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Review

Frailty and the role of nutrition in older people A review of the current literature

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Abstract. Frailty and malnutrition are both highly prevalent in the older population and have therefore become principle topics in geriatric research. Frailty is of multifactorial origin and is regarded as a fundamental risk factor for deteriorating health status and disability in older people. It is estimated that prevalence rates for frailty and pre-frailty reach as high as 27% and 51%, respectively. The role of nutritional deficiency in the development of frailty was suggested long ago, however research conducted in this area is relatively recent. The critical role of micronutrients in this context suggests the need to improve the quality of food eaten by older people – not just the quantity. This review summarizes the recent literature on the nutritional pathways to frailty with particular focus on the effect of energy, protein and micronutrients. (www.actabiomedica.it)

Key words: Frailty, nutrition, malnutrition, functionality, elderly, micronutrients, antioxidants

Introduction

Over the past century, the world has seen enormous changes, including a historically unprecedented decline in mortality and increase in population growth. This century will see a new set of demographic challenges such as the subsequent aging of populations in both developing and developed countries. The 20th century was the century of population growth; the 21st century will go into the history books as the century of aging (1). Since the increase of life expectancy at birth did not parallel health expectancy, the rise in morbidity of the aging population will increase the medical costs and the burden on national healthcare systems. Both health and ageing are social and cultural constructs in addition to being biologically determined. Cultural and political factors also influence the health of older people. One has also to recognize that the health of the older is influenced by events throughout the course of their lives (life course perspective). This life course perspective leads to important policy and strategy decisions. It is clearly possible (and indeed desirable) to improve the health status of women and men when they are old. Yet, a complementary approach to improving the health of older people would focus on appropriate interventions from a much earlier age in order to prevent frailty, which is now seen as a multi-system disorder and one of the central geriatric syndromes. The operationalization of the frailty syndrome by Fried and Rockwood has to be regarded a "breakthrough" as a scientific issue (2-4). Frailty can be triggered by multiple pathophysiological processes such as malnutrition, hormonal dysbalances, chronic inflammation and multimorbidity. Frailty often leads to deterioration of health status, immobilization, disability and death and is particularly characterized by a reduced functional reserve and increased vulnerability to internal and external stressors (4). Frailty imposes therefore an increased risk on older people to recover inadequately from even minor events such as gastroenteritis or change of residence. An overview on the influencing factors on frailty or frailty-related parameters proposed is given in Table 1. Due to the diversity of parameters affecting the development of frailty, the

Table 1. Influencing factors on the development or aggravation of frailty or frailty-related parameters (NB: lack of a uniform definition of frailty in cited publications)

Parameter, literature reference	Description
Age (2, 22, 81, 82, 84)	Prevalence of frailty increases with age
Gender (1, 86, 87)	Frailty more prevalent in women
Malnutrition (6, 10, 22, 24, 39, 44, 46, 52, 66, 67, 68, 84)	Loss of appetite, weight loss, sarcopenia. Low energy and protein intake. Low intake and blood levels of vitamins (B, C, D, E, folate), antioxidants (carotenoids) and trace elements (selenium, zinc).
Comorbidity, multimorbidity (2, 53, 54, 55, 83, 84, 85)	Simultaneous presence of one or multiple, mostly chronic diseases (e.g. cardiovascular disease, congestive heart failure, arthrosis, osteoporosis, chronic renal insufficiency). Polypharmacotherapy.
Hormonal dysbalances (52, 56, 57, 58, 59, 60, 62, 63, 64, 65)	Low levels of testosterone, growth hormone, DHEAS, cortisol, IGF-1, leptin, sex hormone-binding globulin. Multiple hormonal deficiencies. Anti-androgen treatment. Increased insulin resistence, metabolic syndrome.
Cytokines, „oxidative stress" (40, 43, 52, 61, 62, 65, 67, 76, 77, 78, 79, 80)	Increased levels of CRP, IL-6, TNF-α and leukocytes. Activation of the coagulation system. (Anemia).
Body composition changes (69, 70, 71, 72)	Changes of body composition: increase of fat mass, decrease of lean body mass (i.e. muscle mass). Sarcopenia. Decrease of bone density.
Neuropsychological disorders (73, 74, 75)	Parkinson's disease, Alzheimer's disease. Depression and other psychoses.
Socio-economic factors (2, 84, 86, 88, 89)	Lack of social involvement (relatives, friends, church, organizations). Low life satisfaction. Low income, low educational level, non-white-collar occupation.

