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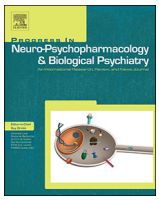

Nutrition and frailty: Current knowledge

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ABSTRACT

Purpose of the review: Nutrition, as part of lifestyle and modifiable environmental factors, constitutes an interesting approach for the prevention of geriatric syndromes. The objective of this review was to examine the most recent evidence on the association between nutrition, from dietary patterns to specific nutrients, and frailty, before the onset of disability, among elderly individuals.

Recent findings: Based on available epidemiological studies, three meta-analyses published in 2018 have outlined a protective effect of greater adherence to a Mediterranean-type diet (MeDi) on the risk for frailty, with up to a 60% reduction in risk. Several studies focusing on particular food groups, macronutrients and micronutrients have also been published and have highlighted that a protein intake of 1 g/kg in body weight per day should be fulfilled (except for patients suffering from kidney or hepatic dysfunction) and that vitamin deficiencies should be avoided. Available interventional studies of nutritional supplements and/or physical activity programs have mainly been limited to disabled participants to date.

Summary: Research efforts should target both developing a better understanding of the mechanisms underlying frailty and improving detection tools and the effectiveness of intervention studies, alongside efforts to address the specific needs of older people. For instance, ensuring an adequate nutritional status, by fighting the age-related increased prevalence of undernutrition or sarcopenic obesity, should be privileged.

1. Introduction

According to the World Health Organization, aging is a continuous process which results from interactions between genetic and environmental factors that alter the structure and function of the organism. Advancing age is accompanied by common geriatric syndromes that can coexist, such as falls and fractures, thinness, isolation, incontinence, sensory disorders, disability, and frailty (Tabue-Teguo et al., 2017a).

For the last two decades, frailty has become a particularly attractive concept because of its place in the continuum from robustness to age-related disability (Tabue-Teguo et al., 2017b). Frailty involves uncompensated adaptation to changes in the environment over time, and the frailty status is characterized by a depletion in the functional reserves of physiological systems. The French Society of Geriatrics and Gerontology defines frailty as “a clinical syndrome expressing a multisystemic reduction of physiological capacities limiting the adaptation to stress” (Rolland et al., 2011). The frail older adult is therefore unable to respond appropriately to situations of stress, from the cellular level to the societal level. The frail older adult thus has an unfavorable prognosis, i.e., is more at risk of adverse health events, disability, loss of autonomy and death (Tabue-Teguo et al., 2017b; Gill et al., 2010; Crow et al., 2018; Gonzalez-Colaco Harmand et al., 2017). However, from a public health point of view, this transitional state is particularly interesting, since it is potentially reversible and is accessible to preventive measures (Clegg et al., 2013; Gill et al., 2006; Santos-Eggimann and Sirven, 2016).

Today, the concept of frailty seems commonly accepted by most medical practitioners in addition to geriatricians, while its translation into clinical practice seems to still be limited due to the absence of a standardized operational definition. Similarly, the underlying pathophysiological processes that lead to frailty are still debated (Gonzalez-Colaco Harmand et al., 2017; Rodriguez-Manas et al., 2013; Aguayo et al., 2018). In the current scientific literature, two ways of thinking coexist; the first defines frailty as the accumulation of deficits, with a multidomain and cumulative approach to pathologies and dependencies (Mitnitski et al., 2002; Rockwood et al., 2005), while the second mainly considers frailty as an impairment of physical function resulting from a pathological process underlying various clinical manifestations (Fried et al., 2001). According to this latter hypothesis, pathologies are excluded from the definition, whereas the loss of lean mass with undernutrition, decreased muscle strength, and decreased metabolic and physical activity are components of a self-sustaining

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circle and are also fueled by adverse external environmental factors (Fried et al., 2001). This phenotype, as proposed by Fried et al., seems to be the most commonly used definition in the scientific literature to date. A third stream of thought has also emerged over several years and favors a multidimensional approach. Social, cognitive and psychosocial components, as well as factors associated with decreasing the elderly's physiological reserves, including nutritional factors, define different scores of frailty (Aguayo et al., 2018; Avila-Funes et al., 2009; Gobbens et al., 2010).

Frailty is therefore part of a multifactorial dynamic process in which the nutritional status appears as a key element in the assessment of frailty. Moreover, the main hypothesis of the present article is that nutrition should also be considered as a modifiable environmental factor which potentially could be associated with the prevention of the frailty status. The purpose of this article is to create a nonexhaustive inventory of the relationship between nutrition and frailty in the elderly, summarizing the work of observational studies up to the intervention trials already established.

2. Text of the review

2.1. Prevalence of frailty

The French “Haute Autorité de Santé” suggests identifying frailty in people over 70, free from serious illness, by tools that are complementary to standardized geriatric evaluation. Among the most commonly used tools is the Short Physical Performance Battery (SPPB), which is the sum of the scores on three criteria: balance test, walking speed and chair lift test. The walking speed alone, at the 0.8 m / s threshold, is also a relevant criterion and a marker of health status (Abellan van Kan et al., 2009; Studenski et al., 2011). Other scales derived from the frailty phenotype items of Fried et al. have been proposed, such as the “SOF (Study of Osteoporotic Fracture) criteria for frailty” (Ensrud et al., 2008), which combines chronic fatigue, chair lift and weight loss, or the “FRAIL scale”, which combines fatigue, resistance, ambulation, diseases and weight loss (Morley et al., 2012). The common feature of these numerous scales is their ability to predict the higher risk for adverse events in frail individuals (Aguayo et al., 2018).

