Large, long-term, randomized controlled trials are needed to test the efficacy of combined behavioral, nutritional, physical, and pharmacological interventions on frailty, cognitive impairment and health outcomes.

Screening for malnutrition is important for frailty prevention

A multi-national research initiative identified that malnutrition, and the risk of malnutrition, are present in over two-thirds of older people in various formal care settings (ie, hospitals, nursing homes, and rehabilitation centers). Professor Cornel Sieber, Chair of Internal Medicine-Geriatrics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, suggested that the weight loss cut-off to indicate a nutrition issue in the Fried frailty criteria may underestimate the problem of malnutrition in older adults.

“As the presence of unintentional weight loss (>10 pounds [4.5 kg] in 1 year) is one of the five criteria evaluated for an individual to be considered frail, adequate nutrition is very important for healthy and active aging”

The Mini Nutritional Assessment (MNA®) may be a more sensitive screening method, as it is the only malnutrition screening/assessment tool specifically developed for older people. Data show that use of the MNA® is more closely indicative of survival risk than the use of the Fried criteria, since the MNA® also takes into account depression, dementia, motivation, fatigue and mobility. “Malnutrition measured by the MNA® is closely linked to reduced strength, functionality and mobility, and therefore to frailty risk,” said Prof Sieber, “so it is important to routinely screen for malnutrition in older patients”.

“Notably, 90% of the at-risk/malnourished population detected by the MNA® are also pre-frail/frail. Thus, among those who screen positive for malnutrition/risk, it is important to proactively evaluate for and manage frailty issues”

Nutrition and exercise have demonstrated benefits for the frail

Over the last few years evidence has been mounting to support a significant role for vitamin D in the treatment of frailty, partly at least because of its signaling effect on muscle explained Professor Heike A. Bischoff-Ferrari, Chair of the Department of Geriatrics and Ageing Research at the University of Zurich, Switzerland.

Numerous meta-analyses show the positive impact of supplemental vitamin D on fall prevention (reduced by up to 34%), a fact recognized in guidelines and recommendations from several national and international societies. Vitamin D status also has other positive benefits on mobility and physical performance measures, and in chronic conditions such as cardiovascular disease. The largest ongoing longevity trial funded by the European Commission Framework 7, a public-private partnership with numerous sponsors including Nestlé Health Science, is testing the clinical and economic impact of three broadly applicable interventions: vitamin D, omega-3 fatty acids and exercise on five primary endpoints (fractures, functional decline, blood pressure, cognitive decline, and infections) in 2,152 people aged 70 years and older. The results will be published in due course.

“The benefits of remaining active, although intuitive, have now been demonstrated in frail people. Dr Dennis T. Villareal of the University of New Mexico, USA, described several studies in which exercise in older adults led to improvements in physical performance.

An association between obesity and the frailty syndrome has also been noted, with obese elderly people having poor muscle quality. Since obesity is an increasing problem, healthcare professionals should be aware of how to manage it in the context of frailty. Evidence shows that...
exercise programs, along with dietary interventions, are successful in reducing aspects of frailty, including in obese older patients, as well as improving quality of life. However, Dr Villareal recommended that interventions should be personally tailored.

“Studies suggest that exercise should be an integral part of the strategy to reduce frailty”

“It is necessary to individualize exercise programs according to the older individual’s health condition and ability, and to start slow and go slow to promote adherence and minimize musculoskeletal injuries”

Further information on the exact type, duration, frequency, setting and intensity of exercise training is still required.

**Hip fracture is a common problem in the frail, requiring multi-component intervention**

Older people and particularly the frail are at risk of hip fracture if they suffer a fall. There is an ever-increasing personal, social and economic burden associated with hip fractures. A drastic change in lean body mass occurs during the first 60 days after hip fracture. In comparison, fat mass is relatively stable during that period. The prevalence rate of sarcopenia increases 1.5 fold between pre-fracture to 60 days post-fracture. Among individuals with no previous impairment, 90% are unable to climb five stairs unassisted at 12 months post-fracture.

Professor Jay Magaziner from the Department of Epidemiology and Public Health at the University of Maryland, Baltimore, USA, explained that hip fracture is a multi-faceted problem which requires multi-component, multi-disciplinary treatments and intervention programs to improve short- and long-term outcomes.

Over the past 25 years the Baltimore Hip Studies have aimed to identify gaps, develop evidence and evaluate strategies to optimize recovery from hip fracture. These studies have recorded numerous functional and quality of life deficits following hip fracture, and identified an orderly sequence of functional recovery which seems to parallel the process by which function is lost. Research is ongoing into multidisciplinary/multi-component interventions that have the greatest impact at specific times post-fracture.

Professor Magaziner gave his thoughts on the direction of future investigations: “As systems of care delivery change to improve outcomes and reduce costs, we need to evaluate the cost-effectiveness of patient-focused/need-based interventions”.

“Possible components of treatment for hip fracture recovery include surgical repair; nutritional supplementation (ie, vitamin D, calcium and protein); psychological, physical, and occupational therapy; and pharmacological (ie, bone strengthening) agents”

**Improving quality of life and maintaining independence for frail people**

Professor Leocadio Rodríguez Mañas, Head of the Department of Geriatrics at Hospital Universitario de Getafe, Madrid, Spain, asked: “There is a complex relationship between longevity and frailty, but do they share the same determinants?” Some cellular and chemical mechanisms operate mainly on longevity, while others operate on frailty. Although some mechanisms may be shared, longevity and frailty cannot work on exactly the same pathway, otherwise all elderly would be frail, which is not the case. Evidence suggests that physical inactivity, inflammation and sex hormones play important roles in both reducing longevity and promoting frailty.