term "frailty puzzle" has been coined (6). Recognition and treatment of the causes for frailty and the frailty syndrome itself represent a key approach to improving the care for older people, particularly as frailty is highly prevalent in this population (7, 8). A recent publication implementing Fried`s criteria identified prevalence rates in various European countries ranging from 6% to 27% for frailty and from 35% to 51% for prefrailty in persons above age 65 (9). Such high prevalence rates qualify for the term "epidemic". Malnutrition of both macro- and micronutrients has been identified as an important risk factor for the development and severity progression of frailty in older people (10). This review aims at summarizing the recent literature on the nutritional links to frailty, frailty components and frailty-related parameters such as low muscle strength and low walking speed. Data on the prevalence of inadequate nutritional intake among older people and its association with frailty will be examined. The influence of energy and protein intake and particularly the role of micronutrients such as vitamins, antioxidants and trace elements will be discussed in the light of the most relevant publications.

Frequency of inadequate nutritional intake among older people

Although food intake declines with aging which is possibly due to lower caloric requirement to maintain reduced lean body mass, inadequately low nutritional intake is frequently observed among older people, especially in those with increased care needs (11). The U.S. National Health and Nutrition Examination Survey (NHANES III) identified low energy and nutrient intake in up to 21% of the free-living older study population (12). The InCHIANTI study (Invecchiare in Chianti/Aging in the Chianti area, Italy) which examined nutritional status and nutrient intake in the general population including old and very old people, found a strong age-dependency of low energy, protein and micronutrient intake (13). Study participants older than 85 years had the lowest dietary intake of any examined nutrient which was in many cases below official recommendations. Twenty-nine percent of women and 38% of men in this age group did not meet their recommended protein intake. This proportion was even higher for some vitamins and trace ele-

ments. Gariballa and Forster examined food diaries completed by community-living older people in the UK immediately following hospital discharge (14). The mean energy intake in this population met only roughly two thirds of the reference values, which was attributed to difficulties with shopping and cooking, isolation, depression and other bad health conditions.

Two recent studies on nursing home residents found an even higher prevalence of poor nutrient intake. Inadequate energy intake was identified in 60% of the examined population, and inadequate micronutrient intake of vitamin E, vitamin B_6, folate, magnesium and zinc in 70% (15, 16). Although inadequate nutritional intake may be temporary and does not necessarily equal overt malnutrition or nutritional risk, similar findings were obtained when screening tools suitable for the older population such as the Mini Nutritional Assessment (MNA®) were applied in the nursing home setting. Kulnik et al. found that 38% of nursing home residents were malnourished, while another 48% were assessed as "at risk" of malnutrition (17). Wikby et al. reported 20% of nursing home residents to be malnourished and an additional 50% to be "at risk" (18).

Data on dietary intake in hospitalized older patients is rather scarce, which may be due to the shorter length of stay in hospitals compared to long-term care units and the time-consuming character of most methods which directly measure dietary intake (19). A recent study from the UK revealed inadequate food consumption, defined as having eaten less than three-quarters of the served dishes, in 67% of geriatric acute care patients (20). These findings should be interpreted considering the growing evidence that older people hospitalized for acute disease may require a higher protein intake to maintain a positive nitrogen balance than previously assumed and officially recommended in healthy older people (21).

Association of inadequate nutritional intake with frailty

If frailty in older people is promoted by poor nutritional intake, an association between these entities must be confirmed in observational studies. The majority of data on this topic have been derived from the aforementioned Italian InCHIANTI study and the U.S. Women's Health and Aging Study (WHAS) which have systematically examined the relationship between nutritional status and frailty in large, longitudinal studies. Bartali and colleagues established a link between deficient nutritional intake and the frailty syndrome based on InCHIANTI study data implementing Fried's criteria (10). Twenty percent of the InCHIANTI population was frail and out of those who were frail more than 53% showed deficient intake of at least one out of nine examined nutrients. About one third of the frail persons had an inadequate intake of more than three nutrients. An energy intake of less than 21 kcal/kg body weight/day was strongly associated with being frail. This observation was also valid for some micronutrients even independently from energy intake. The odds ratio for being frail associated with having three or more nutrient deficiencies compared to two deficiences or less was 2.12. Based on data from the WHAS, Semba and colleagues identified low serum micronutrient concentrations as frailty predictors (22). At baseline, one third of the study participants were frail with significantly lower serum concentrations of numerous micronutrients (vitamin E, vitamin D, selenium, zinc) as compared to their non-frail peers. In the course of regular follow-up examinations about one third of the non-frail study participants became frail. Low micronutrient concentrations in non-frail persons at baseline were identified as an independent risk factor for becoming frail during the follow-up period. Also, the number of nutritional deficiencies was associated with an increased risk of becoming frail. Thus, as exemplified by the two mentioned studies, inadequate intake of energy and low serum concentrations of micronutrients have been associated with an increased prevalence of frailty and an increased risk of becoming frail in the future.

