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Sustaining an ageing population: the role of micronutrients in frailty and cognitive impairment

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Age-related frailty and cognitive decline are complex multidimensional conditions that significantly impact the ability of older adults to sustain functional capacity and independence. While underlying causes remain poorly understood, nutrition continually emerges as one associated risk element. Many studies have addressed the importance of adequate nutrition in delaying the onset of these conditions, but the specific role of micronutrients is not well established. The consideration of pre-frailty as an outcome variable is also limited in the current literature. In this review, we focus on the potential value of maintaining micronutrient sufficiency to sustaining the health of the ageing population. Using data from the Irish longitudinal study on ageing, we consider several vitamins known to have a high prevalence of low status in older adults and their impact on pre-frailty, frailty and cognitive impairment. They include vitamin B_{12} and folate, both of which are associated with multiple biological mechanisms involved in long-term health, in particular in cognitive function; vitamin D, which has been associated with increased risk of musculoskeletal disorders, depression and other chronic diseases; and the carotenoids, lutein and zeaxanthin, that may help mitigate the risk of frailty and cognitive decline via their antioxidant and anti-inflammatory properties. We show that low concentrations of folate and carotenoids are implicated in poorer cognitive health and that the co-occurrence of multiple nutrient deficiencies confers greatest risk for frailty and pre-frailty in the Irish longitudinal study on ageing cohort. These health associations contribute to evidence needed to optimise micronutrient status for health in the older adult population.

Micronutrients: Frailty: Cognitive decline: Ageing: Healthspan

Abbreviations: COVID-19, coronavirus disease; FA, folic acid; HCA, homocysteine; RCT, randomised controlled trials; TILDA, The Irish longitudinal study on ageing.

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Background

Global population ageing

Unprecedented technological developments coupled with advances in medicine and public health over the past two centuries has contributed to exponential growth in the global population from 1 billion in 1800, to a projected 8 billion in 2023[1–3]. This population growth can be attributed to profound reductions in child mortality and the rapid increase in life expectancy from 40 to 80 years in developed countries[4–6]. The extension in life expectancy has resulted in an increasing population of older adults, a situation exacerbated by lower fertility rates, especially in developed countries[7]. In 2018, for the first time in human history, the number of people aged ≥65 years surpassed those aged ≤5 years of age globally[8]. The combination of these two demographic phenomena has resulted in a growing, yet increasingly ageing population throughout the developed world; with similar patterns emerging in the developing world[7]. By 2030, one-in-six Europeans will be aged over 60 years and by 2040 one-in-four older adults will be aged over 85 years[9]. This global phenomenon of population ageing presents pressing challenges to the sustainability of our healthcare, social care and welfare systems, particularly if increases in lifespan are decoupled from increases in healthspan.

Lifespan and healthspan

Increases in the total number of years lived (lifespan) are not keeping pace with gains in the number of years lived free of disease and disability (healthspan). The gap between lifespan and healthspan is estimated at 9 years[10]. More pessimistic estimates suggest that as much as one-fifth of life may be lived with chronic disease[11]. Chronic conditions of mid- and later-life account for 4 out of every 5 years lived with disability, while four conditions – CVD, cancer, diabetes and respiratory diseases – account for 80 % of chronic disease-related deaths[12,13].

Current health and social care strategies are largely ineffective in closing the gap between lifespan and healthspan. The increasing demand on healthcare and social support services resulting from living longer, with a growing burden of disease and disability, is becoming ever more apparent to governments, policy makers, service planners and stakeholders.

This is underscored by high profile programmes targeting the extension of healthy lifespan such as the United Nations Sustainable Development Goals and the WHO Decade of Healthy Ageing. To achieve measurable gains in healthspan, thereby sustaining the ageing population, a more coordinated and cohesive approach across medicine, science, government and wider civic society will be necessary[14]. Fundamental to this will be targeting modifiable risk and ameliorating factors that are useful in terms of preventing, monitoring and intervening in the onset and progression of age-related conditions.

Biological v. *chronological age*

Chronological age is associated with declines in physical and cognitive health, the risk of adverse health outcomes and mortality, and the increased use of health and social care services[13,15]. However, older adults of the same age are not at the same risk for these outcomes[16]. Ageing is a dynamic and heterogeneous process and there is substantial variability in how we age biologically. Biological ageing occurs due to damage and dysregulation at the cellular (macromolecules and cells), physiological (tissue, organ, system) and functional (organismal) level, ultimately manifesting in the decline of physical and cognitive function[17,18]. Indeed, the heterogeneity in the pace of biological ageing becomes more pronounced, with more divergent trajectories, at older ages[17,19]. During the recent coronavirus disease (COVID-19) pandemic, many countries advised adults aged ≥70 years to shield to prevent infection and mortality and protect health services[20]. However, using chronological age to characterise individual mortality risk as the basis to implement a blanket policy for older adults at the population level had its problems. Such policies did not take account of the heterogeneity in the pace of ageing among older adults and failed to recognise the consequent harms of physical deconditioning, social isolation, loneliness, depression and decreased quality of life[21–23].

In this narrative review, we will focus on the potential value of micronutrients and maintaining micronutrient sufficiency, to sustaining the health of the ageing population. We will pay particular attention to two common and interlinked conditions of ageing, frailty and cognitive impairment, which significantly impact the ability of older adults to sustain functional capacity and independence. The graphical abstract depicts the role of micronutrient status and the physiological systems that underpin frailty and cognitive impairment.

Frailty and cognitive decline in older adults

Frailty and the disability cascade

As discussed earlier, not everyone of the same age is at the same risk of adverse health outcomes. Frailty captures this differential biological risk that is distinct from, but related to, chronological ageing[24]. It is a common condition in older adults, although it is not an inevitable part of ageing. While recognised as a clinical syndrome, frailty is not a medical diagnosis because it can have different underlying causes in different individuals. Frailty is characterised by multisystem loss of physiological reserve, systemic decompensation in response to stressors (e.g. infection, medication change or a change in living arrangements) and increased risk of adverse outcomes including falls, disability and mortality, independently of chronological age[25]. It is also predictive of increased use of health and social care services[26]. Frailty is a dynamic process that can be viewed on a continuum. An older person can transition in either direction between robustness or non-frailty, pre-frailty (an intermediate sub-clinical state) and frailty[27–29].

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Thus, it can represent a transition between healthy ageing and disability, and is a target condition for the prevention of disability and the extension of healthy life years[30–32].

The gold standard methodology for the assessment and management of frailty is comprehensive geriatric assessment. Comprehensive geriatric assessment is a holistic and interdisciplinary assessment of the individual, resulting in a personalised care plan, and has been demonstrated to reduce the risk of disability, cognitive decline, long-term residential care and death[33,34]. However, this approach is unfeasible for systematic case finding at the population level. The frailty phenotype[35,36], the frailty index[37,38] and the clinical frailty scale[39,40] are widely accepted screening instruments for diagnosing frailty at the population level. The choice of frailty instrument depends largely on the type of clinical or research setting, the participant or patient group, availability of trained personnel, time constraints and administrative burden[41]. Internationally, the prevalence of frailty is 4–59 % among adults aged ≥65 years, depending on the frailty instrument applied and population under study[42].

Associations between frailty and cognitive impairment

The study of the relationship between frailty and cognitive decline is complex with several different approaches considered including the examination of effects of separate domains on one another, temporal studies and bidirectionality.

Physical function (often as individual components of the frailty phenotype) and its association with cognitive impairment have been examined. For example, slow gait speed[43] and a decline in grip strength[44] have been linked to cognitive impairment and poorer performance on tests of memory, verbal skills, spatial skills and processing speed, respectively. Further, some studies have investigated the temporal relationship between the reduction of muscle strength and cognitive ability, suggesting that cognitive decline may precede physical decline[45,46], although the evidence suggests that this effect is attenuated when other comorbidities are considered[47].

