Prevention of Late-life Cognitive Disorders: Diet-Related Factors, Dietary Patterns, and Frailty Models

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Abstract The need for preventing or postponing the onset of Alzheimer's disease (AD) and delaying or slowing its progression is a direct consequence of the current symptomatic approach of existing drugs for the treatment of AD. Dietary factors may affect the risk of AD and dementia, with a substantial body of evidence suggesting that certain diets have been associated with a lower incidence of AD and late-life cognitive disorders. Among healthy diets, higher adherence to a Mediterranean-type diet and to the Dietary Approaches to Stop Hypertension diet was associated with decreased cognitive decline, although the Mediterranean diet (MeDi) combines several foods, micro-, and macronutrients already separately proposed as potential protective factors against dementia. Higher adherence to the MeDi was associated with a reduced risk of cognitive impairment, MCI, and AD, as well as the transition from MCI to AD, and decreased all-causes mortality in AD patients. Influencing some age-related conditions, such as frailty, may have an impact on the prevention of late-life cognitive decline. Frailty reflects a nonspecific state of vulnerability and a multisystem physiological change and it is a widely recognized risk factor for adverse health outcomes in older persons. At present, no operational definition has been

established, although nutritional status, cognition, and mood have been proposed as markers of frailty. Physical frailty may be associated with late-life cognitive impairment/decline, incidence of AD, vascular dementia, non-AD dementias, and AD pathology in older persons with and without dementia, also suggesting the definition of cognitive frailty as a new clinical condition. The reviewed evidence supports the hypothesis that frailty could be important in the prevention of late-life cognitive disorders, and nutritional influences may be of major relevance. Nutritional interventions might be able to address the impaired nutrition and weight loss of frailty. There is a critical need for randomized, controlled trials investigating the role of nutrition on late-life cognitive disorders and frailty that might open new routes for the prevention and management of cognitive decline and AD, supplementing existing symptomatic approaches, also through the nutritional prevention of frailty.

Keywords Diet · Alzheimer's disease · Dementia · MCI · Dietary patterns · Frailty · Nutrition · Cognitive frailty

Introduction

The greatest known risk factor for Alzheimer's disease (AD) is advancing age and, due to aging populations, dementia and late-life cognitive disorders are reaching epidemic proportions [1]. The causes of AD and dementia syndromes are, at present, unclear, but some studies have suggested that they may be prevented [2–7]. In a general rethinking of the field, the 2011 criteria developed by National Institute on Aging and the Alzheimer's Association proposed three stages of AD, i.e., preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD [8–10], different from the stages currently used to describe AD, also suggesting that the disease begins before the development of symptoms and that new

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diagnostic procedures may have the potential to identify brain changes that precede the development of symptoms [10]. In fact, recent studies on familial [11] and sporadic AD [12•] showed a prolonged preclinical phase of more than two decades before the onset of dementia in which β -amyloid ($A\beta$) deposition is slow and protracted, so confirming the new proposed diagnostic procedures [8–10], and suggesting prevention trials in asymptomatic genetic forms of AD and in cognitively normal individuals suspected to be at an asymptomatic stage of sporadic AD. However, these amyloid-based prevention trials started only at the end of 2013 [13], and lowering the burden of $A\beta$ with a strategy against the production and the accumulation of this peptide have represented a large portion of the many therapeutic approaches currently under development for the treatment of AD [14, 15]. However, drugs currently used for the treatment of AD produce limited clinical benefits, partially stabilizing patients' symptoms, without disease-modifying potential. Therefore, at present, the management of potential risk factors is believed to be the most effective means of preventing dementia, AD, and MCI.

Growing epidemiological evidence supported the hypothesis that modifiable vascular, metabolic, and lifestyle-related factors were associated with the development of cognitive disorders in late life, opening new routes for the prevention and management of these syndromes [2, 5–7]. Currently, one of the most intriguing and appealing links hypothesized in recent years is the association between lifestyle factors, such as diet and dietary habits, and the occurrence of AD [16–18]. If advancing age is the driving risk factor for AD, some age-related conditions may be strictly linked to dementia and late-life cognitive disorders. Among these conditions, frailty is a multidimensional geriatric syndrome reflecting a nonspecific state of vulnerability and a multisystem physiological change [19]. Frailty also has been associated with an increased risk of adverse health-related outcomes in older persons, including falls, disability, hospitalizations, and mortality [19, 20]. Genetic, epigenetic, and environmental factors, such as nutrition and physical activity, are strongly related to frailty [21•, 22•]. However, not only physical but also psychological, cognitive, and social factors contribute to this multidimensional syndrome and need to be taken into account in its definition and treatment. Cognition already has been considered as a component of frailty [23], and it has been demonstrated that it is associated with adverse health outcomes [24, 25]. Therefore, the prevention of frailty is important in preventing cognitive-related adverse health outcomes, including delirium [26] and late-life cognitive disorders [27]. In this narrative review article, we examined the possible role of macronutrients, food nutrients, dietary patterns, and different frailty models in modulating the risk of AD, dementia, and late-life cognitive disorders, with a focus on the role of nutrition on frailty, in an attempt to explain some underlying mechanisms of the

proposed associations between diet-related factors and cognition in older age.

Diet-Related Factors, Dietary Patterns, and Late-Life Cognitive Disorders

Micro-, Macronutrients, Foods, and Food Groups and Cognition

Deficiencies of some micronutrients (especially, vitamins B1, B2, B6, B12, C, and folate) have been described quite frequently in older people and found to be significantly associated with cognitive impairment [17]. In fact, for example, there is a large body of evidence that maintaining healthy vitamin C levels can have a protective function against AD, but avoiding vitamin C deficiency is likely to be more beneficial than taking supplements [28]. In observational studies and in preclinical models of AD, dietary supplementation of antioxidants [29], B vitamins [30], and polyphenols [31] appeared to be beneficial for AD [32, 33], although many of the results from randomized, controlled trials are contradictory to that of epidemiological and animal studies [34, 35]. Furthermore, a recent population-based study, the Québec Longitudinal Study on Nutrition and Successful Aging, found that low levels of phyloquinone (vitamin K) were related to poor verbal episodic memory performance in older individuals free of cognitive impairment [36].

However, while the impact of micronutrients in cognitive decline has been extensively investigated, few data were available on the role of macronutrient intakes and single foods or food groups in the pathogenesis of age-related cognitive decline and dementia syndromes [5, 17, 18, 33, 37, 38]. Elevated saturated fatty acids could have negative effects on age-related cognitive decline and MCI [39]. Furthermore, at present, epidemiological evidence suggested a possible association among fish consumption, monounsaturated fatty acids (MUFA) [40, 41], and polyunsaturated fatty acids (PUFA) (particularly, n-3 PUFA) and reduced risk of cognitive decline, AD, and dementia [39, 42, 43]. Data from randomized, controlled trials (RCTs) showed that supplementation with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) compared with placebo did not slow the rate of cognitive decline and functional decline [44–46]. However, in the PREDIMED-NAVARRA, a RCT with a follow-up of 6.5 years in older persons, the group supplemented with an extra-virgin olive oil supplement, very rich in MUFA content, had better cognitive performance, and was less likely to become demented [47••]. The contradictory results between observational studies and RCTs might be due to the duration of RCTs, often not long enough. Therefore, based on the current evidences from human and animal studies, it is not possible to make definitive dietary recommendations in relation to the AD risk

on fish consumption and the lower intake of saturated fat from meat and dairy products [39, 48] as well as on unsaturated consumption or lower intake of saturated fat in relation to the risk for dementia and cognitive decline. However, a high consumption of fats from fish, vegetable oils, vegetables, and nuts should be encouraged because this dietary advice is in accordance with recommendations for lowering the risk of cardiovascular disease, obesity, diabetes, and hypertension [39, 48].