The role of protein in frailty

Several studies have established a link between insufficient dietary protein intake and low serum protein concentrations to frailty or frailty-related parameters of functionality in older people. In community-dwelling older people examined by the U.S. Health, Aging and

Body Composition Study (Health-ABC), Houston and colleagues demonstrated that low dietary protein intake was associated with loss of lean body mass (i.e. muscle mass) as measured by dual energy x-ray absorptiometry (DEXA) (23). All participants in the Health-ABC study lost muscle mass during the three-year follow-up period, but those with lowest protein intake at baseline (0.7 g/kg body weight/day) lost more than 40% more muscle mass than those with highest protein intake (1.1 g/kg body weight/day). Continuing loss of muscle mass eventually leads to sarcopenia which has been termed "nutritional frailty" to clarify the close interrelationship between poor nutritional status, loss of muscle mass and muscle strength, and functional decline (24). It was furthermore demonstrated on Health-ABC study data that lower serum albumin concentrations, even within the normal range, was associated with greater loss of muscle mass in a five-year follow-up (25). Unfortunately, no functional parameters were included to examine the implication of muscle mass loss on physical function in older persons.

Kwon and colleagues examined serum albumin and vitamin D, which are physiologically interconnected in muscle function and metabolism, and their association with physical performance among community-dwelling older Japanese (26, 27). Study participants with isolated deficiencies of either albumin or vitamin D had poor muscle strength as assessed by knee-extension power and hand-grip strength (one of Fried's criteria) and impaired balance capability as assessed by the timed up-and-go test and functional reach. Even worse functionality, though, was found in persons with deficient serum concentrations of both albumin and vitamin D. These results illustrate the supposed synergistic effect of protein and vitamin D on muscle strength, which is of particular interest with regard to the high prevalence of vitamin D deficiency in the older population (28, 29). Serum albumin was found to be a predictor of future loss of muscle strength by Schalk and colleagues from the Longitudinal Aging Study Amsterdam (30). Even at baseline of this study, lower albumin values (<43 g/l) were associated with decreased muscle strength as measured by hand-grip strength. In a three-year follow-up examination, lower baseline serum albumin levels were significantly associated with an increased loss of muscle strength. Notably, such "lower" albumin levels were still higher than commonly reported cut-off values between 35 and 38 g/l which might emphasize the role of serum albumin as an early marker of muscle strength decline (30).

The role of micronutrients in frailty

The association between frailty and micronutrients, particularly those with antioxidative capacity, has come into research focus during the last years. "Oxidative stress" caused by free radicals is considered a major damaging influence on macromolecules (enzymes, lipids, DNA), a contributor to aging at the cellular level and an influencing factor on disability and mortality in older people (31-36). Many vitamins have antioxidative capacity, e.g. the vitamins A (retinol), C (ascorbate), D (cholecalciferol) and E (tocopherol group). Carotenoids constitute another group of antioxidants and comprise vitamin precursors and vitamin-like molecules like β-carotene, α-carotene, lycopene, lutein and several more which are of utmost importance to scavenging free radicals (36). The main food source for carotenoids is fresh fruits and vegetables. Carotenoid serum concentrations are regarded the most valid markers of such intake (37). Some trace elements, too, like selenium bear antioxidative capacity after integration into proteins (selenoenzymes) where selenium constitutes the active centre. Zinc, another trace element, is involved in immune function and wound healing which are highly relevant attributes particularly at an advanced age (38). In some cases the physiological processes responsible for the protective effect of antioxidants is being uncovered. With regard to selenium, it was hypothesized that Il-6 takes the role of a mediator between selenium and muscle strength via the nuclear factor kappa-B (NF-κB). Thereby higher selenium levels lead to a decreased concentration in NF-κB which then results in a downregulation of IL-6, which has been shown to be related to muscle weakness and sarcopenia (42, 43). A similar pathway has been suggested for carotenoids (36). In other cases the pathways leading from micronutrient deficiencies to frailty and further on to disability and death are not yet fully explained.