While a number of studies have linked frailty to cognitive decline[48], with some indicating frailty predicts global cognitive decline and incident Alzheimer's disease[49], many investigations have focused on the associations between frailty and individual domains of cognitive function. In a recent longitudinal study, participants who were frail showed deficits on assessments of verbal fluency and information processing speed over a 12-year period[50].

Current evidence suggests that worsening frailty among older adults is considered a precursor to cognitive impairment, to a lesser extent, the reverse may also be true[43,44]. Frailty and cognitive impairment have a variety of underlying causes, both conditions can predict incident dementia, and each may influence the other. As they are highly correlated with advancing age, it is expected that the two will interact as people age[45,46]. Understanding their co-occurrence and interplay could therefore shed light on pathophysiology, management and prevention. The combination of two perspectives that are typically treated individually presents a challenge in the study of frailty and cognitive impairment. Additionally, only a few studies have explicitly investigated frailty and cognitive impairment in this manner. Although frail older persons may perform poorly on cognitive tests, they may not show significant changes in the cognitive tests, according to research that looked at the bidirectionality of frailty and individual domains of cognitive function[50,51]. Conversely, some researchers have examined a bidirectional association between components of frailty indices, namely physical function, and cognition. A significant predictive value of baseline handgrip strength on the onset of further cognitive decline was recently confirmed by a longitudinal study conducted on an American population over a 20-year period[52]. Interestingly, the authors also highlighted a significant bidirectional relationship in which the absence of cognitive deficit or the presence of increasing baseline cognitive deficit severity related to progressively higher risks of weaker handgrip strength[52]. The consistent bidirectional association between physical and cognitive functions has also been validated in a large Korean population over 8 years, with results suggesting that these conditions might share common pathways such as oxidative stress or chronic inflammation[53]. Oxidative stress[54] and chronic inflammation[55] are associated with both frailty and with cognitive decline.

No matter the method of measurement, frailty is a broader, more comprehensive concept that incorporates deficits across various domains and incorporates many aspects of physical function. Thus, rather than focusing solely on physical function, using the concept of frailty allows for the assessment of a more comprehensive measure of health and susceptibility. Few longitudinal studies have explored a bidirectional relationship between frailty and cognitive impairment. One such study by Godin *et al.*[56] identified a significant bi-directional relationship across two waves of SHARE, a study based in Europe.

Cognitive frailty

Another strategy for the exploration of the relationship between frailty and cognitive impairment is the concept of cognitive frailty. Defined by the International Academy of Nutrition and Aging/International Association of Gerontology and Geriatrics as '*the simultaneous presence of physical frailty operationalized with the frailty phenotype model and cognitive impairment diagnosed with a CDR score of 0·5 among older adults without concurrent Alzheimer's disease (AD) or any other form of dementia*', it is used to characterise people who have both features but have not been clinically diagnosed with dementia[57]. The inclusion of cognitive measures in the assessment of frailty can improve the predictive validity of the phenotype regarding unfavourable health and is important for assessing both physical and cognitive function in older adults for the planning of timely interventions.

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The role of nutrition in frailty and cognitive impairment

Nutrition and frailty are intrinsically linked. Unintentional weight loss is a key susceptibility factor for frailty, according to Fried *et al.*[36]. Primary sarcopenia, due in part to macro- and micro-nutrient deficiencies, is common among frail populations[58,59] with up to 90 % of older persons who are malnourished also being more frail[58,60,61].

While many studies have focused on the impact of macronutrient (e.g. protein) intake on frailty, fewer have reported associations between explicit frailty and the circulating micronutrients captured within the scope of this review[62–68] (Table 1). Previous investigations have exhibited design limitations including modest or female-only or relatively young samples or have used a single frailty measure[62–67]. However, a study from our research group used a large representative sample of adults aged 50 and over, to demonstrate that lower levels of lutein, zeaxanthin and vitamin D were associated with three different measures of frailty, and also that these relationships were evident in measures of prefrailty (Fig. 1)[68].

Nutrition is a modifiable risk factor that has been associated with many non-communicable diseases linked to dementia, such as diabetes and CVD[69,70]. Lifelong nutrition may also have a direct effect on brain function, for example, longitudinal studies have reported associations between certain dietary patterns or nutrients and brain-volume loss[71,72] and integrity[73], with some clinical trials confirming these results[74,75]. Oxidative stress is thought to be a major contributor to neurodegeneration and depression[76]; thus, antioxidants such as vitamin C[77–80], E[81] and β-carotene may be important[82], but no clear conclusions can be made. Overall, a substantial body of research, largely from observational studies, points to a direct impact of lifelong nutrition on clinical indicators of cognitive status in older persons.

Vitamin B_{12} and folate

The role of vitamin B_{12} and folate in frailty

Vitamin B_{12} and folate have been linked to various chronic diseases of ageing such as CVD, diabetes and cognitive impairment[83,84]. These water-soluble micronutrients are essential co-factors in one-carbon metabolism, DNA-methylation and nucleotide synthesis, serving a regulatory effect in all tissues in the body, including systemic inflammation[84]. Therefore, it has been proposed that these B vitamins provide a fundamental framework for comprehending the onset and development of frailty, by their modulating effect on cellular processes. Deficiency or low serum levels of vitamin B_{12} (<400 pg/ml, equivalent to <295·1 pM/l) seem to have a negative effect on conditions such as sarcopenia[85] and other musculoskeletal disorders[86] related to frailty. Conversely, it has been observed that ageing and frailty can lead to vitamin B_{12} deficiency[60]. Low folate has also been independently associated with frailty[62,64], but this relationship has not been observed consistently[67,68].

The role of vitamin B_{12} and folate in cognitive impairment

B-vitamins that are involved in one-carbon metabolic pathways have been studied extensively for their potential effect on cognitive impairment and dementia[87]. Both vitamin B_{12} and folate, in addition to vitamin B_6 and riboflavin, are required for DNA synthesis and repair, amino acid metabolism and methylation reactions. Further, these B-vitamins are required for efficient metabolism of homocysteine (HCY), a cytotoxic intermediary amino acid that is a downstream product of biological methylation reactions[87]. Observational evidence suggests that the inhibition of methylation reactions may influence cognitive impairment in ageing[87] and there is growing interest in the possibility that a loss of cognitive function may partly be explained by inadequate status of these vitamins[88–91]. Severe vitamin B_{12} deficiency, such as that seen in pernicious anaemia, causes severe neurological consequences including sensory and motor neuropathy. Low or deficient vitamin B_{12} status is associated with depression[92] and altered mental status and cognitive decline[93]. It also reduces the availability of folate for DNA synthesis[93]. Age-related deficiencies in folate transport and metabolism, use of anti-folate drugs, genetic factors and excessive alcohol consumption are among the factors that contribute to vitamin B_{12} and folate insufficiency[94], frequently seen in older persons[95]. In Irish longitudinal study on ageing (TILDA), the prevalence of older people with deficient or low vitamin B_{12} (<185 pM/l) and folate (<10 nM/l) status was 12 % and 15 %, respectively[96].

Several epidemiological studies have shown cross-sectional and prospective associations between low vitamin B_{12}[93] and folate[97–106], and the risk of cognitive impairment and dementia. As demonstrated previously by our group[107], low baseline folate levels can predict a reduction in overall cognitive function and episodic memory in older persons who were cognitively healthy, making them a potential key marker for the risk of early decline (Fig. 2). This was consistent with other studies showing low folate status was associated with higher risks of cognitive impairment or dementia[97–106].

In addition, selected observational data have suggested that older adults with simultaneous low vitamin B_{12} and high folate status had higher risks of anaemia and cognitive impairment or decline[108–110], given that high-dose folic acid (FA) treatment was shown to temporarily mask clinical symptoms in persons with pernicious anaemia[111]. However, the causal relevance of these associations remains uncertain with conflicting results[112–114]. TILDA reported that those with low B_{12} combined with high folate status did not have any adverse associations with cognitive performance compared. In contrast, the study demonstrated that higher concentrations of folate were associated with small, but statistically significant higher scores for global cognitive performance in this setting[115].