Among macronutrient intakes, single foods, and food groups, poorer cognitive function [49•], and an increased risk for vascular dementia (VaD) [50] were found to be associated with a lower consumption of milk or dairy products. However, the consumption of whole-fat dairy products may be associated with cognitive decline in the elderly [5]. The limited available literature supported the concept that high dairy consumption may be associated with a lower likelihood of cognitive impairment; however, high intakes of full-fat dairy and/or dairy fats may be associated with declines in cognitive performance [49•, 51]. Dairy may reduce the risk for cognitive impairment by modifying vascular factors linked to detrimental brain changes, particularly via weight reduction [5]. Multiple mechanisms associated with diabetes-related glucose and insulin dysregulation can lead to vascular and neuronal damage [6]. During the past two decades, multiple studies have examined the possible association of diabetes mellitus and different forms of dementia and cognitive impairment [52]. Therefore, a diet high in carbohydrates may be detrimental to AD [53, 54]. However, glycemic load reflexing carbohydrate content in food was not associated with a higher risk of AD [55], not supporting low carbohydrate diets for the prevention of AD in older age. No reliable data from RCTs on a diet high in carbohydrate and AD were available [32]. The limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supported a protective role of these macronutrients against cognitive decline, dementia, and AD [5]. However, a very recent meta-analysis on six studies analyzed fruit and vegetables separately and five of them found that higher consumption of vegetables, but not fruit, was associated with a decreased risk of dementia or cognitive decline in older age [56].

Among diet-associated factors, some case-control and cross-sectional and longitudinal population-based studies evaluated the long-term effects on brain function and provided some evidence that coffee, tea, and caffeine consumption or higher plasma caffeine levels may be protective against cognitive impairment and dementia [57, 58, 59•]. In particular, several cross-sectional and longitudinal population-based studies suggested a protective effect of coffee, tea, and caffeine use against cognitive impairment/decline, although the association was not found in all cognitive domains investigated and there was a lack of a distinct dose-response association, with a stronger effect among women than men [59•].

Furthermore, for dementia and AD prevention, some studies with baseline examination in midlife pointed to a lack of association, although other case-control and longitudinal population-based studies with briefer follow-up periods supported favourable effects of coffee, tea, and caffeine consumption against AD [57, 58]. Finally, light-to-moderate alcohol use may be associated with a reduced risk of incident dementia and AD, whereas for VaD, cognitive decline, and predementia syndromes the current evidence is only suggestive of a protective effect [60]. Indeed, the body of epidemiological evidence of all research published within the past 10 years suggested that light-to-moderate alcohol use may be associated with a reduced risk of unspecified incident dementia and AD, whereas for VaD, cognitive decline, and predementia syndromes, the current evidence is only suggestive of a protective effect [61–63]. Protective effects of moderate alcohol consumption against cognitive decline are suggested to be more likely in the absence of the AD-associated apolipoprotein E (APOE) $\epsilon 4$ allele and where wine is the beverage [60]. At present, there is no indication that light-to-moderate alcohol drinking would be harmful to cognition and dementia, and attempts to define what might be deemed beneficial levels of alcohol intake in terms of cognitive performance would be highly problematic and contentious [60].

Dietary Patterns and Late-Life Cognitive Decline

Dietary factors may affect the risk of cardiovascular disease, also influencing the risk of AD and dementia [40, 64], with a substantial body of evidence suggesting that certain diets have been associated with a lower incidence of AD and late-life cognitive disorders [65–67, 68•, 69, 70, 71•, 72•, 73]. Single-nutrient analyses ignored the complexity of the diet, and defining dietary exposures as a dietary pattern, a combination of food components that summarizes an overall diet for a study population, may better predict disease risk [74].

Compared with traditional single-food or nutrient methods, the whole-diet or dietary pattern approach is appealing for several reasons. Indeed, the analyses of single nutrients ignore important interactions (additive, synergistic, or antagonist effects) between components of diet and more importantly people did not eat isolated nutrients [5]. Among different dietary patterns, in a recent Japanese population-based study, higher adherence to a dietary pattern characterized by a high intake of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice was associated with reduced risk of dementia [71•]. These findings suggested that a traditional Japanese diet characterized by increased intake of fish and plant foods (soybean products, seaweeds, vegetables, and fruits) and decreased intake of refined carbohydrates and animal fats (meat) may be protective against dementia. On the contrary, a high-fat Western diet characterized by higher intake of red and processed meats,

refined grains, sweets, and desserts may contribute to the development of AD with increased A β deposition and oxidative stress [75, 76]. Although epidemiological findings from studies exploring Western diet and the risk of AD were not available [32], a dietary pattern similar to that of Western diet and characterized by a high intake of meat, butter, high-fat dairy products, eggs, and refined sugar has been found in AD patients in a small study [77]. Another study also have examined a posteriori-extracted dietary patterns in relation to AD, with a dietary pattern strongly associated with lower AD risk and characterized by higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and a lower intake of high-fat dairy products, red meat, organ meat, and butter [78]. Two other studies have focused on the cross-sectional link between cognitive function and “healthy” dietary patterns extracted by cluster analysis [65, 79]. In fact, a healthy diet, characterized by higher consumption of fish by men and fruits and vegetables by women, was also reported to be associated with better cognitive performance [65]. In another population-based study, higher intake of “whole food” diet (rich in fruit, vegetables, dried legume, and fish) was associated with lower and high consumption of “processed food” (rich in processed meat, chocolates, sweet desserts, fried food, refined cereals, and high-fat dairy products) with higher odds of cognitive deficit [79]. Furthermore, two population-based studies used middle-age dietary exposure assessment, which is critical when focusing on diseases requiring several decades to develop [67, 69]. In a first study on 525 subjects, persons with a high adherence to healthy diet in mid-life, with healthy diet index >8 points (an index constructed to assess healthy and unhealthy diet components), had a decreased risk of AD after a 14-year follow-up [67]. Finally, in the Supplementation en Vitamines et Minéraux Antioxydant, 1994–2002 (SU.VI.MAX) study, in a cohort of 3,054 participants, adherence to a healthy dietary pattern in mid-life (consumption of fruit, whole grains, fresh dairy products, vegetables, breakfast cereal, tea, vegetable fat, nuts, and fish) was positively associated with better cognitive functioning, independently of other health behavior factors [69].

Therefore, maintaining a healthy diet may have an impact on many possible risk factors for cognitive decline, and the models to follow seem to be the Mediterranean diet (MeDi) and the Dietary Approaches to Stop Hypertension (DASH) diet [68, 70, 72, 73]. In particular, the DASH diet, a recommended dietary plan for all Americans, especially those with hypertension [80, 81], contains a high intake of plant foods, fruits, vegetables, fish, poultry, whole grains, low-fat dairy products, and nuts, while minimizing intake of red meat, sodium, sweets, and sugar-sweetened beverages. In a RCT on 124 participants with elevated blood pressure, subjects on the DASH diet or with DASH dietary modification plus weight loss exhibited greater cognitive improvements

compared with control subjects [82]. In the population-based Cache County Memory Study (CCMS), the DASH score was one of six behaviors assessed in relation to incident dementia or AD, with dietary behaviors in conjunction with others associated to a decreased risk of incident dementia in a 6-year follow-up [83]. In another analysis from the CCMS, a significant reduction in rates of global cognitive decline was observed with higher levels of accordance with both the DASH and Mediterranean-style dietary patterns in older men and women during an 11-year period [84]. The Mediterranean-style diet is characterized by abundant plant foods consumption in the form of fruits, vegetables, breads, other forms of cereals, potatoes, beans, nuts and seeds; fresh fruit as the typical dessert; olive oil as the main source of MUFA; dairy products as principally cheese and yogurt; a low-to-moderate consumption of fish; a low-to moderate consumption of poultry; fewer than four eggs consumed per week; low amount of red meat and wine consumed in low-to-moderate amounts, normally during meals [50]. Adherence to a Mediterranean-type diet could be associated with slower cognitive decline, reduced risk of progression from MCI to AD, reduced risk of AD, and decreased mortality in AD patients, with some notable exceptions [5, 72, 85]. Some very recent systematic reviews and meta-analyses found that a higher adherence to the MeDi was associated with a reduced risk of cognitive impairment, MCI, and AD, as well as the transition from MCI to AD [68, 86, 87]. Two RCTs are available on this topic [88, 89]; one found inconsistent results although with an inordinately short follow-up of only 10 days [88], whereas the PREDIMED-NAVARRA suggested that nutritional intervention with MeDi supplemented with either extra-virgin olive oil or mixed nuts was associated with improved global cognition in a 6.5-year follow-up, independently of potential confounders [89]. This evidence is confirmed by a specific nutrient/food model based of the MeDi in which elevated dietary MUFA, n-3 PUFA, and high fish consumption, alongside high levels of antioxidants from fruit and vegetables, and moderate alcohol consumption may have a beneficial effect on the risk of dementia [73].