Table 2 summarizes the available studies on micronutrient intake or micronutrient blood levels with

Table 2. Overview on studies on the association of micronutrients with frailty or related parameters

Original Study	Author, year	Examined micronutrients	Examined parameter (frailty, function, outcome)	Description
WHAS	Semba et al., 2009 (91)	Vitamin D	Mortality	Low levels of vitamin D are associated with an increased risk for all-cause mortality
WHAS	Alipanah et al., 2009 (92)	Carotenoids	Walking speed	Low serum carotenoids are associated with decline in walking speed
WHAS	Beck et al., 2007 (42)	Selenium	Hand-grip strength (HGS)	Low serum selenium levels associated with poor HGS
WHAS	Semba et al., 2007 (33)	Carotenoids	Walking speed	Low serum carotenoids predict walking disablility
WHAS	Michelon et al., 2006 (39)	Vitamin E, vitamin D, carotenoids, selenium, zinc	Frailty	Association between serum micronutrient levels and frailty
WHAS	Semba et al., 2006 (22)	Carotenoids, vitamin D, and others	Frailty	Low serum micronutrient levels associated with incresed frailty risk. Frailty risk increases with number of deficiencies.
WHAS	Bartali et al., 2006 (10)	Vitamins B6, vitamin B12, selenium	Disablility	Low serum micronutrient levels predictive for disability (defined by ADL function)
WHAS	Ray et al., 2006 (41)	Carotenoids, selenium	All-cause mortality	Low serum micronutrients predict mortality
CVHS#	Walston et al., 2002 (40)	Carotenoids, selenium	Il-6, mortality	Higher serum micronutrient levels associated with lower Il-6 levels and lower mortality
InCHIANTI	Shardell et al., 2009 (94)	Vitamin D	Frailty	Low vitamin D levels increase frailty risk in men, not women
InCHIANTI	Semba et al., 2009 (90)	Vitamin D	Mortality	Low serum levels of vitamin D are associated with an increased risk for all-cause mortality
InCHIANTI	Bartali et al, 2008 (45)	Vitamin E	Short physical performance battery (SPPB)	Low serum vitamin E levels associated with decline in SPPB functions
InCHIANTI	Lauretani et al., 2008 (47)	Carotenoids	Hip strength (HS), Knee-extension strength (KES), HGS	Low plasma carotenoids associated with decline in muscle strength
InCHIANTI	Lauretani et al., 2008 (37)	Carotenoids	Walking speed	Higher serum carotenoids associated with lower risk of developing walking disability
InCHIANTI	Lauretani et al., 2008 (48)	Carotenoids	Mortality	Low plasma carotenoids associated with increased mortality
InCHIANTI	Lauretani et al., 2007 (49)	Selenium	HGS, KES, HS	Low plasma selenium associated with muscle strength
InCHIANTI 2008 (50)	Lauretani et al.,	Selenium	Mortality	Low plasma selenium associated with increased mortality
InCHIANTI	Houston et al., 2007 (93)	Vitamin D	SPPB	Low vitamin D levels are associated with poor physical performance
InCHIANTI	Ble et al., 2006 (44)	Vitamin E	Frailty	Association between low plasma vitamin E levels and frailty
InCHIANTI	Cesari et al., 2004 (46)	Vitamin C, α-tocopherol, γ-tocopherol, β-carotene	KES, SPPB	Higher dietary micronutrient intake associated with higher KES and SPPB

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frailty, related physical parameters and outcome parameters such as mortality. Again, the majority of data comes from the WHAS and the InChianti study. Although the WHAS lacks data on men and some of the reported publications did not examine frailty *per se* but more or less isolated performance parameters or even disability, which may be regarded the state "beyond" frailty, these findings give a hint towards the impact of micronutrient deficiencies on physical well-being, functionality and even mortality in older people.

Other nutrition-related causes for frailty

From WHAS data it was shown that chewing and swallowing problems and use of dentures influence dietary intake and represented a risk factor for malnutrition, frailty and mortality (51). Denture users had significantly lower serum levels of carotenoids and vitamin D. Denture use was particularly high among frail study participants and an increased five-year mortality risk was observed for those denture users who complained about swallowing and chewing difficulties. Given the high prevalence of denture use among older people, the maintenance of masticatory function and oral health seems crucial to uphold the ability to adequate and satisfactory nutrition.