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Table 1. Summary of the existing relationship between selected micronutrients, frailty and cognitive impairment

Micronutrient	Major sources	Main findings associated with frailty and related measures (references)	Main findings associated with cognitive impairment and related measures (references)
Vitamin B_{12}	Animal products	• Low serum B_{12} concentrations associated with frailty[62] • Increasing MMA – 1·66–2·33 times greater odds of being frail compared to non-frail[66] • Serum B_{12} 15 % lower in individuals with sarcopenia[60,69]	• Low or deficient B_{12} concentrations associated with depression[92] and cognitive decline[93]
Folate	Animal products; milk; leafy vegetables; legumes	• Low serum folate associated with frailty[62] • Higher folate significantly and negatively associated with frailty[60,64,85] • Supplementation with folate, vitamins B_6, B_{12}, D and calcium improves frailty among community-living older persons[166]	• Low folate associated with the risk of cognitive impairment and dementia[97–106]
Vitamin D	Fish oils; red meat; fortified foods (e.g. ready to eat breakfast cereals, milk)	• Odds of being frail were higher for those participants with lowest vitamin D[62,63] • Higher vitamin D was significantly and negatively associated with frailty[64] • Three measures of frailty were associated with lower levels vitamin D[68] • Vitamin D supplementation is linked to improved gait speed and muscle strength in the elderly[129]	• Lower vitamin D was linked to faster cognitive ageing and worsening cognitive test scores[143,144]
Xanthophyll carotenoids (lutein, zeaxanthin)	Leafy vegetables and eggs	• Association between frailty and lutein/zeaxanthin[62] • Lowest quartile of serum carotenoids – increased risk of becoming frail[63] • Measures of frailty were associated with lower levels of lutein and zeaxanthin[68] • Zeaxanthin lower in subjects who are physically, cognitively or psychologically frail[162] • Lower plasma lutein and zeaxanthin concentrations were linked to decreased grip, hip and knee strength in community-dwelling older women, according to a cross-sectional study[163]	• Higher lutein and zeaxanthin have been positively associated with cognitive performance[164]
Composite of micronutrients		• Frail women were more likely to have at least two or more micronutrient deficiencies (a-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene, retinol, α-tocopherol, 25 (OH) D, vitamin B_6, B_{12} and folate)[62] • The number of nutritional deficiencies (retinol, α-tocopherol, 25-hydroxyvitamin D, vitamin B_6, vitamin B_{12}, folate, selenium, zinc and total carotenoids) associated with incident frailty[63] • Low intake of more than three (protein, vitamin D, E, C and folate)[64] • Three separate measures of frailty were associated with deficiencies in 5 – of B_{12}, folate, vitamin D lutein and zeaxanthin[68]	

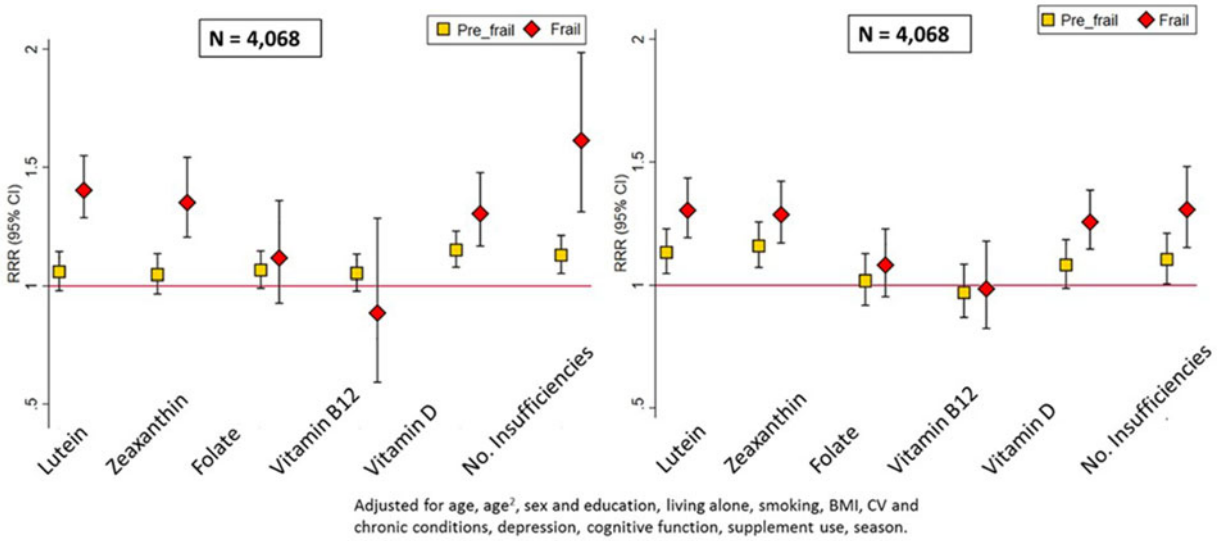

Fig. 1. Micronutrient insufficiency associated with pre-frailty and frailty as indexed by the frailty phenotype and frailty index. Adapted from O'Halloran *et al*., *J Am Med Dir Assoc*. 2020.

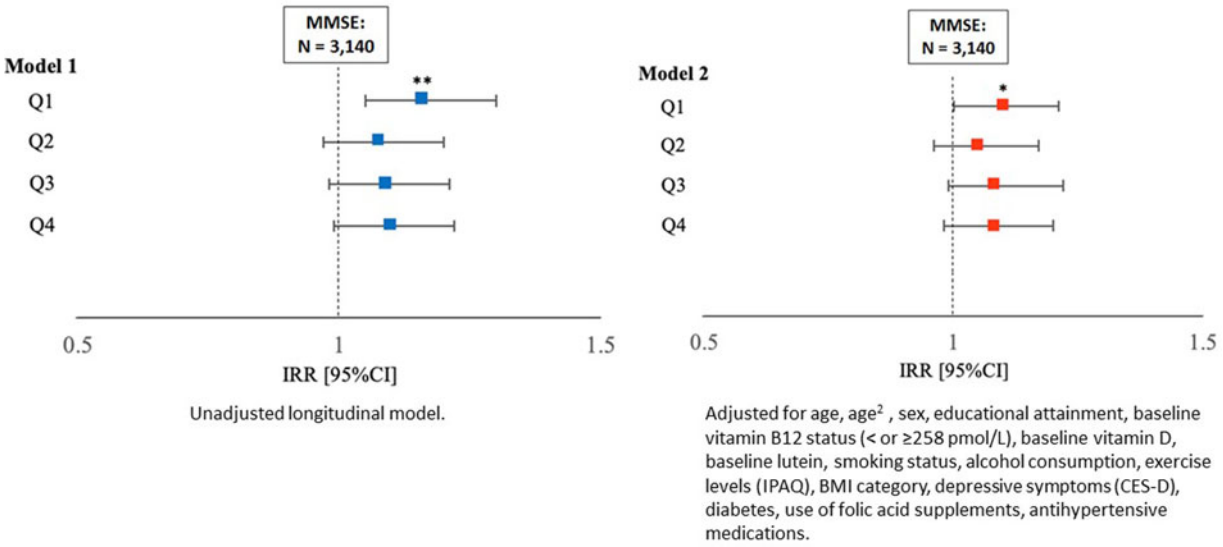

Fig. 2. Low folate predicts cognitive decline over 8 years. Adapted from O'Conner *et al*., *Eur J Clin Nutr*. 2022.