Cognitive Frailty: Epidemiological Evidence of a New Clinical Condition

Operational Definitions of Frailty and Proposed Models

Among potentially modifiable risk factors, the impact of several operational definitions of frailty [19, 24, 25] (Table 1) on late-life cognitive decline and dementia has been the subject of recent interest [27, 90]. Epidemiological and clinical studies focused their attention on an increasingly important concept in both clinical care of older persons and research in aging, i.e., frailty, a biological syndrome of decreased ability

Table 1 Principal studies on the association of different operational definitions of frailty or frailty instruments with late-life cognitive decline, mild cognitive impairment (MCI), dementia, Alzheimer's disease (AD), vascular dementia (VaD), and other different cognitive outcomes

Reference	Study design and sample	Frailty and cognitive assessment	Principal results
Gill et al., 1996 [135]	Population-based, longitudinal study; 945 respondents from the Project Safety cohort, aged 72 years and older	A composite measure of physical performance, ADL, and MMSE	The risk of dependence increased with worsening performance on both objective measures of physical skills and standardized assessment of cognitive status. Impairments in physical performance and cognitive status were shown to contribute independently to the risk of functional dependence, even after controlling for potential confounders
Strawbridge et al., 1998 [136]	Population-based, longitudinal study; 574 Alameda County Study respondents, aged 65–102 years	1994 Frailty Measure with four items assessing cognitive functioning	Frail persons reported reduced activities, poorer cognitive function, and lower life satisfaction. Cumulative predictors over the previous three decades included heavy drinking, cigarette smoking, physical inactivity, depression, social isolation, fair or poor perceived health, prevalence of chronic symptoms, and prevalence of chronic conditions
Fried et al., 2001 [19]	Population-based, longitudinal study; 5,745 older individuals from the CHS, aged 65 years and older	CHS frailty phenotype and MMSE	Lower cognition was associated with the frailty physical phenotype (despite exclusion of those with MMSE < 18)
Rockwood et al., 2004 [24]	Population-based, longitudinal study; 9,008 older individuals from the CSHA aged 65 years and older	The operational and rules-based definition of frailty of the CSHA was based on the GSS, a scale combining aspects of cognitive and functional performance to describe various degrees of frailty; cognitive functions were also measured with the 3MS	Among those participants described as mildly frail, 71.3 % had functional impairment alone, 14.4 % had cognitive impairment alone, and 14.3 % had both. For those who were moderately or severely frail, coincident functional and cognitive impairments were more common, occurring in 28.1 %
Ottensbacher et al., 2005 [134]	Population-based, longitudinal study (1 year); 621 Mexican American men and women aged 70 and older from the H-EPESE	MMSE and physical frailty phenotype operationalized slightly modifying the CHS criteria based on four frailty components and excluding physical activity	The baseline MMSE total score was significantly predictive of frailty at 1-year follow-up in men, but not in women
Rockwood et al., 2005 [25]	Population-based, longitudinal study; 2,305 older individuals from the CSHA aged 65 years and older	CSHA Clinical Frailty Scale and 3MS	Participants with higher scores on the CSHA Clinical Frailty Scale were more likely to be cognitively than those with lower scores. This frailty instrument performed better than measures of cognition, function or comorbidity in assessing risk for death
Rockwood et al., 2007 [114]	Population-based, longitudinal study; 728 institutionalized older adults in the second clinical examination cohort of the CSHA aged 65 years and older	CSHA Frailty Index, CSHA Clinical Frailty Scale, CHS phenotype, and 3MS	All three frailty measures were significantly associated with an increased risk of mortality, disability and cognitive decline, measured with the modified 3MS. When pairs of frailty measures were included in the models, only the CSHA Frailty Index was associated with a higher risk of mortality and decline in the 3MS
Buchman et al., 2007 [137]	Population-based, longitudinal study (3 years); 823 older persons (mean age: 80.4 years) without dementia who participated in the Rush Memory and Aging Project	Physical frailty phenotype operationalized slightly modifying the CHS criteria and based on four frailty components. Diagnoses of AD and DLB were made according to the NINCDS-ADRDA and the Report of the Consortium on DLB International Workshop. The MMSE was used to describe the cohort, while scores on other 19 neuropsychological tests were used to create a composite	Both baseline level of frailty and annual rate of change in frailty were associated with an increased risk of incident AD. Furthermore, the level of frailty and rate of change in frailty were also associated with the rate of cognitive decline

Table 1 (continued)

Reference	Study design and sample	Frailty and cognitive assessment	Principal results
Buchman et al., 2008 [145]	Population-based, longitudinal study; brain autopsies from 165 deceased participants from the Rush Memory and Aging Project	measure of global cognitive function. The CIM was used for diagnostic classification purposes only Physical frailty phenotype operationalized slightly modifying the CHS criteria and based on four frailty components. Diagnoses of AD and DLB were made according to the NINCDS-ADRDA and the Report of the Consortium on DLB International Workshop criteria. Neuropathological measures of AD pathology, Lewy bodies, and cerebral infarcts were also obtained	Physical frailty proximate to death was related to level of AD pathology on postmortem examination but was not related to the presence of cerebral infarcts or LBD. This association was similar in persons with and without dementia
Samper-Tement et al., 2008 [138]	Population-based, longitudinal study (10 years); 1,370 noninstitutionalized Mexican American men and women aged 65 years and older from the H-EPESE with a MMSE ≥ 21 at baseline	Physical frailty phenotype operationalized slightly modifying the CHS criteria based on four frailty components and excluding physical activity and MMSE	A statistically significant association between frailty and subsequent decline in cognitive function over a 10-year period was found in older Mexican Americans
Sarkisian et al., 2008 [140]	Population-based, longitudinal study; 1,118 high-functioning subjects aged 70–79 years from the MacArthur Study of Successful Aging	Physical frailty phenotype operationalized slightly modifying the CHS criteria. Cognitive function was assessed using reliable tests of language, executive function, spatial ability, and verbal and nonverbal memory	Two subdimensions of frailty were identified, and cognitive impairment was part of a frailty subdimension, including slower gait, weaker grip, and lower physical activity, further increasing evidence that physical performance tests are sensitive indicators of cognitive impairment, and further supporting the hypothesis that cognitive impairment may be intrinsic to frailty
Pilotto et al., 2009 [119]	Hospital-based, longitudinal study; 262 patients aged 65 years and older with a diagnosis of dementia	The CGA-based MPI and diagnosis of dementia according to the DSM-IV, NINCDS-ADRDA, and NINDS-AIREN criteria	The MPI accurately stratified hospitalized elderly patients with dementia into groups at varying risk of short- and long-term all-cause mortality
Avila-Funes et al., 2009 [23]	Population-based, cross-sectional and longitudinal study (4 years); 6,030 older individuals aged 65–85 years from the Three-City Study	Physical frailty phenotype operationalized slightly modifying the CHS criteria, MMSE, and IST. Diagnosis of dementia according to the DSM-IV criteria	Frail individuals with cognitive impairment have a higher risk of IADL and ADL disability and of incident hospitalization and dementia than subjects with none of these conditions, even after adjusting for potentially confounding variables
Boyle et al., 2010 [139]	Population-based, longitudinal study (12 years); 761 older persons (mean age: 79 years) without cognitive impairment at baseline who participated in the Rush Memory and Aging Project	Physical frailty phenotype operationalized slightly modifying the CHS criteria and based on four frailty components. Diagnoses of AD and MCI were made according to the NINCDS-ADRDA criteria and CSHA clinical criteria. The MMSE was used to describe the cohort, while scores on other 19 neuropsychological tests were used to create a composite measure of global cognitive function. The CIM was used for diagnostic classification purposes only	Higher level of physical frailty predicted the development of MCI and is associated with an accelerated rate of cognitive decline in older persons
Sourial et al., 2010 [100]	Three population-based, longitudinal studies; 839 individuals aged 75 years and older from the MUNS, 1,600 individuals aged 65 years and older from the CSHA, and 1,164 individuals aged 65 years and older from the SIPA	Seven domains of frailty were evaluated: nutrition, physical activity, mobility, strength, energy, cognition, and mood	In two of these population-based studies (CSHA and MUNS) presence of deficits for all domains separated from absence of deficits. In the SIPA, there was separation in all domains except cognition
Raji et al., 2010 [149]	Population-based, longitudinal study (10 years); 942 non-frail Mexican American men and women aged 65 years and older from the H-EPESE	MMSE and physical frailty phenotype operationalized slightly modifying the CHS criteria based on four frailty components and excluding physical activity	Non-frail older Mexican Americans with low cognitive scores were significantly more likely to acquire one or more components of frailty