Because of the lack of a standardized definition, prevalence data for frailty in the elderly community vary widely. From 2012, Collard et al. reported a prevalence in the order of 4 to 60%. Overall, the weighted prevalence of frailty in their analysis was 10.7%, based on 21 studies involving nearly 61,500 participants aged 65 and over, with an increased prevalence with age and among women, compared to men (Collard et al., 2012).

2.2. Nutritional status of frail elderly people

According to the definition of Fried et al., unintentional weight loss is a susceptibility criterion for frailty. Therefore, undernutrition is frequent among frail populations (Bollwein et al., 2013a; Lorenzo-Lopez et al., 2017). Although undernutrition and frailty are two distinct entities, according to the studies, up to 90% of malnourished elderly people are also more frequently frail (Bollwein et al., 2013a; Verlaan et al., 2017). Moreover, the recent concept of sarcopenic obesity should be introduce in this field (Batsis and Villareal, 2018). Indeed, although apparently in satisfying health due to overweight, elderly individuals are also likely to lose muscle mass and strength, a phenomenon called sarcopenia (Cruz-Jentoft et al., 2018). Few studies have been interested in the association between sarcopenic obesity and frailty. One cross-sectional analysis of the National Health and Nutrition Survey (NHANES) database reported that frail older adults exhibited higher adiposity (expressed as % of body fat) and greater average waist circumference than non-frail participants (Crow et al., 2019). There is to date a single longitudinal analysis on the CHAMP participants (100% Australian men, n = 1685, aged 77 years on average), which reported that low muscle mass and sarcopenic obesity were associated with a significantly doubled risk for frailty over a 5-y period (Hirani et al., 2017). Overall, these studies confirmed that an altered nutritional status, as evaluated by both undernutrition and over-nourishment, should be considered as helpful criteria for the identification of frail individuals. This hypothesis was already suggested by Buch et al. who reported that central obesity or diabetes can provide useful marker of frailty among obese young elderly (Buch et al., 2018).

2.3. Relationship between energy, macronutrients and frailty

Much of the literature concerns the contributions of total energy and macronutrients, especially proteins (Lorenzo-Lopez et al., 2017; Bonnefoy et al., 2015; Yannakoulia et al., 2017). It is noted in the majority of cross-sectional studies that frail participants have the lowest energy intakes (Lorenzo-Lopez et al., 2017; Bonnefoy et al., 2015; Yannakoulia et al., 2017); the threshold of 21 kcal / kg / d or less was significantly associated with a higher prevalence of frailty. Similarly, protein intake is inversely associated with frailty, except in one study where the distribution of daily protein intake, rather than the quantity itself, could explain this result (Bollwein et al., 2013b). Animal or vegetable protein sources are not essential in the relationship between protein intake and frailty (Kobayashi et al., 2013). This finding is particularly true in our cohort of seniors who responded to a thorough dietary survey (cohort 3-City) (Feart et al., 2007): a protein intake of nearly 1 g / kg / day was associated with a lower prevalence of frailty (odds ratio = 0.41, 95% confidence interval 0.19–0.89), and this was independent of total energy intake (set at 30 kcal / kg / d, alone not associated with frailty) (Rahi et al., 2016). Longitudinal studies confirm these results, showing that participants with the lowest protein intake are the most at risk of becoming frail over time (Artaza-Artabe et al., 2016; Beasley et al., 2010; Sandoval-Insausti et al., 2016).

2.4. Relationship between micronutrients and frailty

To date, several studies have focused on micronutrients in relation to frailty, with a particular interest in vitamin D. Older people often suffer from hypovitaminosis D; in 2000, in our 3-City cohort, we observed a nearly 60% level of moderate impairment (25 (OH) D = 25–50 nmol / L) and a 24% level of deficit (25 (OH) D = 12.5–25 nmol / L2) (Feart et al., 2017). Elderly frail participants also exhibited low circulating levels of vitamin D, which are themselves significantly associated with an increased risk of frailty among the robust (Artaza-Artabe et al., 2016). Two metabolic pathways are involved, namely, phosphocalcic metabolism, since vitamin D plays an essential role in bone mineralization, and muscle strength, since vitamin D binds its receptor in skeletal muscle cells to induce protein synthesis (Lorenzo-Lopez et al., 2017; Yannakoulia et al., 2017; Artaza-Artabe et al., 2016).

For other micronutrients, data from the Italian InCHIANTI cohort are among the most interesting: frail participants consume significantly less vitamin D, E, C and folate, regardless of energy consumption, than nonfrail participants (Bartali et al., 2006). Rates of vitamin E levels were also associated with an increased risk of frailty over time (Semba et al., 2006; Ble et al., 2006). These results were partly confirmed by other studies: the lowest levels of consumption or circulating biomarkers of carotenoids, such as β-carotene, lutein and zeaxanthin, vitamin A, vitamin E, and vitamin B6, were associated with a higher prevalence and an increased risk of frailty (Lorenzo-Lopez et al., 2017; Yannakoulia et al., 2017). Semba et al. suggested that the higher the number of nutritional deficits is, the higher the risk of frailty (Semba et al., 2006). In the Spanish Seniors-ENRICA cohort, also interested in the associations between micronutrient intakes and the frailty risk, an analysis of more than 1600 aged individuals reported that poor intake of several vitamins (B6, C, E and folates), and non-adherence to the