Evidence from randomised controlled trials (RCT) of B-vitamins has shown no consistent benefit of supplementation on cognitive outcomes. FA supplementation was associated with improved domain-specific cognitive performance in RCT with relatively large samples and ≥2 years follow-up[116–118]. One trial that examined individuals with high HCY to exclude causes other than low folate concentrations and FA supplementation (0·8 mg oral FA daily) was associated with improved memory, processing speed and sensorimotor speed after 3 years[117]. Supplementation was more effective in improving processing speed in those with high baseline HCY levels (>12·9 μM/l) and in improving information processing and sensorimotor speed in those with low baseline vitamin B_{12} concentrations (<250 pM/l)[117].

In another trial, testing combinations of folate, vitamins B_6 and B_{12}, and *n*-3 fatty acids for 4 years were effective in preserving semantic memory or temporal orientation in a subgroup of participants with previous coronary artery disease or ischaemic stroke, but not in the total trial population of 1748 men and women aged 45–80 years[119]. These observations suggest that individuals with high baseline HCY, low baseline vitamin B concentrations or established cardiovascular and cerebrovascular disease might benefit most from vitamin B supplementation.

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While most trials that have been carried out have been underpinned by the hypothesis that lowering HCY, which is associated with cognitive impairment, by B-vitamin supplementation, it is plausible that biological mechanisms other than hyperhomocysteinaemia may underlie the associations between B-vitamins and cognitive impairment. Other proposed mechanisms include impaired methylation and misincorporation of uracil into DNA. Vitamins and nutrients often function as a collection of cofactors, therefore interventions using singular or closely related compounds may have too narrow a focus and do not account for the complexity of the synergistic interactions between nutrients. This is illustrated by another trial using FA, B_6 and B_{12}, showing treatment was effective only in those with high baseline *n*-3 fatty acid concentrations. In fact, *n*-3 fatty acid status was protective against brain atrophy only in the presence of B-vitamin supplementation, suggesting that both are needed for effectiveness[120].

Vitamin D

The role of vitamin D in frailty

Due to its well-established relationship with bone and muscle health, vitamin D intake is vital for the ageing population. Vitamin D is known to regulate calcium homeostasis, bone mineralisation and inflammatory response. Vitamin D deficiency (25(OH)D < 30 nM/l) has been consistently reported to be highly prevalent in older adults[121] with data from TILDA suggesting a prevalence of 13 %[122]. Low vitamin D also has been consistently associated with frailty[62–64] and prefrailty in the TILDA cohort (Fig. 1)[68] Evidence linking low vitamin D levels and incident phenotype frailty has been shown in both meta- and longitudinal analyses[123–128]. After a 3-year follow-up, Vogt *et al.* observed that participants (>65 years) with baseline vitamin D levels <37·5 nM/l, compared with ≥75 nM/l, were more likely to become pre-frail or frail[127]. A meta-analysis revealed that vitamin D supplementation is linked to improved gait speed and muscle strength in the older persons[129]. Similar to this, a meta-analysis of intervention trials reported that calcium and vitamin D supplementation may help prevent fractures in older persons[57]. In addition, vitamin D supplementation was associated with increased global DNA methylation levels and reduced epigenetic ageing[130,131]. However, the exact role of vitamin D intake in older adults remains unclear, in part due to limitations in intervention study design and targeting of appropriate populations.

Frailty, COVID-19 and vitamin D

The presence of co-morbidity and frailty in older adults has been associated with a higher risk of undesired outcomes and mortality due to COVID-19 and poorer response to COVID-19 vaccination[132]. Therefore, the identification of potentially accessible and low-cost health and lifestyle behaviours that could attenuate this risk in those with frailty remains a high priority.

Recent research has highlighted that vitamin D may have an important function within the immune system. Expression of the vitamin D receptor has been identified on a variety of cells of the immune system including macrophages, T lymphocytes, dendritic cells and monocytes and may act as a modulator through its ability to alter cytokine secretion[133]. For instance, low vitamin D status has been previously associated with markers of inflammation and an enhanced pro-inflammatory profile in older Irish adults[134]. Pro-inflammatory cytokines have been implicated in increased severity of COVID-19 and positive modulation of these interleukins by vitamin D has been hypothesised[135]. Early observational evidence suggested that countries with either a programme of mandatory vitamin D food fortification or higher exposure to UVB vitamin D forming light had lower incidence of COVID-19 and death rates in comparison to countries without fortification or low light exposure[135,136]. Actual vitamin D intervention studies have produced mixed results with little to no effect in healthy populations but positive effects in the at-risk frail populations[137].

The role of vitamin D in cognitive impairment

The body of evidence for the function of vitamin D in maintaining brain health has been growing since the discovery of the vitamin D receptor in the brain[138]. Several different neurobiological pathways have been linked[139]. A meta-analysis[140] observed an inverse dose–response relationship between the concentrations of vitamin D and risk of dementia or Alzheimer's disease.

Systematic reviews and meta-analyses have demonstrated that Alzheimer's disease patients' serum vitamin D status is lower than that of healthy controls, and that this is related to worse cognitive results[141,142]. Reduced vitamin D status has been linked to faster cognitive ageing and worsening cognitive test scores, according to longitudinal studies[143,144]. In addition, Hooshmand *et al.* used MRI to show that having more vitamin D was linked to larger brain volumes[145].

Large cross-sectional and prospective investigations revealed that a higher risk of depression was associated with decreased serum vitamin D status[146–149]. A thorough systematic analysis that incorporated data from cross-sectional, prospective and RCT studies concluded that having reduced vitamin D status may increase the chance of developing late-life depression[147]. More recently, an extensive meta-analysis of 41 RCT (*n*53 235) found that vitamin D supplementation reduced the occurrence of depressive symptoms[150]. However, experimental evidence of the effect of vitamin D supplementation is scarce, with a recent review suggesting that a role for vitamin D supplementation in enhancing cognition (separate from depression) in adults cannot be supported based on evidence to date[151]. The variability of vitamin D concentrations, cognitive tests used, supplementation doses and the samples' characteristics (i.e. ethnicity or number of participants who are deficient) may explain the ambiguity in the findings.

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Lutein and zeaxanthin

The role of lutein and zeaxanthin in frailty

Xanthophyll carotenoids have long been implicated in improving visual outcomes and disease progression in individuals with age-related macular degeneration. More recently, a putative protective role for these compounds in other chronic diseases of ageing has emerged, including cancer[152], CVD[153], diabetes[154], neurodegenerative disease[155] and bone health[156]. Citrus fruits, spinach, kale, broccoli, maize and other vegetables and fruits are the main sources of lutein and zeaxanthin in the diet[157]. The biological mechanisms underpinning these associations may lie in their antioxidant[158] and anti-inflammatory properties[159,160] and the promotion of cell membrane stabilisation[161]. These mechanisms likely explain why inverse associations between carotenoid levels and disease risk have been observed for several age-associated conditions with an inflammatory or oxidative stress aetiology. Consequently, they may influence multi-system dysregulation which has been proposed to underlie the frailty syndrome.

Several studies have shown associations between lutein and zeaxanthin and frailty[62,63,68,162], in addition to physical deficits including decreased grip, hip and knee strength in community-dwelling older women, according to a cross-sectional study[163]. Fig. 1 displays the results of a recent cross-sectional examination from our group that demonstrated that plasma lutein and zeaxanthin concentrations were negatively correlated with prefrailty and frailty across three different frailty instruments[68].

The role of lutein and zeaxanthin in cognitive impairment

Carotenoids have been proposed to have anti-inflammatory effects in addition to their antioxidant characteristics, by interacting with inflammatory cellular signalling cascades[159]. Lutein and zeaxanthin – xanthophyll carotenoids with antioxidant and anti-inflammatory characteristics – are present in the retina and the brain and have neuroprotective properties. High concentrations of these carotenoids have been positively related to cognitive performance[164]. Higher plasma lutein and zeaxanthin were independently associated with better composite scores in the areas of executive function, memory and global cognition. Additionally, Feeney *et al.* discovered evidence linking increased plasma zeaxanthin with better processing speed[164]. Although the results of large population studies and clinical trials have been somewhat mixed, a recent review demonstrated a direct relationship among cognitive functions, macular pigment and the intake of lutein and zeaxanthin[165].