Table 1 (continued)

Reference	Study design and sample	Frailty and cognitive assessment	Principal results
Armstrong et al., 2010 [115]	Database of 23,952 patients receiving community care in the home or in long-term care institutions across Ontario, Canada, with subjects aged 81.7 ± 7.4 years	CSHA Frailty Index, CHESS scale, and EFS and diagnosis of dementia (criteria not specified)	over 10 years than those with higher cognitive scores Among participants, 40 % classified in the frailest category had a diagnosis of dementia compared with 11 % of those in the least frail category
Aranda et al., 2011 [150]	Population-based, longitudinal study (2 years); 963 non-frail older subjects persons aged 75 years and older who participated in the H-EPESE	MMSE and physical frailty phenotype operationalized slightly modifying the CHS criteria based on four frailty components and excluding physical activity	Respondents at risk of increasing frailty had lower levels of cognitive functioning at baseline
Mitnitski et al., 2011 [116]	Population-based, longitudinal study (5 years); 2,305 individuals from the CSHA sample subjects aged 75.8 ± 7.1 years	CSHA Frailty Index and five-year change in errors on 3MS grouped into categories of 3	Frailty at baseline associated with cognitive change in men and women
Mitnitski et al., 2011 [117]	Population-based, longitudinal study (5 years); 2,305 individuals from the CSHA sample of subjects aged 83.1 ± 6.9 years	CSHA Frailty Index, CSHA Clinical Frailty Scale, CHS frailty phenotype and five-year change in errors on 3MS grouped into categories of 3	All measures of frailty at baseline associated with cognitive decline
Song et al., 2011 [118]	Population-based, longitudinal study (5 and 10 years); 5,909 individuals from the CSHA aged 65 years and older	Frailty Index of “non-traditional” risk factors for dementia and diagnosis of dementia according to the DSM-III-R and diagnosis of AD according to NINCDS-ADRDA criteria	Frailty at baseline was associated with the incidence of AD and dementia of all types over 5-year and 10-year intervals
Auyeung et al., 2011 [141]	Population-based, cross-sectional study; cognitively normal people aged 65 years and older and living in Hong Kong.	BMI, grip strength, chair stand, step length, slowed walk, composite score on neuromuscular test and 4-year change in MMSE	Underweight, grip strength, and chair stand predicted cognitive decline in men, whereas only grip strength predicted lower MMSE at follow-up in women
Avila-Funes et al., 2011 [124]	Population-based, cross-sectional study; 475 community-dwelling subjects aged 70 years and older from the Mexican Study of Nutritional and Psychosocial Markers of Frailty	Physical frailty phenotype operationalized slightly modifying the CHS criteria, cognitive impairment was assessed with MMSE, and IST and considered as an additional frailty criterion	Low physical activity and cognitive impairment appeared to be the more important contributors of functional disability
O’Halloran et al., 2011 [126]	Cross-sectional convenient sample of 384 community dwelling participants over 60 years from Ireland	Physical frailty phenotype operationalized with the CHS criteria and SART Task	More errors and greater variability in performance speed in frail compared to non-frail participants
Jacobs et al., 2011 [123]	Population-based, cross-sectional and longitudinal study (5 years); 840 individuals from the Jerusalem Longitudinal Cohort Study sample of subjects aged 85 years	Physical frailty phenotype operationalized with the CHS criteria and MMSE	Frailty status was significantly associated with cognitive impairment. After adjustment, frailty alone was predictive of subsequent 5-year mortality
Ní Mhaoláin et al., 2011 [125]	Participants were recruited through the cross-sectional ECAD study from an Irish tertiary center; 115 patients were assessed, of which 95 with a diagnosis of AD and 20 with a diagnosis of MCI mean age was 74 years	Physical frailty phenotype operationalized slightly modifying the CHS criteria and probable AD diagnosed according to the NINCDS-ADRDA criteria and MCI according to international consensus criteria	Frailty was a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of cognitive decline and illness severity
Solfrizzi et al., 2012 [127]	Population-based, longitudinal study (3 and 7 years); 2,581 individuals from the ILSA sample of 5,632 subjects aged 65–84 years	Physical frailty phenotype operationalized slightly modifying the CHS criteria and diagnosis of dementia according to the DSM-III-R, NINCDS-ADRDA, and ICD-10 criteria	Lower cognition was associated with physical frailty. Frail demented patients were at higher risk of all-cause mortality over 3- and 7-year follow-up periods, but not of disability
Jurschik et al., 2012 [128]	Population-based, cross-sectional study; 628 individuals from community dwelling adults aged 75+ in Spain; mean age: 81.3 ± 5 years	Physical frailty phenotype operationalized with the CHS criteria and Pfeiffer’s Test for cognitive function. Cognitive impairment was ≥ 3 errors	Cognitive impairment was 20 % in frail population compared to 5.3 % in non-frail older subjects
Doba et al., 2012 [121]	Population-based, longitudinal study (5 years); 407 individuals from the Japanese Health Research Volunteer Study sample of subjects aged 78 ± 5 years	MDS cognitive performance scale. Self-reported cognitive change and 5-year change in CSHA Clinical Frailty Scale	Subjective cognitive changes at baseline were significantly associated with development of frailty at follow up. There was no significant association between

Table 1 (continued)