recommended dietary allowances for thiamine, niacin and vitamin B6 were all independently associated with the frailty risk over 3.5y (Balboa-Castillo et al., 2018). As with food consumption, we recently developed an original approach that consisted of building a pattern of circulating biomarkers of micronutrients. As part of the European project FRAILOMIC (study case-control design) (Erusalimsky et al., 2015), we pooled 4 cohorts (including InCHIANTI and 3-City) for which blood tests of α- and β-carotene, lycopene, cryptoxanthin, lutein and zeaxanthin, retinol, α- and γ-tocopherol and 25 (OH) D3 were assessed from 1324 participants. We identified 3 different nutrient patterns and observed that frail participants had significantly lower vitamin E and A levels (component 2), but there was no association between the patterns characterized by either the carotenoid levels (component 1) or by the vitamin D levels (component 3) and frailty (Pilleron et al., 2018). Even more surprisingly, no nutrient pattern was associated with the risk of frailty in this sample, suggesting that these patterns were only status markers and were not predictive of the risk of frailty (Pilleron et al., 2018). These results raise the question of the reverse causality bias that may have been observed in previous studies: the underlying frailty may have led to changes in eating behavior rather than the reverse. Nevertheless, to our knowledge, this original and unique study should be reproduced before forming a definitive conclusion about this relationship.

Recently, omega-3 fatty acids have gained interest regarding the preservation of muscle mass. We already observed that a higher circulating long-chain omega-3 fatty acid status (high in EPA and DHA) was associated with lower odds of exhibiting low gait speed among 3-City participants (Frison et al., 2017). Another longitudinal study confirmed that a higher intake of omega-3 fatty acids contributed to a lower risk of frailty development (Leon-Munoz et al., 2015). To our knowledge, no additional studies have assessed this association in a different context.

2.5. Relationship between food and frailty

With regard to food consumption and its relationship to frailty, studies are rare. Fruits and vegetables represent the food group that has attracted the most interest, including in our cohort. In collaboration with Spanish colleagues, we have studied the relationship between fruit and vegetable consumption and the risk of frailty in three European cohorts (Garcia-Esquinas et al., 2016). Among a sample of 2926 people aged 65 and over, followed for up to 2.5 years, the initial intake of at least 3 fruits per day was significantly associated with a 52% decrease in the risk of developing frailty, while a consumption of 2 servings of vegetables a day led to a 44% decrease in the risk of frailty. Combined, the daily consumption of 5 or more servings of fruits and vegetables was significantly associated with a nearly 70% reduction in the risk of frailty among elderly people in the community. These results suggested a beneficial effect of fruit and vegetable consumption on the short-term risk of frailty, even among people who were almost 70 years old on average (Garcia-Esquinas et al., 2016). Regarding other food groups, a recent Spanish study has also underlined a significant association between sugar consumption and a higher risk for frailty, but this finding was limited to sugars from processed foods (i.e., added sugars) and not naturally occurring sugar in food (Laclaustra et al., 2018). Overall, it is important to emphasize that participants with a high consumption of plant products are also people who, in general, have a healthier diet and lower added sugar intake, which is now encouraging researchers to take into account for all food intake within the context of dietary patterns.

2.6. Relationship between dietary patterns and frailty

There are several methods of developing dietary patterns: either we have a priori assumptions about the beneficial or deleterious effects of food groups on health, which allow us to build scores for each participant whether or not they conform with these hypotheses (i.e., Mediterranean diet, Diet Quality Index), or we apply multidimensional statistical techniques to observational data, thus allowing the identification of dietary patterns specific to the studied sample (i.e., prudent diet, Western diet). An advantage of these approaches by pattern is the ability to capture the potential interactions between microconstituents, whether they are synergistic, additive or antagonistic (Hu, 2002).

These methodologies have been developed in the field of frailty. Thus, the Mediterranean diet would also have beneficial effects applicable to frailty, in addition to the well-known benefits on cardiovascular health and longevity (Sofi et al., 2014; Psaltopoulou et al., 2013). Several studies, including some recently published studies, confirmed that greater adherence to a diet of Mediterranean-type food was associated with a lower odds/risk of frailty over time (Bollwein et al., 2013c; Talegawkar et al., 2012; Leon-Munoz et al., 2014; Milaneschi et al., 2010; Veronese et al., 2017; Ntanasi et al., 2018). Using data from the 3-City cohort, our analysis focused specifically on a representative sample of people aged 75 years and older, for whom a significant 68% decreased risk of developing frailty in the next 2 years was observed, suggesting that, even at advanced ages, this eating behavior could be beneficial (Rahi et al., 2018). We had already shown that following a Mediterranean-type diet was beneficial in terms of the risk of disability in the 3-City cohort; these last projects emphasized the importance of this dietary pattern in the phase that precedes this state of disability and suggested a long-term effect of the eating habits on health (Feart et al., 2011). Results from these studies on the Mediterranean diet and the risk of frailty were recently included in a meta-analysis, where participants who had the highest scores - with the strongest adherence to this dietary pattern - had a significantly decreased risk of frailty by 56%, signaling a major strength of association (Kojima et al., 2018). More recently, a report observed that the benefit of a higher adherence to a Mediterranean diet on preventing frailty was also obvious on at-risk older women from the Nurses' Health Study suffering from type-2 diabetes (Lopez-Garcia et al., 2018). In addition to eating a Mediterranean diet to fight frailty, adopting a Mediterranean lifestyle would be a deterrent to frailty (Voelker, 2018; Bach-Faig et al., 2011). Moreover, as chronic inflammation may play a role in frailty, an *a priori* dietary pattern marker of foods and nutrients intakes associated with inflammation has been built in the Seniors-ENRICA cohort. The authors observed that the highest adherence to the “dietary inflammatory index” was associated with a higher risk for frailty (and slow gait speed) among 1948 participants followed for up to 4 years (Laclaustra et al., 2019). To our knowledge, this is the single study interested in the inflammatory part of the usual diet in the field.