Dietary patterns, frailty and cognitive impairment

It is important to acknowledge the complex and synergistic relationships between nutrients. Vitamins and micronutrients often act as collections of co-factors, therefore interventions using singular or closely related compounds may have a focus that is too narrow. Interestingly, several studies have reported an increasing likelihood of frailty[62–64,68] with increasing accumulation of micronutrient insufficiencies. This is supported by a study that found supplementation with folate, vitamins B_6, B_{12}, D and calcium improved frailty among community-living older persons[166].

Because of the complex biological interactions between the various components of the diet, it has been suggested that using a whole-diet approach, through the study of dietary patterns rather than individual nutrients or food groups, might help to elucidate the role of diet in chronic diseases, such as frailty and cognitive impairment in older people. The Mediterranean diet is a good example of using dietary patterns to characterise dietary intake. Adherence to a Mediterranean-type diet pattern, known for its benefits on cardiovascular health and longevity[167,168], has also been linked to a decreased risk of frailty[169–174] and cognitive impairment[175].

With respect to frailty, data from a 6-year longitudinal study revealed a lower risk of frailty in participants with a high Mediterranean diet score[173]. A recent meta-analysis, examining adherence to the Mediterranean diet and risk of frailty, indicated those with strongest adherence had a 56 % decreased risk of frailty[176]. Further, a study found that older women with type-2 diabetes who were at risk for frailty from the nurses' health study benefited from better adherence to a Mediterranean diet[177]. Therefore, it seems in addition to consuming a Mediterranean-type diet to possibly treat frailty, later adoption of a Mediterranean-type diet may act as a limiting factor for the development of frailty[177,178].

Other dietary patterns have shown comparable results. Higher healthy eating index scores were inversely related to lower risks of physical frailty in US older adults, according to Fan *et al.*[179]. Another study using the 'dietary inflammatory index', a dietary pattern marker of foods and nutrient intakes related with inflammation, which may contribute to frailty, found that among 1948 participants who were tracked for up to 4 years, those with the highest adherence to the index had a higher risk of frailty and slower gait speed[180].

The majority of observational studies examining cognitive impairment point to an association between higher adherence to the Mediterranean diet and slower performance decline on various cognitive test batteries, as well as a decreased risk of dementia, mild cognitive impairment or progression from mild cognitive impairment to dementia. Two clinical trials that compared the Mediterranean diet pattern with nuts or olive oil to recommendations to limit dietary fat confirm these findings[181,182].

These approaches have the benefit of capturing potential interactions between microconstituents of diet, whether they are additive, antagonistic or synergistic[183]. Applying similar approaches to the study of frailty and cognitive impairment may yield more informative insights than focusing on single nutrients alone.

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Summary and way forward

In this review, we have focused on selected micronutrients that have been demonstrated to have a high prevalence of insufficiency and/or deficiency among older adults. We have reviewed the evidence, from TILDA and other studies, for their impact on age-related pre-frailty, frailty and cognitive decline. We have shown that low concentrations of folate and carotenoids are implicated in poorer cognitive health and that the co-occurrence of multiple nutrient deficiencies confers greatest risk for pre-frailty and frailty in the TILDA cohort of older adults. These findings are largely, if not consistently, supported by other epidemiological studies internationally. While the results from RCT often fail to support these relationships, there may be design reasons for this, such as relatively short follow-up times during RCT and the exclusion of those older adults with morbidities, frailty and cognitive problems. Inconsistent relationships for individual micronutrients with these outcomes in older adults may be overcome by assessing sup-optimal levels of several micronutrients simultaneously and using the accumulation of micronutrient insufficiencies/deficiencies, as demonstrated by TILDA data (Fig. 1). Single measurements can lead to misclassification, and the cut-off points routinely used to define deficiency may identify an acute rather than a chronic deficiency in older age groups. The complex synergistic interactions between nutrients are also important to consider. Vitamins and nutrients often function as a collection of co-factors, therefore interventions using singular or closely related compounds may have too narrow a focus. Also, given that older adults tend to experience malabsorption of nutrients, some micronutrients may be absorbed differently or less efficiently among older age groups. This may mean that definitions of micronutrient insufficiency and deficiency may be less accurate at older ages and chronic low/sub-optimal status could have less well-understood negative impacts on health. These biological changes coupled with diminution of appetite may partly explain the consistent observation that older adults struggle to maintain sufficient dietary intakes and circulating levels of several micronutrients with advancing age. Among previous TILDA studies, our group has demonstrated that the current custom of voluntary micronutrient fortification in Ireland is not effective in maintenance of sufficient micronutrient status among older age groups[96,122].

Sustaining the health of a globally ageing population requires strategies that will prolong healthspan by delaying the onset of age-related diseases until later in the life course. Therefore, it is important to focus on modifiable factors, such as micronutrients, that can be intervened upon, particularly in 'at-risk' groups if they can be identified early, i.e. those who have pre-frailty and/or indications of cognitive decline. Testing for micronutrient insufficiencies/deficiencies in these 'at-risk' groups may be used to both monitor the health of older adults and as an intervention target to support biological function and decelerate biological ageing and the onset of physical and cognitive decline. To achieve this, public health policies and awareness programmes are required that highlight the importance of maintaining micronutrient sufficiency via mandatory fortification and/or supplementation to support health as we age.

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Conflict of Interest

None.

Authorship

The authors had sole responsibility for all aspects of preparation of this paper.

References

1. Mack CA (2011) Fifty years of Moore's law. *IEEE Trans Semicond Manuf* **24**, 202–207.
2. Mackenbach JP (1996) The contribution of medical care to mortality decline: McKeown revisited. *J Clin Epidemiol* **49**, 1207–1213.
3. Cutler D & Miller G (2005) The role of public health improvements in health advances: the twentieth-century United States. *Demography* **42**, 1–22.
4. Christensen K, Doblhammer G, Rau R *et al.* (2009) Ageing populations: the challenges ahead. *Lancet* **374**, 1196–1208.
5. Human Mortality Database (2020) [Internet]. [cited 22/09/2022]. www.mortality.org.
6. Collaborators GBDM (2017) Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: a systematic analysis for the global burden of disease study 2016. *Lancet* **390**, 1084–1150.
7. Population GBD & Fertility C (2018) Population and fertility by age and sex for 195 countries and territories, 1950–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* **392**, 1995–2051.
8. The world population is changing: for the first time there are more people over 64 than children younger than 5 [Internet]. Our World in Data. 2019 [cited 19 Sept 2022]. https://ourworldindata.org/population-aged-65-outnumber-children.
9. United Nations DoEaSA (2017) Population division. World population ageing 2017 (ST/ESA/SER.A/408).

https://doi.org/10.1017/S0029665123002707 Published online by Cambridge University Press