Reference	Study design and sample	Frailty and cognitive assessment	Principal results
			MDS and development of frailty at follow-up
Sourial et al., 2012 [101]	Database from five different population-based studies (2 EPESE sites, LASA, MHAS, and NuAge); a total of 14,217 individuals with mean age ranged from 72.4 to 75.6 years	Seven frailty domain measures (nutrition, physical activity, mobility, strength, energy, cognition, and mood) were selected from each study and dichotomized into presence or absence of a frailty marker	Among frailty markers consistently aggregated in the five samples, strength had the highest contribution overall in explaining differences among participants across the samples; mobility and energy followed as the next most discriminating markers; and nutrition and cognition appeared to be least discriminating
Langlois et al., 2012 [131]	Cross-sectional study; 83 community dwelling adults aged between 69 and 81 recruited through advertisement in newspapers and locally	Frail if present 2 of the following 3 criteria: physical frailty phenotype with the CHS criteria or CSHA Frailty Index or low score on MPP, MMSE and evaluation of the following cognitive domains: verbal abstract reasoning, episodic memory, working memory, speed of processing and executive function	Presence of frailty affected executive function and processing speed. No effect on working memory, episodic memory, or abstract verbal reasoning
Macuco et al., 2012 [129]	Population-based, cross-sectional study; 487 individuals from the FIBRA study sample (Brazil) of subjects aged 65 years and over	Physical frailty phenotype operationalized with the CHS criteria and MMSE	Frail older adults had significantly worse performance on the MMSE
Yassuda et al., 2012 [130]	Population-based, cross-sectional study; 487 individuals from the FIBRA study sample (Brazil) of subjects aged 65 years and over	Physical frailty phenotype operationalized with the CHS criteria, MMSE, and the BCSB	Frail older adults performed lower than non-frail in most cognitive variables
Bilotta et al., 2012 [142]	Cross-sectional and longitudinal study (1 year); 109 participants attending an outpatient geriatric clinic in Italy aged 65 years and older (median age 84 years)	Physical frailty phenotype operationalized with the SOF criteria and diagnosis of AD according to the DSM-IV-Text Revised	Among AD patients, 50 % were frail, 28 were pre-frail, and 22 % were robust. Frail, demented patients were at higher risk of all-cause mortality over 1-year follow-up period
Bilotta et al., 2012 [143]	Cross-sectional and longitudinal study (1 year); 265 participants attending an outpatient geriatric clinic in Italy aged 65 years and older (mean age 81.5 years)	Physical frailty phenotype operationalized with the SOF criteria and diagnosis of dementia according to the DSM-IV-Text Revised	Dementia in 45 % of frail participants compared with 32 % in pre-frail and 33 % robust, although differences were not statistically significant
Cano et al., 2012 [153•]	Population-based, longitudinal study (10 years); 1,815 Mexican American men and women aged 67 years and older from the H-EPESE	Physical frailty phenotype operationalized slightly modifying the CHS criteria and MMSE > 21	As MMSE score declined over time, the percent of frail individuals increased in a linear fashion. Frailty and cognitive impairment are independent risk factors for mortality after controlling for all covariates. When both cognitive impairment and frailty were added to the model, hazard ratio for individuals with cognitive impairment was no longer statistically significant
Avila-Funes et al., 2012 [147]	Population-based, longitudinal study (7 years); 5,480 older individuals aged 65–85 years from the Three-City Study	Physical frailty phenotype operationalized slightly modifying the CHS criteria, MMSE, and IST. Diagnosis of dementia according to the DSM-IV criteria and VaD according to the NINDS-AIREN criteria	Frailty was marginally associated with greater risk of all types of dementia and was not associated with incident AD, but frailty status was independently associated with incident VaD
Solfrizzi et al., 2013 [146]	Population-based, longitudinal study (3.5 years); 2,581 individuals from the ILSA sample of 5,632 subjects aged 65–84 years	Physical frailty phenotype operationalized slightly modifying the CHS criteria and diagnosis of dementia according to the DSM-III-R, NINCDS-ADRDA, and ICD-10 criteria	Over a 3.5-year follow-up, frailty syndrome was associated with a significantly increased risk of overall dementia and, in particular, VaD, while the risk of AD or other types of dementia did not significantly change in frail individuals compared with subjects without frailty syndrome
Shimada et al., 2013 [132]	Population-based, cross-sectional study ; 5,104 older individuals from the Obu Study of Health Promotion for the Elderly (OSHPE) sample of	Physical frailty phenotype operationalized slightly modifying the CHS criteria and MCI diagnosed according to international consensus criteria	The overall prevalence of frailty, MCI, and frailty and MCI combined was 11.3 %, 18.8 %, and 2.7 %, respectively. A significant

Table 1 (continued)

Reference	Study design and sample	Frailty and cognitive assessment	Principal results
Gray et al., 2013 [148]	subjects aged 65 years or older, mean age 71 years Population-based, longitudinal study (6.5 years); 2,619 individuals from the Adult Changes in Thought (ACT) study sample of subjects aged 65 years and older	Physical frailty phenotype operationalized with the CHS criteria and diagnosis of dementia according to the DSM-IV, diagnosis of possible and probable AD according to NINCDS-ADRDA criteria. Non-AD dementia consisted of all dementias not classified as possible or probable AD	relationships between frailty and MCI also was found Frailty was associated with higher risk of developing non-AD dementia but not AD. Although frailty was not associated with all-cause dementia in the entire sample, an association did exist in participants with higher cognitive scores
Kulmala et al., 2014 [144]	Population-based, cross-sectional study; 654 persons aged 76–100 years (mean 82±4.6 years) from the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study, Kuopio, Finland	Physical frailty phenotype operationalized with the CHS criteria, diagnosis of dementia, AD, and VaD according to the DSM-IV criteria and cognitive impairment evaluated with MMSE	Frail persons were almost 8 times more likely to have cognitive impairment, 8 times more likely to have some kind of dementia, almost 6 times more likely to have VaD, and over 4 times more likely to have AD than persons who were robust
Han et al. 2014 [133]	Population-based, cross-sectional study; 10,388 nationally representative sample aged 65 years and older from the 2008 Living Profiles of Older People Survey, South Korea	Physical frailty phenotype operationalized with the CHS criteria and cognitive function was assessed using the Korean version of the MMSE	Frail subjects showed a higher percentage of cognitive impairment, with some gender differences (55.8 % in men, 35.2 % in women). Cognitive impairment was associated with a higher likelihood of frailty in community-dwelling older men and women

ADL, activities of daily living; MMSE, Mini Mental State Examination; CHS, Cardiovascular Health Study; CSHA, Canadian Study of Health and Aging; GSS, Geriatric Status Scale; 3MS, modified Mini Mental State Examination; H-EPESE, Hispanic Established Population for the Epidemiological Study of the Elderly; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association; DLB, dementia with Lewy bodies; CIM, Complex Ideational Material; CGA, Comprehensive Geriatric Assessment; MPI, Multidimensional Prognostic Index; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; NINDS-AIREN, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences; IST, Isaac Set Test; IADL, instrumental activities of daily living; MUNS, Montreal Unmet Needs Study; SIPA, French acronym of the System of Integrated Services for Older Persons study; CHESS, Changes in Health, End-Stage Disease and Signs and Symptoms; EFS, Edmonton Frail Scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders-III revised; BMI, body mass index; SART, Sustained Attention Response Time; ECAD, Enhancing Care in Alzheimer’s Disease; ILSA, Italian Longitudinal Study on Aging; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; MDS, Minimum Data Set; LASA, Longitudinal Aging Study Amsterdam; MHAS, Mexican Health and Aging Study; NuAge, Nutrition as a determinant of successful aging; MPP, Modified Physical Performance; BCSB, Brief Cognitive Screening Battery; SOF, Study of Osteoporotic Fractures

to respond to stressors and an increased vulnerability to adverse outcomes [19]. However, frailty is, at present, a more elusive concept, and how best to operationalize this syndrome is still controversial [91]. Some definitions are based on physical diminution in the elderly person [19, 92, 93]. In particular, the “phenotypic” or physical definition of frailty or the “biological syndrome model” was proposed by Fried and colleagues working with the Cardiovascular Health Survey (CHS) [19]. By convention, the CHS definition of physical frailty proposes five items: unintentional weight loss, exhaustion, weakness, slow walking speed, and low levels of physical activity. An older individual is said to be frail when three or more are present, “pre-frail” when they exhibit only one or two of these characteristics, and “robust” when they have none [19]. Other definitions, criticizing this concept [94–97], suggested that an integral approach is needed for the concept of frailty, an approach in which the focus is not exclusively on physical problems in older people, but which also incorporates psychological and social problems, and is thus based on the

integral functioning of the individual [98, 99]. A recent integral conceptual working definition of frailty takes into account of the principles formulated earlier and combines essential components of existing conceptual definitions of frailty [98, 99]. This definition indicates frailty as a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes [99]. Therefore, an emerging consensus promotes a definition of frailty on the basis of a multidimensional approach [99–102], so the evaluation of frailty employs a frailty index, which is calculated by considering a number of potential deficits. These deficits can be symptoms, signs, diseases, disabilities or abnormal laboratory values [102], so developing an integral conceptual definition of frailty as a multisystem physiological change occurring in the elderly that determine an increase of risk for accelerated physical and cognitive decline, disability and death even in absence of specific diseases [99–102].