Using the alternative approach of dietary pattern creation, namely, techniques without a priori hypotheses, we observed that the elderly men of the cohort 3-City who were characterized by a high consumption of pasta and women who were characterized by a higher consumption of biscuits and snacking, had a 2-fold greater risk of frailty after 12 years of follow-up (Pilleron et al., 2017). By a similar approach, “cautious” or “traditional” profiles identified among Spanish or Dutch participants were also significantly associated with a lower risk of frailty 3.5 to 4 years later (Leon-Munoz et al., 2015; de Haas et al., 2017). Since these dietary patterns are derived from observational data, they are not strictly comparable in terms of foods that comprise them, and the accumulation of knowledge in other elderly populations is required before drawing definitive conclusions. As a proof, an *a posteriori* inflammatory dietary pattern identified among the Spanish older individuals enrolled in the Seniors-ENRICA study failed to be associated with the frailty risk, while the *a priori* pattern was, in part due to the lack of reproducibility of such *a posteriori* patterns to other populations than the original ones (Laclaustra et al., 2019).

2.7. Nutritional interventions to prevent or delay frailty

Intervention studies provide the best causal evidence in support of associations suggested by observational studies. In the case of

nutritional exposure, it is particularly difficult to set up pragmatic trials to modify dietary behavior, but not impossible (Estruch et al., 2013), and complementary approaches are often preferred. The prevention of frailty at the level of the elderly community includes conventional health prevention messages such as the promotion of physical activity, a healthy diet, the cessation of tobacco, an active social life, weight maintenance, and the control of vascular and metabolic risk factors, such as dyslipidemia, diabetes, and blood pressure (Sternberg et al., 2011). Multidomain interventions, including nutrition and physical activity, seem more relevant than the isolated nutritional approach, although nutrition alone can be considered as a multilevel approach through its potential benefits on several biological, clinical and social systems (Dedeyne et al., 2017).

Overall, frailty is still a field of research where nutritional interventions are rare: participants are more often already frail and benefit from interventions to slow down the process and the onset of disability (Yannakoulia et al., 2017; Cesari et al., 2014; Puts et al., 2017). Here, we described two main trials, but recent reviews will complete this noncomprehensive list (Yannakoulia et al., 2017; Kelaiditi et al., 2015; Kelaiditi et al., 2014; Hernandez Morante et al., 2019). From 2013, a first trial was set up with robust women aged 65 and over who received 1–2 g of long-chain omega 3 fatty acids (EPA and DHA) daily for 6 months (n = 85), while the control group received 1.8 g of oleic acid in the form of olive oil (n = 41). The results showed no effect on the prevalence of frailty as a whole after 6 months, although a slight improvement in walking speed was observed in the intervention group (Hutchins-Wiese et al., 2013). Another trial conducted in Singapore with 151 prefrail and frail women included nutritional supplementation, cognitive training, physical training or a combination of these treatments vs a nonintervention group, for 12 months (Ng et al., 2015). At the end of the intervention, the frailty status was reduced in all groups, including the control group, and was significantly lower in the intervention group than in the control group. This trial has therefore demonstrated the effectiveness of these interventions on the reversibility of frailty (Ng et al., 2015).

While still rare today, the first available RCTs are valuable since they contribute to the improvement of future study plans of nutritional interventions on frailty, whether or not they are coupled with other interventions, and add to the definition of the best strategies for caring for frail people. Thus, hopes are now resting on SPRINTT-type trials, where sarcopenia, defined by a reduction in both mass and muscle strength, is considered the physiological substratum of frailty, while being a separate entity according to the ESPEN (European Society for Clinical Nutrition and Metabolism) (Cruz-Jentoft et al., 2018; Cederholm et al., 2017; Landi et al., 2017). SPRINTT means “Sarcopenia and physical frailty in older people: multicomponent treatment strategies”: for 36 months, 1500 frail and sarcopenic elderly people will follow a multidomain program including structured physical activity programs, dietary counseling and intervention, and information and communication technology intervention vs a healthy aging education program in the control group. The goal is to demonstrate the effectiveness of this intervention on the prevention of disability, evaluated by the inability to walk 400 m in 15 min, without sitting, and without help. The results should help not only in informing better care for frail elderly people at high risk of disability but also in better defining preventive actions.

3. Conclusion

The growing interest in frailty in the scientific community lies in its impact on disability in our aging society. The identification of the frail individual depends primarily on the context, hence our current difficulties in making detection tools operational in a consensual manner. In terms of both diagnosis and prognosis, diet appears to be a major determinant in terms of frailty and its harmful consequences. Altered nutritional status and inadequate protein, energy or micronutrient intake are associated with an increased risk of frailty, while all studies converge to suggest that adopting a Mediterranean-style dietary pattern rich in fruit and vegetable sources of antioxidants would be an effective way to combat the emergence of frailty. However, no scientific evidence is available to date. Research must continue to help better identify frail elderly people by providing validated tools and by testing the effectiveness of prevention interventions. As we move forward in this direction, we will be able to help make dietary recommendations to prevent frailty and its consequences and to meet the specific needs of the aging population.

References

Abellan van Kan, G., Rolland, Y., Andrieu, S., Bauer, J., Beauchet, O., Bonnefoy, M., Cesari, M., Donini, L.M., Gillette Guyonnet, S., Inzitari, M., et al., 2009. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) task force. J. Nutr. Health Aging 13 (10), 881–889.