[Online]. New York: United Nations. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Report.pdf.
10. WHO (2020) World Health Statistics 2020. Monitoring health for the sustainable development goals. World Health Organisation; 13 May 2020.
11. Partridge L, Deelen J & Slagboom PE (2018) Facing up to the global challenges of ageing. *Nature* **561**, 45–56.
12. Collaborators NCDC (2018) NCD countdown 2030: worldwide trends in non-communicable disease mortality and progress towards sustainable development goal target 3·4. *Lancet* **392**, 1072–1088.
13. Cheng X, Yang Y, Schwebel DC *et al.* (2020) Population ageing and mortality during 1990–2017: a global decomposition analysis. *PLoS Med* **17**, e1003138.
14. Garmany A, Yamada S & Terzic A (2021) Longevity leap: mind the healthspan gap. *NPJ Regen Med* **6**, 57.
15. Beard JR, Officer A, de Carvalho IA *et al.* (2016) The world report on ageing and health: a policy framework for healthy ageing. *Lancet* **387**, 2145–2154.
16. Hamczyk MR, Nevado RM, Barettino A *et al.* (2020) Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol* **75**, 919–930.
17. Ferrucci L, Levine ME, Kuo PL *et al.* (2018) Time and the metrics of aging. *Circ Res* **123**, 740–744.
18. Ferrucci L, Gonzalez-Freire M, Fabbri E *et al.* (2020) Measuring biological aging in humans: a quest. *Aging Cell* **19**, e13080.
19. Lowsky DJ, Olshansky SJ, Bhattacharya J *et al.* (2014) Heterogeneity in healthy aging. *J Gerontol A Biol Sci Med Sci* **69**, 640–649.
20. Mueller AL, McNamara MS & Sinclair DA (2020) Why does COVID-19 disproportionately affect older people? *Aging* **12**, 9959–9981.
21. Briggs R, McDowell CP, De Looze C *et al.* (2021) Depressive symptoms among older adults pre- and post-COVID-19 pandemic. *J Am Med Dir Assoc* **22**, 2251–2257.
22. Elliott J, Munford L, Ahmed S *et al.* (2022) The impact of COVID-19 lockdowns on physical activity amongst older adults: evidence from longitudinal data in the UK. *BMC Public Health* **22**, 1802.
23. McGarrigle CA, Ward M, De Looze C *et al.* (2022) Caring in the time of COVID-19, longitudinal trends in well-being and mental health in carers in Ireland: evidence from the Irish longitudinal study on ageing (TILDA). *Arch Gerontol Geriatr* **102**, 104719.
24. Clegg A, Young J, Iliffe S *et al.* (2013) Frailty in elderly people. *Lancet* **381**, 752–762.
25. Howlett SE, Rutenberg AD & Rockwood K (2021) The degree of frailty as a translational measure of health in aging. *Nat Aging* **1**, 651–665.
26. Roe L, Normand C, Wren MA *et al.* (2017) The impact of frailty on healthcare utilisation in Ireland: evidence from the Irish longitudinal study on ageing. *BMC Geriatr* **17**, 203.
27. O'Halloran AM, Hartley P, Moloney D *et al.* (2021) Informing patterns of health and social care utilisation in Irish older people according to the clinical frailty scale. *HRB Open Res* **4**, 54.
28. Romero-Ortuno R & O'Shea D (2013) Fitness and frailty: opposite ends of a challenging continuum! Will the end of age discrimination make frailty assessments an imperative? *Age Ageing* **42**, 279–280.
29. Romero-Ortuno R, Hartley P, Davis J *et al.* (2021) Transitions in frailty phenotype states and components over 8 years: evidence from the Irish longitudinal study on ageing. *Arch Gerontol Geriatr* **95**, 104401.
30. Dent E, Martin FC, Bergman H *et al.* (2019) Management of frailty: opportunities, challenges, and future directions. *Lancet* **394**, 1376–1386.
31. Dent E, Morley JE, Cruz-Jentoft AJ *et al.* (2019) Physical frailty: ICFSR international clinical practice guidelines for identification and management. *J Nutr Health Aging* **23**, 771–787.
32. Hoogendijk EO, Afilalo J, Ensrud KE *et al.* (2019) Frailty: implications for clinical practice and public health. *Lancet* **394**, 1365–1375.
33. Ellis G, Gardner M, Tsiachristas A *et al.* (2017) Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* **9**, CD006211.
34. van Rijn M, Suijker JJ, Bol W *et al.* (2016) Comprehensive geriatric assessment: recognition of identified geriatric conditions by community-dwelling older persons. *Age Ageing* **45**, 894–899.
35. Fried LP, Ferrucci L, Darer J *et al.* (2004) Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* **59**, 255–263.
36. Fried LP, Tangen CM, Walston J *et al.* (2001) Frailty in older adults: evidence for a phenotype. *J Gerontol: Series A* **56**, M146–MM57.
37. Mitnitski AB, Song X & Rockwood K (2004) The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. *J Gerontol A Biol Sci Med Sci* **59**, M627–M632.
38. Rockwood K & Mitnitski A (2007) Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* **62**, 722–727.
39. Rockwood K, Song X, MacKnight C *et al.* (2005) A global clinical measure of fitness and frailty in elderly people. *CMAJ* **173**, 489–495.
40. Theou O, Perez-Zepeda MU, van der Valk AM *et al.* (2021) A classification tree to assist with routine scoring of the clinical frailty scale. *Age Ageing* **50**, 1406–1411.
41. Martin FC & O'Halloran AM (2020) Tools for assessing frailty in older people: general concepts. *Adv Exp Med Biol* **1216**, 9–19.
42. Collard RM, Boter H, Schoevers RA *et al.* (2012) Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* **60**, 1487–1492.
43. Yassuda MS, Lopes A, Cachioni M *et al.* (2012) Frailty criteria and cognitive performance are related: data from the FIBRA study in Ermelino Matarazzo, São Paulo, Brazil. *J Nutr Health Aging* **16**, 55–61.
44. Sternäng O, Reynolds CA, Finkel D *et al.* (2016) Grip strength and cognitive abilities: associations in old age. *J Gerontol B: Psychol Sci Soc Sci* **71**, 841–848.
45. Inzitari M, Baldereschi M, Carlo AD *et al.* (2007) Impaired attention predicts motor performance decline in older community-dwellers with normal baseline mobility: results from the Italian longitudinal study on aging (ILSA). *J Gerontol A: Biol Sci Med Sci* **62**, 837–843.
46. Taekema DG, Ling CH, Kurrle SE *et al.* (2012) Temporal relationship between handgrip strength and cognitive performance in oldest old people. *Age Ageing* **41**, 506–512.
47. Atkinson HH, Rosano C, Simonsick EM *et al.* (2007) Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *J Gerontol A: Biol Sci Medi Sci* **62**, 844–850.
48. Mitnitski A, Fallah N, Rockwood M *et al.* (2011) Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. *J Nutr Health Aging* **15**, 863–867.

https://doi.org/10.1017/S0029665123002707 Published online by Cambridge University Press