Therefore, the second model that emerged in recent years is the frailty index based on accumulation of deficits or cumulative burden index proposed by Rockwood and colleagues [103, 104], in which frailty is defined as an accumulation of health conditions and deficits.

Cognitive Frailty: Multidimensional and Phenotypic Approach

In physical or phenotypic frailty [19] or in frailty indexes with a multidimensional nature [103, 104], this clinical syndrome is generally associated with a greater risk for adverse health-related outcomes, such as falls, disability, hospitalization, permanent institutionalization, and death [105•]. However, in recent years, the prevention of frailty may be important in preventing cognitive-related adverse health outcomes, including delirium [26] and late-life cognitive disorders [27, 90•]. Therefore, physical frailty [106, 107], psychological frailty, and social frailty cannot be seen in isolation from each other, and, in particular, cognition has already been considered as a component of frailty [23]; indeed, this conceptualization of frailty is based on a holistic view of the person [99–101]. In fact, in recent years, frailty is acknowledged to be not only a biological or physiological state, but also a multidimensional concept [20, 102, 108]. The multidimensional nature of the concept of frailty demands a multidisciplinary approach.

A list of eight frailty risk factors that are mentioned to be of great importance to the concept of frailty were identified in a systematic review that evaluated clinimetric properties [102], including in the physical dimension: nutritional status, physical activity, mobility, strength, and energy, in the psychological dimension: cognition and mood, and in the social dimension: lack of social contacts and social support. On this basis, at least 20 frailty instruments have been described [102], and cognition was present in only 40 % of them [27]. All these frailty instruments are multidimensional in nature, and mostly based on a standardized Comprehensive Geriatric Assessment (CGA) [27, 109, 110]. However, the overall results of the assessment by using these frailty instruments suggested that they are mainly developed and validated as risk assessment tools, and not as possible outcome measures [102]. Only a few studies made a comparison between frailty instruments, concluding that different instruments may identify older people at risk of adverse health outcome [111], but they may capture different subpopulations [112, 113]. In particular, in older individuals institutionalized in nursing homes, comparing the CHS physical definition of frailty [19], the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale [25], and the Frailty Index [111], whereas all these frailty measures were significantly associated with an increased risk of mortality, disability and cognitive decline, measured with the Mini Mental State Examination (MMSE) in its modified form (3MS), when pairs of frailty measures were included in the

models, only the Frailty Index was associated with a higher risk of mortality and decline in the 3MS [114] (Table 1). Furthermore, a study examined the relationships among seven frailty domains (nutrition, physical activity, mobility, strength, energy, cognition, and mood), using data from three population-based studies. In two of these studies, presence of deficits for all domains separated from absence of deficits. In the third population-based study, there was separation in all domains except cognition. All these data may suggest that frailty is a multidimensional concept for which the relationships among domains differ according to the population characteristics. These domains, with the possible exception of cognition, appeared to aggregate together and share a common underlying construct [100]. Alternatively, it may be that frailty involves specific aspects of cognition not measured in the three studies, such as executive function or psychomotor speed [106, 107], rather than overall impairment. More recently, the same authors analyzed data from five population-based studies of aging, and among frailty markers consistently aggregated in the five samples, strength had the highest contribution overall in explaining differences among participants across the samples; mobility and energy followed as the next most discriminating markers; and nutrition and cognition appeared to be least discriminating [101]. A Canadian study of 23,952 home care recipients found that 40 % of participants classified in the frailest category using a frailty index based on an accumulation of deficits approach had a diagnosis of dementia compared to 11 % of those in the least frail category [115] (Table 1). Other three Canadian studies, using the population-based sample of the CSHA of adults in the community and institutionalized care, proposed that different measures of frailty at baseline were associated in a 5-year follow-up with cognitive decline [116, 117] and dementia and AD over 5-year and 10-year intervals [118] (Table 1).

Only very few studies explored the multidimensional impairment as a frailty concept in hospitalized older patients. In particular, the Multidimensional Prognostic Index (MPI) was effective in predicting short- and long-term mortality risk in elderly subjects with dementia admitted to a geriatric hospital ward [119] (Table 1), and given that in patients with dementia, clinical outcome and mortality result from a combination of psychological, biological, functional, and environmental factors, tools that effectively identify patients with different life expectancy should be multidimensional in nature. More recently, a multicentre study on 1,306 hospitalized patients in France showed that that screening for frailty with four different indexes based on multidimensional impairment at the beginning of a hospital stay can strongly predict 1-year institutionalization and mortality related to frailty, but not rapid cognitive decline (loss of ≥ 3 points on MMSE) [120] (Table 1). Overall taken together these findings supported the

concept that considering multidimensional aggregate information and frailty syndrome could be very important for predicting short- and long-term all-cause mortality in older subjects with dementia and that it may be important for the identification of the more adequate management of these patients. Finally, a Japanese population-based study also showed a reciprocal relationship, suggesting that cognitive impairment may indicate the development of frailty measured with the CSHA Clinical Frailty Scale [121] (Table 1).

Moreover, the physical or phenotypic definition of frailty has been proposed in several studies linking frailty models and late-life cognitive decline or dementia [27, 90•, 122••]. A series of cross-sectional [23, 123–133] and longitudinal studies [19, 23, 134–141] investigated the relationship between physical/biological frailty and MCI or late-life cognitive impairment/decline (Table 1). In the cross-sectional component of the Italian Longitudinal Study on Aging (ILSA), both lower cognition and greater depressive symptoms were associated with physical frailty [127]. Other findings from the Three-City Study suggested that cognitive impairment improved the predictive validity of the operational definition of physical frailty, increasing the risk to develop disability. On the contrary, risk of death also tended to be higher in cognitively impaired frail participants than in their non-frail counterparts without cognitive impairment, even if the results were not statistically significant [23]. In the Mexican Study of Nutritional and Psychosocial Markers of Frailty, in which physical frailty phenotype was operationalized slightly modifying the CHS criteria and cognitive impairment was considered as an additional frailty criterion, low physical activity and cognitive impairment appeared to be the more important contributors of functional disability [124]. In the Jerusalem Longitudinal Cohort Study, prevalence of cognitive impairment ($\text{MMSE} \leq 24$) in frail older subjects was 53.3 %, with frailty status significantly associated with cognitive impairment [123]. In a population-based study from South Korea, frail older subjects showed a higher percentage of cognitive impairment, with some gender differences (55.8 % in men, 35.2 % in women) [133]. In different population-based studies from Spain and Brazil, the prevalence of cognitive impairment in physical frail older subjects ranged from 20 % [128] to 39 % [129, 130], whereas in a sample of 5,104 older community dwellers in Japan, the combined prevalence of frailty and MCI was only 2.7 %, with a significant relationships between frailty and MCI [132]. Furthermore, in a sample from an Irish tertiary center, frailty was a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of cognitive decline and illness severity [125]. Finally, some cognitive domains were found significantly associated with frailty in some cross-sectional studies on community dwelling older people, i.e., executive functions and processing speed [131], and poorer sustained