Aguayo, G.A., Vaillant, M.T., Donneau, A.F., Schritz, A., Stranges, S., Malisoux, L., Chioti, A., Guillaume, M., Muller, M., Witte, D.R., 2018. Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer, and total mortality in an elderly general population in England: an observational study. PLoS Med. 15 (3), e1002543.

Artaza-Artabe, I., Saez-Lopez, P., Sanchez-Hernandez, N., Fernandez-Gutierrez, N., Malafarina, V., 2016. The relationship between nutrition and frailty: effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. a systematic review. Maturitas 93, 89–99.

Avila-Funes, J.A., Amieva, H., Barberger-Gateau, P., Le Goff, M., Raoux, N., Ritchie, K., Carriere, I., Tavernier, B., Tzourio, C., Gutierrez-Robledo, L.M., et al., 2009. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. J. Am. Geriatr. Soc. 57 (3), 453–461.

Bach-Faig, A., Berry, E.M., Lairon, D., Reguant, J., Trichopoulou, A., Dernini, S., Medina, F.X., Battino, M., Belahsen, R., Miranda, G., et al., 2011. Mediterranean diet pyramid today. science and cultural updates. Public Health Nutr. 14 (12A), 2274–2284.

Balboa-Castillo, T., Struijk, E.A., Lopez-Garcia, E., Banegas, J.R., Rodriguez-Artalejo, F., Guallar-Castillon, P., 2018. Low vitamin intake is associated with risk of frailty in older adults. Age Ageing 47 (6), 872–879.

Bartali, B., Frongillo, E.A., Bandinelli, S., Lauretani, F., Semba, R.D., Fried, L.P., Ferrucci, L., 2006. Low nutrient intake is an essential component of frailty in older persons. J. of Gerontol. 61 (6), 589–593.

Batsis, J.A., Villareal, D.T., 2018. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat. Rev. Endocrinol. 14 (9), 513–537.

Beasley, J.M., LaCroix, A.Z., Neuhouser, M.L., Huang, Y., Tinker, L., Woods, N., Michael, Y., Curb, J.D., Prentice, R.L., 2010. Protein intake and incident frailty in the Women's Health Initiative observational study. J. Am. Geriatr. Soc. 58 (6), 1063–1071.

Ble, A., Cherubini, A., Volpato, S., Bartali, B., Walston, J.D., Windham, B.G., Bandinelli, S., Lauretani, F., Guralnik, J.M., Ferrucci, L., 2006. Lower plasma vitamin E levels are associated with the frailty syndrome: the InCHIANTI study. J. of Gerontol. 61 (3), 278–283.

Bollwein, J., Volkert, D., Diekmann, R., Kaiser, M.J., Uter, W., Vidal, K., Sieber, C.C., Bauer, J.M., 2013a. Nutritional status according to the mini nutritional assessment (MNA(R)) and frailty in community dwelling older persons: a close relationship. J. Nutr. Health Aging 17 (4), 351–356.

Bollwein, J., Diekmann, R., Kaiser, M.J., Bauer, J.M., Uter, W., Sieber, C.C., Volkert, D., 2013b. Distribution but not amount of protein intake is associated with frailty: a cross-sectional investigation in the region of Nurnberg. Nutr. J. 12, 109.

Bollwein, J., Diekmann, R., Kaiser, M.J., Bauer, J.M., Uter, W., Sieber, C.C., Volkert, D., 2013c. Dietary quality is related to frailty in community-dwelling older adults. J. of Gerontol. 68 (4), 483–489.

Bonnefoy, M., Berrut, G., Lesourd, B., Ferry, M., Gilbert, T., Guerin, O., Hanon, O., Jeandel, C., Paillaud, E., Raynaud-Simon, A., et al., 2015. Frailty and nutrition: searching for evidence. J. Nutr. Health Aging 19 (3), 250–257.

Buch, A., Keinan-Boker, L., Kis, O., Carmeli, E., Izkhakov, E., Ish-Shalom, M., Berner, Y., Shefer, G., Marcus, Y., Stern, N., 2018. Severe central obesity or diabetes can replace weight loss in the detection of frailty in obese younger elderly - a preliminary study. Clin. Interv. Aging 13, 1907–1918.

Cederholm, T., Barazzoni, R., Austin, P., Ballmer, P., Biolo, G., Bischoff, S.C., Compher, C., Correia, I., Higashiguchi, T., Holst, M., et al., 2017. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin. Nutr. 36 (1), 49–64.

Cesari, M., Demougeot, L., Boccalon, H., Guyonnet, S., Vellas, B., Andrieu, S., 2014. The Multidomain Intervention to preveNt disability in ElDers (MINDED) project: rationale and study design of a pilot study. Contemp Clin Trials 38 (1), 145–154.

Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. Lancet 381 (9868), 752–762.

Collard, R.M., Boter, H., Schoevers, R.A., Oude Voshaar, R.C., 2012. Prevalence of frailty in community-dwelling older persons: a systematic review. J. Am. Geriatr. Soc. 60 (8), 1487–1492.

Crow, R.S., Lohman, M.C., Titus, A.J., Bruce, M.L., Mackenzie, T.A., Bartels, S.J., Batsis, J.A., 2018. Mortality risk along the frailty spectrum: data from the National Health and Nutrition Examination Survey 1999 to 2004. J. Am. Geriatr. Soc. 66 (3), 496–502.