49. Buchman AS, Boyle PA, Wilson RS *et al.* (2007) Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosom Med* **69**, 483–489.
50. Bunce D, Batterham PJ & Mackinnon AJ (2019) Long-term associations between physical frailty and performance in specific cognitive domains. *J Gerontol B* **74**, 919–926.
51. Ávila-Funes JA, Amieva H, Barberger-Gateau P *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**, 453–461.
52. McGrath R, Vincent BM, Hackney KJ *et al.* (2020) The longitudinal associations of handgrip strength and cognitive function in aging Americans. *J Am Med Dir Assoc* **21**, 634–639.e1.
53. Kim GR, Sun J, Han M *et al.* (2019) Evaluation of the directional relationship between handgrip strength and cognitive function: the Korean longitudinal study of ageing. *Age Ageing* **48**, 426–432.
54. Mulero J, Zafrilla P & Martinez-Cacha A (2011) Oxidative stress, frailty and cognitive decline. *J Nutr Health Aging* **15**, 756–760.
55. Panza F, Seripa D, Solfrizzi V *et al.* (2015) Targeting cognitive frailty: clinical and neurobiological roadmap for a single complex phenotype. *J Alzheimer's Dis* **47**, 793–813.
56. Godin J, Armstrong JJ, Rockwood K *et al.* (2017) Dynamics of frailty and cognition after age 50: why it matters that cognitive decline is mostly seen in old age. *J Alzheimer's Dis* **58**, 231–242.
57. Kelaiditi E, Cesari M, Canevelli M *et al.* (2013) Cognitive frailty: rational and definition from an (IANA/IAGG) international consensus group. *J Nutr Health Aging* **17**, 726–734.
58. Bollwein J, Volkert D, Diekmann R *et al.* (2013) Nutritional status according to the mini nutritional assessment (MNA®) and frailty in community dwelling older persons: a close relationship. *J Nutr Health Aging* **17**, 351–356.
59. Lorenzo-López L, Maseda A, de Labra C *et al.* (2017) Nutritional determinants of frailty in older adults: a systematic review. *BMC Geriatr* **17**, 1–13.
60. Verlaan S, Aspray TJ, Bauer JM *et al.* (2017) Nutritional status, body composition, and quality of life in community-dwelling sarcopenic and non-sarcopenic older adults: a case-control study. *Clin Nutr* **36**, 267–274.
61. Batsis JA & Villareal DT (2018) Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol* **14**, 513–537.
62. Michelon E, Blaum C, Semba RD *et al.* (2006) Vitamin and carotenoid status in older women: associations with the frailty syndrome. *J Gerontol A: Biol Sci Medi Sci* **61**, 600–607.
63. Semba RD, Bartali B, Zhou J *et al.* (2006) Low serum micronutrient concentrations predict frailty among older women living in the community. *J Gerontol A: Biol Sci Medi Sci* **61**, 594–599.
64. Bartali B, Frongillo EA, Bandinelli S *et al.* (2006) Low nutrient intake is an essential component of frailty in older persons. *J Gerontol A: Biol Sci Medi Sci* **61**, 589–593.
65. Kobayashi S, Asakura K, Suga H *et al.* (2014) Inverse association between dietary habits with high total antioxidant capacity and prevalence of frailty among elderly Japanese women: a multicenter cross-sectional study. *J Nutr Health Aging* **18**, 827–836.
66. Matteini AM, Walston JD, Fallin M *et al.* (2008) Markers of B-vitamin deficiency and frailty in older women. *J Nut Health Aging* **12**, 303–308.
67. Smit E, Winters-Stone KM, Loprinzi PD *et al.* (2013) Lower nutritional status and higher food insufficiency in frail older US adults. *Br J Nutr* **110**, 172–178.
68. O'Halloran AM, Laird EJ, Feeney J *et al.* (2020) Circulating micronutrient biomarkers are associated with 3 measures of frailty: evidence from the Irish longitudinal study on ageing. *J Am Med Dir Assoc* **21**, 240–247.e5.
69. Riederer P, Korczyn AD, Ali SS *et al.* (2017) The diabetic brain and cognition. *J Neural Transm* **124**, 1431–1454.
70. Santos CY, Snyder PJ, Wu W-C *et al.* (2017) Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. *Alzheimer's & Dement: Diagn, Assess Dis Monit* **7**, 69–87.
71. Hooshmand B, Mangialasche F, Kalpouzos G *et al.* (2016) Association of vitamin B12, folate, and sulfur amino acids with brain magnetic resonance imaging measures in older adults: a longitudinal population-based study. *JAMA Psychiatry* **73**, 606–613.
72. Luciano M, Corley J, Cox SR *et al.* (2017) Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. *Neurology* **88**, 449–455.
73. Virtanen JK, Siscovick DS, Lemaitre RN *et al.* (2013) Circulating omega-3 polyunsaturated fatty acids and subclinical brain abnormalities on MRI in older adults: the cardiovascular health study. *J Am Heart Assoc* **2**, e000305.
74. Witte AV, Kerti L, Margulies DS *et al.* (2014) Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. *J Neurosci* **34**, 7862–7870.
75. Smith AD, Smith SM, De Jager CA *et al.* (2010) Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS ONE* **5**, e12244.
76. Bishop NA, Lu T & Yankner BA (2010) Neural mechanisms of ageing and cognitive decline. *Nature* **464**, 529–535.
77. Hamer M, Bates CJ & Mishra GD (2011) Depression, physical function, and risk of mortality: National Diet and Nutrition Survey in adults older than 65 years. *Am J Geriatr Psychiatry* **19**, 72–78.
78. Payne ME, Steck SE, George RR *et al.* (2012) Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. *J Acad Nutr Diet* **112**, 2022–2027.
79. Devore EE, Grodstein F, van Rooij FJ *et al.* (2010) Dietary antioxidants and long-term risk of dementia. *Arch Neurol* **67**, 819–825.
80. Luchsinger JA, Tang M-X, Shea S *et al.* (2003) Antioxidant vitamin intake and risk of Alzheimer disease. *Arch Neurol* **60**, 203–208.
81. Banikazemi Z, Mokhber N, Safarian M *et al.* (2015) Dietary vitamin E and fat intake are related to Beck's depression score. *Clin Nutr ESPEN* **10**, e61–ee5.
82. Engelhart MJ, Geerlings MI, Ruitenberg A *et al.* (2002) Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* **287**, 3223–3229.
83. Bailey LB (2009) *Folate in Health and Disease*, 2nd Edition, Boca Raton: CRC Press.
84. Kennedy DO (2016) B vitamins and the brain: mechanisms, dose and efficacy – a review. *Nutrients* **8**, 68.
85. Bulut EA, Soysal P, Aydin AE *et al.* (2017) Vitamin B12 deficiency might be related to sarcopenia in older adults. *Exp Gerontol* **95**, 136–140.
86. Pannérec A, Migliavacca E, De Castro A *et al.* (2018) Vitamin B12 deficiency and impaired expression of

https://doi.org/10.1017/S0029665123002707 Published online by Cambridge University Press