attention [126]. In longitudinal studies, lower cognition was associated with the frailty physical phenotype in the CHS, despite exclusion of those subjects with $\text{MMSE} < 18$ [19]. Several other studies have also reported that physical frailty was associated with low cognitive performance at baseline [134–136]. In particular, in the Hispanic Established Populations Epidemiologic Studies of the Elderly (H-EPESE), the baseline MMSE total score was significantly predictive of frailty at 1-year follow-up in men, but not in women [134]. After adjustment, in Three-City Study, frail persons with cognitive impairment were significantly more likely to develop disability over a 4-year period [23]. Two longitudinal population-based studies indicated frailty syndrome as a predictor of cognitive impairment in a 10-year follow-up [138], and of the rate of cognitive decline in a 3-year period [137]. The Rush Memory and Aging Project also found that physical frailty increased the risk for MCI [139], although there is still controversy as to whether cognitive impairment may be a symptom of frailty or whether MCI is a separate syndrome, or indeed, a sign of early dementia [139]. In a large population-based study conducted in Hong Kong, underweight, grip strength and chair stand predicted cognitive decline in men, while only grip strength predicted lower MMSE at follow-up in women [141]. Finally, a study provided preliminary empirical support for the existence of subdimensions of physical frailty within the CHS model [19]. In particular, two subdimensions were identified, and cognitive impairment was part of a frailty subdimension, including slower gait, weaker grip, and lower physical activity, further increasing evidence that physical performance tests are sensitive indicators of cognitive impairment, and further supporting the hypothesis that cognitive impairment may be intrinsic to frailty [140]. In fact, although some have referred to the CHS model of frailty as the “biological” model of frailty (in contrast to other models that include social and psychological criteria), these findings call this into question, because several variables in the CHS phenotype of frailty appear to be integrally related to cognitive impairment [140].

Also when the cognitive outcomes were dementia, AD, or VaD, a series of cross-sectional [142–144] and longitudinal studies [137, 145–148] investigated these associations with physical/biological frailty (Table 1). In particular, two small Italian studies investigated the prevalence of AD and dementia in patients with frailty identified with Study of Osteoporotic Fractures (SOF) criteria, which operationalized physical frailty with a simpler adaptation of the more complex CHS criteria [142, 143]. In the first study of 109 AD patients attending an outpatient geriatric clinic, 50 % were frail, 28 % were pre-frail, and 22 % were robust [142]. In the second study of 265 outpatients, dementia was identified in 45 % of frail participants compared with 32 % in pre-frail, and 33 % robust, although differences were not statistically significant [143]. In a cross-sectional population-based study in Finland, frail

persons were almost eight times more likely to have cognitive impairment, eight times more likely to have some kind of dementia, almost six times more likely to have VaD, and more than four times more likely to have AD than persons who were robust [144]. Furthermore, different studies have reported that physical frailty may be associated with incidence of AD [137], VaD [146, 147], non-AD dementias [148], and AD pathology in older persons with and without dementia [145] (Table 1). In the unadjusted model of the Three-City Study, being frail at baseline led to twice the cumulative risk of dementia at 4 years, although after adjusting for sociodemographic and health covariates frailty status did not remain a statistically significant predictor of dementia [23]. Findings from the Rush Memory and Aging Project raised the possibility that AD pathology may contribute to frailty or that frailty and AD pathology share a common pathogenesis [145]. In fact, physical frailty proximate to death was related to level of AD pathology on postmortem examination but was not related to the presence of cerebral infarcts or Lewy body disease. This association was similar in persons with and without dementia and was unchanged even after considering level of physical activity, various physical performance measures, and chronic diseases [145]. One longitudinal population-based study has examined the association of frailty or change in frailty with incident AD [137]. In fact, other findings from the Rush Memory and Aging Project on 820 subjects during a 3-year follow-up showed that the risk of developing AD was 2.5 times higher when physical frailty was present at baseline [137]. Some studies, however, have found associations with frailty and specific dementia subtypes [146–148]. During a 3.5-year follow-up, in the ILSA, frailty syndrome was associated with a significantly increased risk of overall dementia and, in particular, VaD, whereas the risk of AD or other types of dementia did not significantly change in frail individuals compared with subjects without frailty syndrome [146]. A later analysis of the Three City Study confirmed the effect of frailty on incident VaD and overall dementia, but not on AD [147]. Data from the population-based Adult Changes in Thought (ACT) study also suggested an association between frailty and incident non-AD dementia (all dementias not classified as possible or probable AD), but not with AD [148]. Finally, some studies showed a reciprocal relationship indicating that cognitive impairment also may indicate the development of frailty [149, 150] (Table 1). In fact, a low MMSE score was independently associated with increased risk of physical frailty over a 10-year period in older Mexican Americans [149] and over a 2-year period in the same sample in adults older than age 75 years [150], suggesting that cognitive status may be an early marker for future risk of physical frailty (Table 1).

On the basis of this growing and extensive body of epidemiological evidence, an international consensus group comprised of investigators from the International Academy of

Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) recently convened in Toulouse, France, to establish a definition for “cognitive frailty” in older adults [125, 151]. “Cognitive frailty” is a heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment [125]. In particular, the proposed criteria defining this novel age-related condition included presence of physical frailty and cognitive impairment, operationalized with the CHS phenotypic/biological model of frailty and with a Clinical Dementia rating Scale (CDR) of 0.5 (questionable dementia, a stage of the dementia continuum similar to MCI), and exclusion of concurrent AD dementia or other dementias [125]. The IANA/IAGG consensus group proposed a series of screening and diagnostic tools exploring and identifying multiple domains/causes of frailty, including cognitive and psychological status, in order to design effective interventions for cognitive frailty [125], a field that needs further development. In 2006, our group used the term “cognitive frailty” in the title of a review article on predementia syndrome and vascular risk factors, suggesting a particular state of cognitive vulnerability in MCI and other similar clinical entities exposed to vascular risk with a subsequent increased progression to overt dementia [152]. Therefore, cognitive frailty should be validated as a possible determinant of the principal health-related outcomes of the different frailty models, i.e., disability, hospitalizations, and mortality. Some longitudinal population-based studies investigated cognitive frailty models linked to increased disability and all-cause mortality [23, 127, 142, 153•] (Table 1). In the ILSA, frail, demented patients were at higher risk of all-cause mortality over 3- and 7-year follow-up periods, but not of disability [127]. Other two recent studies investigated the survival of patients with frailty and cognitive impairment. Findings from the Three-City Study suggested that cognitive impairment improved the predictive validity of the operational definition of physical frailty, increasing the risk to develop disability. On the contrary, risk of death also tended to be higher in cognitively impaired frail participants than in their non-frail counterparts without cognitive impairment, even if the results were not statistically significant [23]. In a small Italian study of 109 AD patients attending an outpatient geriatric clinic, 1 year after enrolment, frailty was an independent predictor of death after correction for age, sex, dependence in the basic activities of daily living (ADL), severity of cognitive impairment, and comorbidity [142]. Finally, more recently, in the H-EPESE, the cognitive frailty construct was operationalized with the CHS frailty phenotype plus MMSE < 21 and followed as a possible determinant of all-cause mortality in a 10-year follow-up [153•]. As MMSE score declined over time, the percent of frail individuals increased and frailty and cognitive impairment were independent risk factors for mortality after controlling for all covariates. However, when both cognitive impairment and frailty

(“cognitive frailty”) were added to the model, hazard ratio for individuals with cognitive impairment was no longer statistically significant [153•], suggesting that frailty may be a stronger predictor of mortality than cognitive impairment at least in this population of older Mexican Americans.

Nutrition and Frailty

Current epidemiological evidence supported the hypothesis that modifiable vascular, lifestyle-related, and metabolic factors also may be associated with the development of frailty syndrome and frailty components in later life [154–156], opening new potential routes for the prevention of these disability-related conditions. In particular, among potentially modifiable risk factors, the impact of several nutritional factors on frailty and its components has been the subject of recent interest [22•, 154, 157, 158]. A more sedentary lifestyle, a reduction in metabolic cell mass and, consequently, lower energy expenditure and dietary intake are important contributors to the progression of frailty. A decline in intake is in turn associated with the risk of developing a suboptimal nutritional state or multiple micronutrient deficiencies [159]. In fact, undernutrition may be a major cause of frailty [160, 161], and older persons with protein energy undernutrition, a treatable condition, have poorer cognitive performance [162•, 163].