“Today, the focus of healthcare should be on improving quality of life rather than increasing longevity. By addressing issues early and improving nutritional status, we can impact an improvement in functional status”

What is becoming clear is that overlaps exist between definitions of frailty and sarcopenia. Sarcopenia is also emerging as a major threat to quality of life in our aging society. Initiating early strategies to maintain independence and avoid disability must be key goals for patients with these conditions.

Sarcopenia is a syndrome characterized by progressive loss of muscle mass and strength with a risk of adverse outcomes, whereas frailty is a syndrome with multiple causes, characterised by diminished strength and endurance that increases vulnerability for dependency and death. Although there are differences in these conditions, clear overlaps are
apparent. Both sarcopenia and frailty are catabolic conditions with negative effects on function and outcomes in older and ill adults, and these conditions are associated with a rise in age-related inflammation and its associated reactions in the body – which has been termed ‘inflammaging’. Professor Tommy Cederholm, Head of Department for Clinical Nutrition and Metabolism at Uppsala University in Sweden, said the management of frailty and sarcopenia is currently similar in terms of screening, assessment, treatment and monitoring, but as more becomes known, differences might be revealed.

“Sarcopenia and frailty are ‘the new giants of geriatric syndromes’, and awareness of both conditions needs to be increased across all healthcare organizations, particularly in primary care, so that diagnosis and treatment are routinely co-ordinated”

Future pharmacological therapies for frailty in the pipeline

What can be done in the future to address the pharmacotherapy of frailty? Professor Shalender Bhasin, Director of the Research Program in Men’s Health: Ageing and Metabolism at Harvard Medical School, USA, presented ongoing research on pharmaceutical agents currently in development for frailty, such as promyogenic agents (eg, testosterone and selective androgen receptor modulators [SARMs]), orexigenic agents and fast troponin activators. These agents are designed to address the balance between the regulation of atrophy and the regulation of growth, and to target four interconnected signaling pathways that are considered to be major regulators of skeletal muscle mass.

“The considerable number of products in research and development for age-related functional limitations emphasizes the importance being placed on this area of medicine”

A call to action for healthcare professionals to address frailty in clinical practice

The care of older people should be improved, and strategies should be initiated before individuals become disabled and institutionalized, a prophylactic approach that has already been successfully implemented in other conditions such as cancer and cardiovascular disease.

Professor Bruno Vellas of the Department of Internal Medicine and Geriatrics at the Université de Toulouse, France, summed up the large-scale changes that need to occur: In order to support this shift of focus we need to build the infrastructure to care for older patients before frailty develops.

“Overall, frailty needs to be moved up the healthcare agenda globally in order to reduce the burden of frailty on healthcare resources and society in general”

International interest and urgency in addressing frailty is increasing. Data show that interventions in older patients, such as comprehensive geriatric assessment in hospital and preventive home visitation programs, do produce benefits such as decreasing physical and functional decline, decreasing mortality, decreasing nursing home use and increasing the possibility of remaining at home. The Gerontopôle example of implementing frailty into clinical practice incorporates a screening tool for frailty (that factors-in the opinion of the GP), a multidisciplinary team approach across France, health promotion efforts for older people in the community, and targeted interventions with structured follow-up and re-evaluation for identified people at risk. There is also a considerable body of ongoing research into areas such as sarcopenia and nutritional aspects of frailty.

The quest to better understand and increase awareness of the expanding geriatric syndrome of frailty is underway. There are many facets to the condition, so there are many challenges ahead. With international expertise focused on the epidemiology and pathophysiology of frailty, and the exploration of new treatments, improved outcomes for frail older adults are on the horizon.

“Today, treatments clearly exist and frailty can be reversed.
Management starts with simple screening tests. A consensus paper from six medical societies recommends...
All persons older than 70 years and all individuals with significant weight loss (>5%) due to chronic disease, should be screened for frailty”
Ongoing research into exercise, nutrition and pharmacological interventions is creating the potential for future multi-modal solutions, not just to the physical and cognitive aspects of frailty but also to the social and economic challenges associated with this condition.

Key references

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<tr>
<td><strong>September 2014</strong></td>
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<td><strong>36th ESPEN Congress</strong></td>
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<td>6–9 September 2014</td>
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<td>Geneva, Switzerland</td>
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**10th International Congress of the EUGMS**

17–19 September 2014

Rotterdam, The Netherlands

**Organizer:**
European Union Geriatric Medicine Society (EUGMS)


**ESICM LIVES 2014 Annual Congress**

27 September – 1 October 2014

Barcelona, Spain

**Organizer:**
The European Society of Intensive Care Medicine (ESICM)

**Web site:** http://www.esicm.org/events/annual-congress

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<td>San Francisco, California, USA</td>
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**2014 AAP National Conference and Exhibition**

11–14 October 2014

San Diego, California, USA

**Organizer:**
American Academy of Pediatrics (AAP)

**Web site:** www.aapexperience.org

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The European Society for Swallowing Disorders (ESSD)

**Web site:** http://www.essd2014.org/

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American College of Allergy, Asthma & Immunology (ACAAI)

**Web site:** www.acaai.org/annual_meeting/Pages/default.aspx

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<td>4–6 December 2014</td>
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<td>Orlando, Florida, USA</td>
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Crohn’s & Colitis Foundation of America (CCFA)

**Web site:** http://www.advancesinibd.com/
Malnutrition is associated with a 3 times higher infection rate and higher mortality rate\textsuperscript{1,2}.

**MNA\textsuperscript{®}:** The **GOLD** standard in nutrition screening for the older adult

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- Quick, convenient and easy to use
- Identifies patients who need nutrition intervention
- Most commonly used nutrition screening tool by geriatricians\textsuperscript{3}
- The new Self-MNA\textsuperscript{®} is valid for use by older adults\textsuperscript{4}

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