Crow, R.S., Lohman, M.C., Titus, A.J., Cook, S.B., Bruce, M.L., Mackenzie, T.A., Bartels,

S.J., Batsis, J.A., 2019. Association of Obesity and Frailty in Older Adults: NHANES 1999-2004. J. Nutr. Health Aging 23 (2), 138–144.
Cruz-Jentoft, A.J., Bahat, G., Bauer, J., Boirie, Y., Bruyere, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A.A., et al., 2018. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing (e-pub ahead of print).
de Haas, S.C.M., de Jonge, E.A.L., Voortman, T., Graaff, J.S., Franco, O.H., Ikram, M.A., Rivadeneira, F., Kiefte-de Jong, J.C., Schoufour, J.D., 2018 Oct. Dietary patterns and changes in frailty status: the Rotterdam study. Eur. J. Nutr. 57 (7), 2365–2375. https://doi.org/10.1007/s00394-017-1509-9.
Dedeyne, L., Deschodt, M., Verschueren, S., Tournoy, J., Gielen, E., 2017. Effects of multidomain interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic review. Clin. Interv. Aging 12, 873–896.
Ensrud, K.E., Ewing, S.K., Taylor, B.C., Fink, H.A., Cawthon, P.M., Stone, K.L., Hillier, T.A., Cauley, J.A., Hochberg, M.C., Rodondi, N., et al., 2008. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch. Intern. Med. 168 (4), 382–389.
Erusalimsky, J.D., Grillari, J., Grune, T., Jansen-Duerr, P., Lippi, G., Sinclair, A.J., Tegner, J., Vina, J., Durrance-Bagale, A., Minambres, R., et al., 2016. In search of 'omics'-based biomarkers to predict risk of frailty and its consequences in older individuals: The FRAILOMIC initiative. Gerontology 62 (2), 182–190. https://doi.org/10.1159/000435853.
Estruch, R., Ros, E., Salas-Salvado, J., Covas, M.I., Corella, D., Aros, F., Gomez-Gracia, E., Ruiz-Gutierrez, V., Fiol, M., Lapetra, J., et al., 2013. Primary prevention of cardiovascular disease with a Mediterranean diet. N. Engl. J. Med. 368 (14), 1279–1290.
Feart, C., Jutand, M.A., Larrieu, S., Letenneur, L., Delcourt, C., Combe, N., Barberger-Gateau, P., 2007. Energy, macronutrient and fatty acid intake of French elderly community dwellers and association with socio-demographic characteristics: data from the Bordeaux sample of the Three-City Study. Br. J. Nutr. 98, 1046–1057.
Feart, C., Peres, K., Samieri, C., Letenneur, L., Dartigues, J.F., Barberger-Gateau, P., 2011. Adherence to a Mediterranean diet and onset of disability in older persons. Eur. J. Epidemiol. 26 (9), 747–756.
Feart, C., Helmer, C., Merle, B., Herrmann, F.R., Annweiler, C., Dartigues, J.F., Delcourt, C., Samieri, C., 2017. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. Alzheimer's and Dementia 13 (11), 1207–1216.
Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., et al., 2001. Frailty in older adults: evidence for a phenotype. J. of Gerontol. 56 (3), M146–M156.
Frison, E., Boirie, Y., Peuchant, E., Tabue-Teguo, M., Barberger-Gateau, P., Féart, C., 2017. Plasma fatty acid biomarkers are associated with gait speed in community-dwelling older adults: the Three-City-Bordeaux study. Clin. Nutr. 36 (2), 416–422.
Garcia-Esquinas, E., Rahi, B., Peres, K., Colpo, M., Dartigues, J.F., Bandinelli, S., Feart, C., Rodriguez-Artalejo, F., 2016. Consumption of fruit and vegetables and risk of frailty: a dose-response analysis of 3 prospective cohorts of community-dwelling older adults. Am. J. Clin. Nutr. 104 (1), 132–142.
Gill, T.M., Gahbauer, E.A., Allore, H.G., Han, L., 2006. Transitions between frailty states among community-living older persons. Arch. Intern. Med. 166 (4), 418–423.
Gill, T.M., Gahbauer, E.A., Han, L., Allore, H.G., 2010. Trajectories of disability in the last year of life. N. Engl. J. Med. 362 (13), 1173–1180.
Gobbens, R.J., Luijkx, K.G., Wijnen-Sponselee, M.T., Schols, J.M., 2010. Towards an integral conceptual model of frailty. J. Nutr. Health Aging 14 (3), 175–181.
Gonzalez-Colaco Harmand, M., Meillon, C., Bergua, V., Tabue Teguo, M., Dartigues, J.F., Avila-Funes, J.A., Amieva, H., 2017. Comparing the predictive value of three definitions of frailty: Results from the Three-City study. Arch. Gerontol. Geriatr. 72, 153–163.
Hernandez Morante, J.J., Gomez Martinez, C., Morillas-Ruiz, J.M., 2019. Dietary factors associated with frailty in old adults: a review of nutritional interventions to prevent frailty development. Nutrients 11 (1).
Hirani, V., Naganathan, V., Blyth, F., Le Couteur, D.G., Seibel, M.J., Waite, L.M., Handelsman, D.J., Cumming, R.G., 2017. Longitudinal associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: the concord health and ageing in men project. Age Ageing 46 (3), 413–420.
Hu, F.B., 2002. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr. Opin. Lipidol. 13 (1), 3–9.
Hutchins-Wiese, H.L., Kleppinger, A., Annis, K., Liva, E., Lammi-Keefe, C.J., Durham, H.A., Kenny, A.M., 2013. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. J. Nutr. Health Aging 17 (1), 76–80.
Kelaiditi, E., van Kan, G.A., Cesari, M., 2014. Frailty: role of nutrition and exercise. Curr. opin. in clin. nutr. and metab care 17 (1), 32–39.
Kelaiditi, E., Guyonnet, S., Cesari, M., 2015. Is nutrition important to postpone frailty? Curr. opin. in clin. nutr. and metab care 18 (1), 37–42.
Kobayashi, S., Asakura, K., Suga, H., Sasaki, S., 2013. Three-generation study of women on D, Health Study G: high protein intake is associated with low prevalence of frailty among old Japanese women: a multicenter cross-sectional study. Nutr. J. 12, 164.
Kojima, G., Avgerinou, C., Iliffe, S., Walters, K., 2018. Adherence to Mediterranean Diet reduces incident frailty risk: systematic review and meta-analysis. J. Am. Geriatr. Soc. 66 (4), 783–788. https://doi.org/10.1111/jgs.15251.
Laclaustra, M., Rodriguez-Artalejo, F., Guallar-Castillon, P., Banegas, J.R., Graciani, A., Garcia-Esquinas, E., Ordovas, J., Lopez-Garcia, E., 2018. Prospective association between added sugars and frailty in older adults. Am. J. Clin. Nutr. 107 (5), 772–779.