The transition from independence to disability in older adults is characterized by detectable changes in body composition and physical function. Epidemiologic studies have shown that weight loss, reduced caloric intake, and the reduced intake of specific nutrients are associated with such changes [155]. The mechanisms underlying these associations remain unclear, and different hypotheses have been suggested, including the reduction of the antioxidant effects of some nutrients. Among macronutrients, low protein intake was associated with higher prevalence of frailty among InCHIANTI study participants older than 65 years of age [157]. Consumption of specific micronutrients also has been associated with frailty-related outcomes. In the InCHIANTI study, higher dietary intake of vitamin C was significantly correlated with measures of knee extension and lower extremity performance [164], whereas the same study also reported an association between low intake of vitamin D, E, and C with prevalence of frailty [157]. Nutrient biomarkers have been extensively studied in association with physical function and frailty-related outcomes. An association between low circulating levels of vitamin E and the presence of frailty in the InCHIANTI sample also was found [158]. In the Women’s Health and Aging Study (WHAS), at baseline,

frail women had significantly lower serum concentrations of vitamins D, E, and B6 and carotenoids compared with their non-frail peers [165, 166]. Moreover, non-frail women in the lowest quartiles of serum α -tocopherol, 25-hydroxyvitamin-D [25(OH)D], and carotenoids had an increased risk of becoming frail during the follow-up [165]. Furthermore, women in the lowest quartile of serum concentrations of vitamin B6, B12, and selenium had significantly higher risk of developing disability in ADL during a 3-year follow-up compared with women in the upper quartiles [167]. Finally, observational and clinical trials testing the relationship between vitamin D and physical performance provided mixed results [168, 169]. These suggestions also proposed to examine dietary patterns rather than single nutrients. In community-dwelling older adults, after a 6-year follow-up, higher adherence to a Mediterranean-style diet was associated with lower odds of developing frailty compared with those with lower adherence [170•]. A higher adherence to a Mediterranean-style diet at baseline was associated with a lower risk of low physical activity and low walking speed but not with feelings of exhaustion and poor muscle strength [170•]. Moreover, more recently, higher adherence to MeDi score was cross-sectionally associated with lower risk of being frail [171]. A cohort study conducted in French elderly community dwellers showed an inverse association between adherence to a Mediterranean-style diet and risk of disability in women, whereas no association was evidenced in men [172]. Among frailty components, high adherence to a Mediterranean-style diet was associated with a slower decline of mobility over 8 years of follow-up in community dwelling older persons [173], and walking speed over 8 years was faster among those with higher MeDi adherence at baseline [174], suggesting a long-term effect of this diet on mobility performance in older age.

Nutrition and physical exercise may be important and modifiable factors potentially affecting the frailty status of the older person [21•, 22•]. Some systematic reviews of home-based and group-based exercise interventions for frail older people showed that exercise have the potential to improve outcomes of mobility and functional ability [175, 176]. Furthermore, nutritional interventions might be able to address the impaired nutrition and weight loss of frailty. In fact, prefrailty and frailty were associated with lower nutritional status and higher food insufficiency in the participants older than age 60 years of the Third National Health and Nutrition Examination Survey (NHANES III) [177, 178]. Frailty also was associated with increased risk of malnutrition in men and women older than age 75 years [179]. An observational study of nutritional intervention with

400 kcal liquid meal, frail individuals showed lower hunger recuperation compared to non-frail individuals, 4 h after supplementation [180]. A recent meta-analysis of 12 studies on more than 1,800 older persons suggested that complete caloric nutritional supplements not only produced weight gain but also improved cognition [181•]. In frail nursing home residents, a nutrient- and energy-dense oral nutritional supplement not only improved nutritional status but also tended to improve quality of life [182]. On the other hand, one RCT that investigated the effects of exercise and nutritional supplementation in 100 frail elderly people in long-term care reported that such supplementation had no effect on muscle strength, gait speed, stair climbing, or physical activity [183]. However, more recently, one RCT among frail individuals aged 65 years and older with low socioeconomic status, showed that after 12 weeks of protein-energy supplementation, usual gait speed decreased by 1.0 % in the intervention compared with the control group, while there was no difference in hand-grip strength between the two groups [184]. The role of both nutrition and exercise was examined in only one pilot RCT conducted among Chinese men and women aged 65–79 years. The intervention groups received either nutritional consultation or problem-solving therapy (psychotherapy model) and the control groups had neither nutritional consultation nor problem-solving therapy. Primary outcome was improvement of the CHS phenotype of frailty by at least one category (from pre-frail to robust, or from frail to pre-frail or robust). The group that received nutritional consultation showed significantly higher improvement of the frailty phenotype compared to the control group after 3 months of intervention, but not at 6 and 12 months [185••].

Conclusions

Given the very limited therapeutic value of drugs currently used in the treatment of cognitive impairment and dementia, it results evident the necessity to potentially individualize new strategies able to prevent and to slow down the progression of MCI and dementia. Higher adherence to a Mediterranean-type diet was associated with cognitive decline although the MeDi combines several foods and nutrients already separately proposed as potential protective factors against dementia syndromes and late-life cognitive decline. Therefore, maintaining a healthy diet may have an impact on many possible risk factors for cognitive decline, and the models to follow seem to be the MeDi and DASH diets among healthy diets. On the basis of this evidence, the evaluation of the MeDi or DASH diets on cognitive

outcomes seems of particular interest and recent prospective studies focusing on AD and dementia appeared to be really promising. Among different dietary patterns, higher adherence to the MeDi was associated with a reduced risk of cognitive impairment, MCI, and AD, as well as the transition from MCI to AD, and decreased all-causes mortality in AD patients. These findings suggested that adherence to the MeDi may affect not only the risk for AD, but also for MCI, probably influencing the evolution of cognitive performances over time and subsequent disease progression. However, while for the vascular hypothesis there was clear evidence about a protective role of DASH diet, and particularly MeDi and its nutrients in preventing all cardiovascular conditions linked to dementia, for the other possible mechanisms it was only possible to suggest hypothetical biological pathways taken into account the results from animal studies. Therefore, the lack of reproducibility in some results on the linked between healthier diet and cognitive decline and the speculative aspect of the biological pathways presented, suggested us to be cautious.

Other modifiable, age-related conditions linked to late-life cognitive decline may be important for the prevention of these devastating disorders. Among these conditions, frailty in older adults is a syndrome corresponding to a vulnerability to stressors and it tends to be considered as a major risk for adverse outcomes in older age. A recent and growing body of epidemiological evidence suggested that frailty may increase the risk of future cognitive decline and that cognitive impairment may increase the risk of frailty suggesting that cognition and frailty may interact in advancing aging. The etiology of frailty is multifactorial and besides hormonal and inflammatory processes, nutritional influences may be of major relevance. Nutritional interventions might be able to address the impaired nutrition and weight loss of frailty. There have been a limited number of RCTs investigating the role of nutrition on late-life cognitive disorders and frailty. There are difficulties in the design and conduction of RCTs in older persons, especially targeting complex conditions as frailty or AD and dementia. For example, if a change of dietary habits may play a major part on the prevention of frailty and late-life cognitive disorders, what is the role of genetic risk factors, or if these associations may be valid in populations with different dietary patterns? Other questions may address the underlying mechanisms and which is the most relevant component, among dietary micro- and macronutrients and their possible interactions. Answers to these questions will help us to better define the target populations for future preventive and therapeutic strategies also in older age. However,

the reviewed epidemiological evidence clearly indicate the need to design and develop RCTs possibly addressing possible interactions in different populations with genetic factors and other possible confounders, and whether change in dietary patterns may protect against cognitive decline and AD, also through the nutritional prevention of frailty.

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Compliance with Ethics Guidelines

Conflict of Interest Francesco Panza, Vincenzo Solfrizzi, Rosanna Tortelli, Francesco Resta, Carlo Sabbà, and Giancarlo Logroscino declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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