Conclusion

Inadequate nutritional intake is frequent among older people and related to increasing dependence and care needs. The association between poor nutritional intake and frailty was demonstrated in numerous recent studies. Not only have energy and protein intake been linked to frailty and frailty-related parameters. Particularly the role of micronutrients in the development of frailty has been highlighted in recent publications. Micronutrient intake has been found to be associated with frailty or related parameters of physical functioning, sometimes even independent from energy intake. In conclusion, macro- as well as micromalnutrition may be regarded as one of the key factors contributing to the development and aggravation of frailty. An increased perception of the role of micronutrients in this process may lead to further improvements in the quality of food eaten by older people - not just the quantity of food. In clinical practice and as part of the management of aging it should therefore be recommended to use a suitable tool for routine screening of nutritional risks. Consequently, the goal will be to raise the general dietary intake of high-quality food to provide sufficiently both macro- and micronutrients.

References

1. Lunenfeld B. An Aging World--demographics and challenges. *Gynecol Endocrinol* 2008; 24(1): 1-3.
2. Fried L, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol* 2001; 56(3): M146-156.
3. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173(5): 489-95.
4. Rockwood K, Abeysundera MJ, Mitnitski A. How should we grade frailty in nursing home patients? *J Am Med Dir Assoc* 2007; 8(9): 595-603.
5. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59(3): 255-63.
6. Kinney JM. Nutritional frailty, sarcopenia and falls in the elderly. *Curr Opin Clin Nutr Metab Care* 2004; 7(1): 15-20.
7. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007; 62(7): 731-7.
8. Abate M, Di Iorio A, Di Renzo D, Paganelli R, Saggini R, Abate G. Frailty in the elderly: the physical dimension. *Eura Medicophys* 2007; 43(3): 407-15.
9. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of Frailty in Middle-Aged and Older Community-Dwelling Europeans Living in 10 Countries. *J Gerontol A Biol Sci Med Sci* 2009; 64(6): 675-81.
10. Bartali B, Frongillo EA, Bandinelli S, et al. Low nutrient intake is an essential component of frailty in older persons. *J Gerontol A Biol Sci Med Sci* 2006; 61(6): 589-93.
11. Keller HH. Promoting food intake in older adults living in the community: a review. *Appl Physiol Nutr Metab* 2007; 32(6): 991-1000.
12. U.S. Department of Agriculture, Agricultural Research Service. 2005. What We Eat In America, NHANES 2001-2002: Usual nutrient intakes from food compared to dietary reference intakes. Available: http://www.ars.usda.gov/ba/bhnrc/fsrg.
13. Bartali B, Salvini S, Turrini A, et al. Age and disability affect dietary intake. *J Nutr* 2003; 133(9): 2868-73.
14. Gariballa SE, Forster SJ. Dietary intake of older patients in