Laclaustra, M., Rodriguez-Artalejo, F., Guallar-Castillon, P., Banegas, J.R., Graciani, A., Garcia-Esquinas, E., Lopez-Garcia, E., 2019 Jan 24. The inflammatory potential of diet is related to incident frailty and slow walking in older adults. Clin. Nutr. https://doi.org/10.1016/j.clnu.2019.01.013. pii: S0261-5614(19)30031-7 [Epub ahead of print].
Landi, F., Cesari, M., Calvani, R., Cherubini, A., Di Bari, M., Bejuit, R., Mshid, J., Andrieu, S., Sinclair, A.J., Sieber, C.C., et al., 2017. The "sarcopenia and physical frailty in older people: multi-componenT treatment strategies" (SPRINTT) randomized controlled trial: design and methods. Aging Clin. Exp. Res. 29 (1), 89–100.
Leon-Munoz, L.M., Guallar-Castillon, P., Lopez-Garcia, E., Rodriguez-Artalejo, F., 2014. Mediterranean diet and risk of frailty in community-dwelling older adults. J. Am. Med. Dir. Assoc. 15 (12), 899–903.
Leon-Munoz, L.M., Garcia-Esquinas, E., Lopez-Garcia, E., Banegas, J.R., Rodriguez-Artalejo, F., 2015. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC Med. 13, 11.
Lopez-Garcia, E., Hagan, K.A., Fung, T.T., Hu, F.B., Rodriguez-Artalejo, F., 2018. Mediterranean diet and risk of frailty syndrome among women with type 2 diabetes. Am. J. Clin. Nutr. 107 (5), 763–771.
Lorenzo-Lopez, L., Maseda, A., de Labra, C., Regueiro-Folgueira, L., Rodriguez-Villamil, J.L., Millan-Calenti, J.C., 2017. Nutritional determinants of frailty in older adults: a systematic review. BMC Geriatr. 17 (1), 108.
Milaneschi, Y., Bandinelli, S., Corsi, A.M., Lauretani, F., Paolisso, G., Dominguez, L.J., Semba, R.D., Tanaka, T., Abbatecola, A.M., Talegawkar, S.A., et al., 2011 Apr. Mediterranean diet and mobility decline in older persons. Exp. Gerontol. 46 (4), 303–308. https://doi.org/10.1016/j.exger.2010.11.030.
Mitnitski, A.B., Graham, J.E., Mogilner, A.J., Rockwood, K., 2002. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr. 2 (1).
Morley, J.E., Malmstrom, T.K., Miller, D.K., 2012. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J. Nutr. Health Aging 16 (7), 601–608.
Ng, T.P., Feng, L., Nyunt, M.S., Niti, M., Tan, B.Y., Chan, G., Khoo, S.A., Chan, S.M., Yap, P., Yap, K.B., 2015. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am. J. Med. 128 (11), 1225–1236 (e1221).
Ntanasi, E., Yannakoulia, M., Kosmidis, M.H., Anastasiou, C.A., Dardiotis, E., Hadjigeorgiou, G., Sakka, P., Scarmeas, N., 2018. Adherence to Mediterranean Diet and frailty. J. Am. Med. Dir. Assoc. 19 (4), 315–322 (e312).
Pilleron, S., Ajana, S., Jutand, M.A., Helmer, C., Dartigues, J.F., Samieri, C., Feart, C., 2017. Dietary patterns and 12-Year risk of frailty: results From the Three-City Bordeaux Study. J. Am. Med. Dir. Assoc. 18 (2), 169–175.
Pilleron, S., Weber, D., Peres, K., Colpo, M., Gomez-Cabrero, D., Stuetz, W., Dartigues, J.F., Ferrucci, L., Bandinelli, S., Garcia-Garcia, F.J., et al., 2019 Feb. Patterns of circulating fat-soluble vitamins and carotenoids and risk of frailty in four European cohorts of older adults. Eur. J. Nutr. 58 (1), 379–389. https://doi.org/10.1007/s00394-017-1602-0.
Psaltopoulou, T., Sergentanis, T.N., Panagiotakos, D.B., Sergentanis, I.N., Kosti, R., Scarmeas, N., 2013 Oct. Mediterranean diet and stroke, cognitive impairment, depression: a meta-analysis. Ann. Neurol. 74 (4), 580–591. https://doi.org/10.1002/ana.23944.
Puts, M.T.E., Toubasi, S., Andrew, M.K., Ashe, M.C., Ploeg, J., Atkinson, E., Ayala, A.P., Roy, A., Rodriguez Monforte, M., Bergman, H., et al., 2017. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. Age Ageing 46 (3), 383–392.
Rahi, B., Colombet, Z., Gonzalez-Colaco Harmand, M., Dartigues, J.F., Boirie, Y., Letenneur, L., Feart, C., 2016. Higher protein but not energy intake is associated with a lower prevalence of frailty among community-Dwelling Older Adults in the French Three-City Cohort. J. Am. Med. Dir. Assoc. 17 (7) 672 e677–672 e611.
Rahi, B., Ajana, S., Tabue-Teguo, M., Dartigues, J.F., Peres, K., Feart, C., 2018. High adherence to a Mediterranean diet and lower risk of frailty among French older adults community-dwellers: results from the Three-City-Bordeaux Study. Clin. Nutr. 37 (4), 1293–1298.
Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D.B., McDowell, I., Mitnitski, A., 2005. A global clinical measure of fitness and frailty in elderly people. CMAJ 173 (5), 489–495.
Rodriguez-Manas, L., Feart, C., Mann, G., Vina, J., Chatterji, S., Chodzko-Zajko, W., Gonzalez-Colaco Harmand, M., Bergman, H., Carcaillon, L., Nicholson, C., et al., 2013. Searching for an operational definition of frailty: a delphi method based consensus statement: the frailty operative definition-consensus conference project. J. of Gerontol. 68 (1), 62–67.
Rolland, Y., Benetos, A., Gentric, A., Ankri, J., Blanchard, F., Bonnefoy, M., de Decker, L., Ferry, M., Gonthier, R., Hanon, O., et al., 2011. Frailty in older population: a brief position paper from the French society of geriatrics and gerontology. Geriatr Psychol Neuropsychiatr Vieil 9 (4), 387–390.
Sandoval-Insausti, H., Perez-Tasigchana, R.F., Lopez-Garcia, E., Garcia-Esquinas, E., Rodriguez-Artalejo, F., Guallar-Castillon, P., 2016. Macronutrients intake and incident frailty in older adults: a prospective cohort study. J. of Gerontol. 71 (10), 1329–1334.
Santos-Eggimann, B., Sirven, N., 2016. Screening for frailty: older populations and older individuals. Public Health Rev. 37, 7.
Semba, R.D., Bartali, B., Zhou, J., Blaum, C., Ko, C.W., Fried, L.P., 2006. Low serum micronutrient concentrations predict frailty among older women living in the community. J. of Gerontol. 61 (6), 594–599.
Sofi, F., Macchi, C., Abbate, R., Gensini, G.F., Casini, A., 2014. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 17 (12), 2769–2782.
Sternberg, S.A., Wershof Schwartz, A., Karunananthan, S., Bergman, H., Mark Clarfield, A., 2011. The identification of frailty: a systematic literature review. J. Am. Geriatr. Soc. 59 (11), 2129–2138.
Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., Brach, J., Chandler, J., Cawthon, P., Connor, E.B., et al., 2011. Gait speed and survival in older