hospital and at home: the validity of patient kept food diaries. *J Nutr Health Aging* 2008; 12(2): 102-6.
15. Grieger JA, Nowson CA. Nutrient intake and plate waste from an Australian residential care facility. *Eur J Clin Nutr* 2007; 61(5): 655-63.
16. Lengyel CO, Whiting SJ, Zello GA. Nutrient inadequacies among elderly residents of long-term care facilities. *Can J Diet Pract Res* 2008; 69(2): 82-8.
17. Kulnik D, Elmadfa I. Assessment of the nutritional situation of elderly nursing home residents in Vienna. *Ann Nutr Metab* 2008; 52 Suppl 1: 51-3.
18. Wikby K, Ek AC, Christensson L. Nutritional status in elderly people admitted to community residential homes: comparisons between two cohorts. *J Nutr Health Aging* 2006; 10(3): 232-8.
19. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, part I: History, examination, body composition, and screening tools. *Nutrition* 2000; 16(1): 50-63.
20. Patel MD, Martin FC. Why don't elderly hospital inpatients eat adequately? *J Nutr Health Aging* 2008; 12(4): 227-31.
21. Gaillard C, Alix E, Boirie Y, Berrut G, Ritz P. Are elderly hospitalized patients getting enough protein? *J Am Geriatr Soc* 2008; 56(6): 1045-9.
22. Semba RD, Bartali B, Zhou J, Blaum C, Ko CW, Fried LP. Low serum micronutrient concentrations predict frailty among older women living in the community. *J Gerontol A Biol Sci Med Sci* 2006; 61(6): 594-9.
23. Houston DK, Nicklas BJ, Ding J, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2008; 87(1): 150-5.
24. Bales CW, Ritchie CS. Sarcopenia, weight loss, and nutritional frailty in the elderly. *Annu Rev Nutr* 2002; 22: 309-23.
25. Visser M, Kritchevsky SB, Newman AB, et al. Lower serum albumin concentration and change in muscle mass: the Health, Aging and Body Composition Study. *Am J Clin Nutr* 2005; 82 (3): 531-7.
26. Kwon J, Suzuki T, Yoshida H, Kim H, Yoshida Y, Iwasa H. Concomitant lower serum albumin and vitamin D levels are associated with decreased objective physical performance among Japanese community-dwelling elderly. *Gerontology* 2007; 53(5): 322-8.
27. Campbell PM, Allain TJ. Muscle strength and vitamin D in older people. *Gerontology* 2006; 52(6): 335-8.
28. Bruyere O, Decock C, Delhez M, Collette J, Reginster JY. Highest prevalence of vitamin D inadequacy in institutionalized women compared with noninstitutionalized women: a case-control study. *Womens Health (Lond Engl)* 2009; 5(1): 49-54.
29. Hirani V, Primatesta P.Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population survey. *Age Ageing* 2005; 34(5): 485-91.
30. Schalk BW, Deeg DJ, Penninx BW, Bouter LM, Visser M. Serum albumin and muscle strength: a longitudinal study in older men and women. *J Am Geriatr Soc* 2005; 53(8): 1331-8.
31. Clarkson PM, Thompson HS. Antioxidants: what role do they play in physical activity and health? *Am J Clin Nutr* 2000; 72(2 Suppl): 637S-46S.
32. Mendoza-Núñez VM, Sánchez-Rodríguez MA, Retana-Ugalde R, Vargas-Guadarrama LA, Altamirano-Lozano MA. Total antioxidant levels, gender, and age as risk factors for DNA damage in lymphocytes of the elderly. *Mech Ageing Dev* 2001; 122(8): 835-47.
33. Mendoza-Núñez VM, Ruiz-Ramos M, Sánchez-Rodríguez MA, Retana-Ugalde R, Muñoz-Sánchez JL. Aging-related oxidative stress in healthy humans. *Tohoku J Exp Med* 2007; 213 (3): 261-8.
34. Semba RD, Ferrucci L, Sun K, et al. Oxidative stress and severe walking disability among older women. *Am J Med* 2007; 120 (12): 1084-9.
35. Semba RD, Ferrucci L, Sun K, et al. Oxidative stress is associated with greater mortality in older women living in the community. *J Am Geriatr Soc* 2007; 55(9): 1421-5.
36. Semba RD, Lauretani F, Ferrucci L. Carotenoids as protection against sarcopenia in older adults. *Arch Biochem Biophys* 2007; 458(2): 141-5.
37. Lauretani F, Semba RD, Bandinelli S, et al. Carotenoids as protection against disability in older persons. *Rejuvenation Res* 2008; 11(3): 557-63.
38. Mocchegiani E. Zinc and ageing: third Zincage conference. *Immun Ageing* 2007; 4: 5.
39. Michelon E, Blaum C, Semba RD, Xue QL, Ricks MO, Fried LP. Vitamin and carotenoid status in older women: associations with the frailty syndrome. *J Gerontol A Biol Sci Med Sci* 2006; 61(6): 600-7.
40. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med* 2002; 162(20): 2333-41.
41. Ray AL, Semba RD, Walston J, et al. Low serum selenium and total carotenoids predict mortality among older women living in the community: the women's health and aging studies. *J Nutr* 2006; 136(1): 172-6.
42. Beck J, Ferrucci L, Sun K, et al. Low serum selenium concentrations are associated with poor grip strength among older women living in the community. *Biofactors* 2007; 29(1): 37-44.
43. Payette H, Roubenoff R, Jacques PF, et al. Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. *J Am Geriatr Soc* 2003; 51(9): 1237-43.
44. Ble A, Cherubini A, Volpato S, et al. Lower plasma vitamin E levels are associated with the frailty syndrome: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2006; 61(3): 278-83.
45. Bartali B, Frongillo EA, Guralnik JM, et al. Serum micronutrient concentrations and decline in physical function among older persons. *JAMA* 2008; 299(3): 308-15.