adults. Jama 305 (1), 50–58.
Tabue-Teguo, M., Grasset, L., Avila-Funes, J.A., Genuer, R., Proust-Lima, C., Péres, K., Féart, C., Amieva, H., Harmand, M.G.C., Helmer, C., et al., 2017a. Prevalence and Co-occurrence of geriatric syndromes in people aged 75 years and older in France: results from the Bordeaux Three-city Study. J. Gerontol. A Biol. Sci. Med. Sci. 73 (1), 109–116.
Tabue-Teguo, M., Simo, N., Harmand, M.G.C., Cesari, M., Avila-Funes, J.A., Féart, C., Amiéva, H., Dartigues, J.F., 2017b. Frailty in elderly: a brief review. Geriatr et Psychol. Neuropsychiatr du Vieillissement 15 (2), 127–137.
Talegawkar, S.A., Bandinelli, S., Bandeen-Roche, K., Chen, P., Milaneschi, Y., Tanaka, T., Semba, R.D., Guralnik, J.M., Ferrucci, L., 2012. A higher adherence to a Mediterranean-style diet is inversely associated with the development of frailty in community-dwelling elderly men and women. J. Nutr. 142 (12), 2161–2166.
Verlaan, S., Ligthart-Melis, G.C., Wijers, S.L.J., Cederholm, T., Maier, A.B., de van der Schueren, M.A.E., 2017. High prevalence of physical frailty among community-dwelling malnourished older adults-a systematic review and meta-analysis. J. Am. Med. Dir. Assoc. 18 (5), 374–382.
Veronese, N., Stubbs, B., Noale, M., Solmi, M., Rizzoli, R., Vaona, A., Demurtas, J., Crepaldi, G., Maggi, S., 2018 Oct. Adherence to a Mediterranean diet is associated with lower incidence of frailty: a longitudinal cohort study. Clin. Nutr. 37 (5), 1492–1497. https://doi.org/10.1016/j.clnu.2017.08.028.
Voelker, R., 2018. The mediterranean diet's fight against frailty. JAMA 319 (19), 1971–1972.
Yannakoulia, M., Ntanasi, E., Anastasiou, C.A., Scarmeas, N., 2017. Frailty and nutrition: from epidemiological and clinical evidence to potential mechanisms. Metabolism 68, 64–76.