46. Cesari M, Pahor M, Bartali B, Cet al. Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. *Am J Clin Nutr* 2004; 79(2): 289-94. Erratum in: *Am J Clin Nutr* 2004; 80(1): 238.
47. Lauretani F, Semba RD, Bandinelli S, et al. Low plasma carotenoids and skeletal muscle strength decline over 6 years. *J Gerontol A Biol Sci Med Sci* 2008; 63(4): 376-83.
48. Lauretani F, Semba RD, Dayhoff-Brannigan M, et al. Low total plasma carotenoids are independent predictors of mortality among older persons: the InCHIANTI study. *Eur J Nutr* 2008; 47(6): 335-40.
49. Lauretani F, Semba RD, Bandinelli S, Ray AL, Guralnik JM, Ferrucci L. Association of low plasma selenium concentrations with poor muscle strength in older community-dwelling adults: the InCHIANTI Study. *Am J Clin Nutr* 2007; 86(2): 347-52.
50. Lauretani F, Semba RD, Bandinelli S, et al. Low plasma selenium concentrations and mortality among older community-dwelling adults: the InCHIANTI Study. *Aging Clin Exp Res* 2008; 20(2): 153-8.
51. Semba RD, Blaum CS, Bartali B, et al. Denture use, malnutrition, frailty, and mortality among older women living in the community. *J Nutr Health Aging* 2006; 10(2): 161-7.
52. Ferrucci L, Cavazzini C, Corsi A, et al. Biomarkers of frailty in older persons. *J Endocrinol Invest* 2002; 25(10 Suppl): 10-5.
53. Volpato S, Onder G, Cavalieri M, et al. Characteristics of nondisabled older patients developing new disability associated with medical illnesses and hospitalization. *J Gen Intern Med* 2007; 22(5): 668-74.
54. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. *J Am Geriatr Soc* 2006; 54(11): 1674-81. Comment in: *J Am Geriatr Soc* 2007; 55(6): 967-8; author reply 968-9.
55. Morley JE, Kim MJ, Haren MT, Kevorkian R, Banks WA. Frailty and the aging male. *Aging Male* 2005; 8(3-4): 135-40.
56. Srinivas-Shankar U, Wu FC. Frailty and muscle function: role for testosterone? *Front Horm Res* 2009; 37: 133-49.
57. Cappola AR, Xue QL, Fried LP. Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging studies. *J Gerontol A Biol Sci Med Sci* 2009; 64(2): 243-8.
58. Maggio M, Cappola AR, Ceda GP, et al. The hormonal pathway to frailty in older men. *J Endocrinol Invest* 2005; 28(11 Suppl Proceedings): 15-9.
59. Ceda GP, Dall'Aglio E, Maggio M,et al. Clinical implications of the reduced activity of the GH-IGF-I axis in older men. *J Endocrinol Invest* 2005; 28(11 Suppl Proceedings): 96-100.
60. Abbatecola AM, Paolisso G. Is there a relationship between insulin resistance and frailty syndrome? *Curr Pharm Des* 2008; 14(4): 405-10.
61. Hsu FC, Kritchevsky SB, Liu Y, et al. Association between inflammatory components and physical function in the health, aging, and body composition study: a principal component analysis approach. *J Gerontol A Biol Sci Med Sci* 2009; 64(5): 581-9.
62. Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW. Nutrition, inflammation, and leptin levels in aging and frailty. *J Am Geriatr Soc* 2008; 56(2): 279-84.
63. Valenti G. Frailty as a dysruption of steroid "syncrinology" in elderly man. *Acta Biomed* 2007; 78 Suppl 1: 222-4.
64. Mohr BA, Bhasin S, Kupelian V, Araujo AB, O'Donnell AB, McKinlay JB. Testosterone, sex hormone-binding globulin, and frailty in older men. *J Am Geriatr Soc* 2007; 55(4): 548-55.
65. Barzilay JI, Blaum C, Moore T, et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med* 2007; 167(7): 635-41.
66. Shardell M, Hicks GE, Miller RR, et al. Association of low vitamin D levels with the frailty syndrome in men and women. *J Gerontol A Biol Sci Med Sci* 2009; 64 (1): 69-75.
67. Semba RD, Ferrucci L, Cappola AR, et al. Low Serum Selenium Is Associated with Anemia Among Older Women Living in the Community: the Women's Health and Aging Studies I and II. *Biol Trace Elem Res* 2006; 112 (2): 97-107.
68. Pramyothin P, Techasurungkul S, Lin J, et al. Vitamin D status and falls, frailty, and fractures among postmenopausal Japanese women living in Hawaii. *Osteoporos Int* 2009; 20 (11): 1955-62.
69. Peterson MJ, Giuliani C, Morey MC, et al. Physical activity as a preventative factor for frailty: the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci* 2009; 64(1): 61-8.
70. Villareal DT, Banks M, Sinacore DR, Siener C, Klein S. Effect of weight loss and exercise on frailty in obese older adults. *Arch Intern Med* 2006; 166(8): 860-6. Comment in: *Clin J Sport Med* 2007; 17(2): 172-3.
71. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc* 2005; 53(6): 927-34. Comment in: *J Am Geriatr Soc* 2005; 53(6): 1069-70.
72. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. *Obes Res* 2004; 12(6): 913-20.
73. Buchman AS, Schneider JA, Leurgans S, Bennett DA. Physical frailty in older persons is associated with Alzheimer disease pathology. *Neurology* 2008; 71(7): 499-504.
74. Ahmed NN, Sherman SJ, Vanwyck D. Frailty in Parkinson's disease and its clinical implications. *Parkinsonism Relat Disord* 2008; 14(4): 334-7.
75. Andrew MK, Rockwood K. Psychiatric illness in relation to frailty in community-dwelling elderly people without dementia: a report from the Canadian Study of Health and Aging. *Can J Aging* 2007; 26(1): 33-8.
76. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *J Am Geriatr Soc* 2007; 55(6): 864-71.
77. Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric

syndrome of frailty: a pilot study. *J Am Geriatr Soc* 2002; 50(7): 1268-71.
78. De Martinis M, Franceschi C, Monti D, Ginaldi L. Inflammation markers predicting frailty and mortality in the elderly. *Exp Mol Pathol* 2006; 80(3): 219-27.
79. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci* 2002; 57(5): M326-32.
80. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol (Oxf)* 2005; 63(4): 403-11.
81. Strandberg TE, Pitkälä KH. Frailty in elderly people. *Lancet* 2007; 369(9570): 1328-9. Erratum in: *Lancet* 2007; 369(9576): 1860.
82. Lally F, Crome P. Understanding frailty. *Postgrad Med J* 2007; 83(975): 16-20.
83. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis* 2004; 43(5): 861-7.
84. Nourhashémi F, Andrieu S, Gillette-Guyonnet S, Vellas B, Albarède JL, Grandjean H. Instrumental activities of daily living as a potential marker of frailty: a study of 7364 community-dwelling elderly women (the EPIDOS study). *J Gerontol A Biol Sci Med Sci* 2001; 56(7): M448-53.
85. Newman AB, Gottdiener JS, Mcburnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M158-66. Comment in: *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M134-5.
86. Alvarado BE, Zunzunegui MV, Béland F, Bamvita JM. Life course social and health conditions linked to frailty in Latin American older men and women. *J Gerontol A Biol Sci Med Sci* 2008; 63(12): 1399-406.
87. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, Rockwood K. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc* 2005; 53(12): 2184-9. Comment in: *J Am Geriatr Soc* 2005; 53(12): 2229-30.
88. Woo J, Goggins W, Sham A, Ho SC. Social determinants of frailty. *Gerontology* 2005; 51(6): 402-8.
89. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. *J Gerontol B Psychol Sci Soc Sci* 1998; 53(1): S9-16.
90. Semba RD, Houston DK, Bandinelli S, et al. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. *Eur J Clin Nutr* 2009.
91. Semba RD, Houston DK, Ferrucci L, et al. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. *Nutr Res* 2009; 29(8): 525-30.
92. Alipanah N, Varadhan R, Sun K, Ferrucci L, Fried LP, Semba RD. Low serum carotenoids are associated with a decline in walking speed in older women. *J Nutr Health Aging* 2009; 13(3): 170-5.
93. Houston DK, Cesari M, Ferrucci L, et al. Association between vitamin D status and physical performance: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2007; 62(4): 440-6.
94. Shardell M, Hicks GE, Miller RR, et al. Association of low vitamin D levels with the frailty syndrome in men and women. *J Gerontol A Biol Sci Med Sci* 2009; 64(1): 69-75.

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