amnionless during aging. *J Cachexia Sarcopenia Muscle* **9**, 41–52.
87. Smith AD & Refsum H (2016) Homocysteine, B vitamins, and cognitive impairment. *Annu Rev Nutr* **36**, 211–239.
88. Raman G, Tatsioni A, Chung M *et al.* (2007) Heterogeneity and lack of good quality studies limit association between folate, vitamins B-6 and B-12, and cognitive function. *J Nutr* **137**, 1789–1794.
89. Smith AD (2008) The worldwide challenge of the dementias: a role for B vitamins and homocysteine? *Food Nutr Bull* **29**(Suppl. 1), S143–SS72.
90. Smith AD & Refsum H (2008) Vitamin B-12 and cognition in the elderly. *Am J Clin Nutr* **89**, 707S–711S.
91. Vogel T, Dali-Youcef N, Kaltenbach G *et al.* (2009) Homocysteine, vitamin B12, folate and cognitive functions: a systematic and critical review of the literature. *Int J Clin Pract* **63**, 1061–1067.
92. Laird E, O'Halloran AM, Molloy AM *et al.* (2021) Low vitamin B12 but not folate is associated with incident depressive symptoms in community-dwelling older adults: a 4 year longitudinal study. *Br J Nutr* **Dec 13**, 1–22.
93. Green R, Allen LH, Bjørke-Monsen A-L *et al.* (2017) Vitamin B 12 deficiency. *Nat Rev Dis Primers* **3**, 1–20.
94. Allen LH (2008) Causes of vitamin B12 and folate deficiency. *Food Nutr Bull* **29**(Suppl. 1), S20–S34.
95. Clarke R, Grimley Evans J, Schneede J *et al.* (2004) Vitamin B12 and folate deficiency in later life. *Age Ageing* **33**, 34–41.
96. Laird EJ, O'Halloran AM, Carey D *et al.* (2018) Voluntary fortification is ineffective to maintain the vitamin B 12 and folate status of older Irish adults: evidence from the Irish longitudinal study on ageing (TILDA). *Br J Nutr* **120**, 111–120.
97. Quadri P, Fragiacomo C, Pezzati R *et al.* (2004) Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. *Am J Clin Nutr* **80**, 114–122.
98. Ramos MI, Allen LH, Mungas DM *et al.* (2005) Low folate status is associated with impaired cognitive function and dementia in the Sacramento area Latino study on aging. *Am J Clin Nutr* **82**, 1346–1352.
99. Ravaglia G, Forti P, Maioli F *et al.* (2005) Homocysteine and folate as risk factors for dementia and Alzheimer disease. *Am J Clin Nutr* **82**, 636–643.
100. Tucker KL, Qiao N, Scott T *et al.* (2005) High homocysteine and low B vitamins predict cognitive decline in aging men: the veterans affairs normative aging study. *Am J Clin Nutr* **82**, 627–635.
101. Tettamanti M, Garrì MT, Nobili A *et al.* (2006) Low folate and the risk of cognitive and functional deficits in the very old: the Monzino 80-plus study. *J Am Coll Nutr* **25**, 502–508.
102. Kim J-M, Stewart R, Kim S-W *et al.* (2008) Changes in folate, vitamin B12 and homocysteine associated with incident dementia. J Neurol *Neurosurg Psychiatry* **79**, 864–868.
103. Michelakos T, Kousoulis AA, Katsiardanis K *et al.* (2013) Serum folate and B12 levels in association with cognitive impairment among seniors: results from the VELESTINO study in Greece and meta-analysis. *J Aging Health* **25**, 589–616.
104. Ma F, Wu T, Zhao J *et al.* (2017) Plasma homocysteine and serum folate and vitamin B12 levels in mild cognitive impairment and Alzheimer's disease: a case-control study. *Nutrients* **9**, 725.
105. Kado DM, Karlamangla AS, Huang M-H *et al.* (2005) Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur studies of successful aging. *Am J Med* **118**, 161–167.
106. Fu J, Liu Q, Zhu Y *et al.* (2022) Circulating folate concentrations and the risk of mild cognitive impairment: a prospective study on the older Chinese population without folic acid fortification. *Eur J Neurol* **29**, 2913–2924.
107. O'Connor D, Scarlett S, De Looze C *et al.* (2022) Low folate predicts accelerated cognitive decline: 8-year follow-up of 3140 older adults in Ireland. *Eur J Clin Nutr* **76**, 950–957.
108. Morris MS, Jacques PF, Rosenberg IH *et al.* (2007) Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr* **85**, 193–200.
109. Morris MS, Selhub J & Jacques PF (2012) Vitamin B-12 and folate status in relation to decline in scores on the mini-mental state examination in the Framingham heart study. *J Am Geriatr Soc* **60**, 1457–1464.
110. Moore EM, Ames D, Mander AG *et al.* (2014) Among vitamin B12 deficient older people, high folate levels are associated with worse cognitive function: combined data from three cohorts. *J Alzheimer's Dis* **39**, 661–668.
111. Ross J, Belding H & Paegel B (1948) The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood* **3**, 68–90.
112. Clarke R, Sherliker P, Hin H *et al.* (2008) Folate and vitamin B 12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK. *Br J Nutr* **100**, 1054–1059.
113. Miller JW, Garrod MG, Allen LH *et al.* (2009) Metabolic evidence of vitamin B-12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate. *Am J Clin Nutr* **90**, 1586–1592.
114. Doets EL, Ueland PM, Tell GS *et al.* (2014) Interactions between plasma concentrations of folate and markers of vitamin B 12 status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland health study. *Br J Nutr* **111**, 1085–1095.
115. O'Connor DMA, Laird EJ, Carey D *et al.* (2020) Plasma concentrations of vitamin B(12) and folate and global cognitive function in an older population: cross-sectional findings from the Irish longitudinal study on ageing (TILDA). *Br J Nutr* **124**, 602–610.
116. de Jager CA, Oulhaj A, Jacoby R *et al.* (2012) Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry* **27**, 592–600.
117. Durga J, van Boxtel MP, Schouten EG *et al.* (2007) Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *The Lancet* **369**, 208–216.
118. Walker JG, Batterham PJ, Mackinnon AJ *et al.* (2012) Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms – the beyond ageing project: a randomized controlled trial. *Am J Clin Nutr* **95**, 194–203.
119. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P *et al.* (2011) Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU. FOL. OM3 randomized trial. *Am J Clin Nutr* **94**, 278–286.
120. Jernerén F, Elshorbagy AK, Oulhaj A *et al.* (2015) Brain atrophy in cognitively impaired elderly: the importance of

https://doi.org/10.1017/S0029665123002707 Published online by Cambridge University Press

long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. *Am J Clin Nutr* **102**, 215–221.
121. Ju SY, Lee JY & Kim DH (2018) Low 25-hydroxyvitamin D levels and the risk of frailty syndrome: a systematic review and dose-response meta-analysis. *BMC Geriatr* **18**, 1–11.
122. Laird E, O'Halloran AM, Carey D *et al.* (2018) The prevalence of vitamin D deficiency and the determinants of 25(OH)D concentration in older Irish adults: data from the Irish longitudinal study on ageing (TILDA). *J Gerontol A Biol Sci Med Sci* **73**, 519–525.
123. Buta B, Choudhury PP, Xue QL *et al.* (2017) The association of vitamin D deficiency and incident frailty in older women: the role of cardiometabolic diseases. *J Am Geriatr Soc* **65**, 619–624.
124. Ensrud KE, Blackwell TL, Cauley JA *et al.* (2011) Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc* **59**, 101–106.
125. Ensrud KE, Ewing SK, Fredman L *et al.* (2010) Circulating 25-hydroxyvitamin D levels and frailty status in older women. *J Clin Endocrinol Metab* **95**, 5266–5273.
126. Puts MT, Visser M, Twisk JW *et al.* (2005) Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol* **63**, 403–411.
127. Vogt S, Decke S, de Las Heras Gala T *et al.* (2015) Prospective association of vitamin D with frailty status and all-cause mortality in older adults: results from the KORA-age study. *Prev Med* **73**, 40–46.
128. Wong YY, McCaul KA, Yeap BB *et al.* (2013) Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the health in men study. *J Clin Endocrinol Metab* **98**, 3821–3828.
129. Muir SW & Montero-Odasso M (2011) Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* **59**, 2291–2300.
130. Chen L, Dong Y, Bhagatwala J *et al.* (2018) Effects of vitamin D3 supplementation on epigenetic aging in overweight and obese African Americans with suboptimal vitamin D status: a randomized clinical trial. *J Gerontol A* **74**, 91–98.
131. Zhu H, Bhagatwala J, Huang Y *et al.* (2016) Race/ethnicity-specific association of vitamin D and global DNA methylation: cross-sectional and interventional findings. *PLoS ONE* **11**, e0152849.
132. Hussien H, Nastasa A, Apetrii M *et al.* (2021) Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones. *BMC Geriatr* **21**, 389.
133. Martens PJ, Gysemans C, Verstuyf A *et al.* (2020) Vitamin D's effect on immune function. *Nutrients* **12**, 1248–1269.
134. Laird E, McNulty H, Ward M *et al.* (2014) Vitamin D deficiency is associated with inflammation in older Irish adults. *J Clin Endocrinol Metab* **99**, 1807–1815.
135. Laird E, Rhodes J & Kenny RA (2020) Vitamin D and inflammation: potential implications for severity of Covid-19. *Ir Med J* **113**, 81.
136. Rhodes JM, Subramanian S, Laird E *et al.* (2020) Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. *Aliment Pharmacol Ther* **51**, 1434–1437.
137. Annweiler G, Corvaisier M, Gautier J *et al.* (2020) Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: the GERIA-COVID quasi-experimental study. *Nutrients* **12**, 3377–3387.
138. Eyles DW, Smith S, Kinobe R *et al.* (2005) Distribution of the vitamin D receptor and 1α-hydroxylase in human brain. *J Chem Neuroanat* **29**, 21–30.
139. Anastasiou CA, Yannakoulia M & Scarmeas N (2014) Vitamin D and cognition: an update of the current evidence. *J Alzheimer's Dis* **42**, S71–S80.
140. Jayedi A, Rashidy-Pour A & Shab-Bidar S (2019) Vitamin D status and risk of dementia and Alzheimer's disease: a meta-analysis of dose-response. *Nutr Neurosci* **22**, 750–759.
141. Annweiler C, Llewellyn DJ & Beauchet O (2013) Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimer's Dis* **33**, 659–674.
142. Van der Schaft J, Koek H, Dijkstra E *et al.* (2013) The association between vitamin D and cognition: a systematic review. *Ageing Res Rev* **12**, 1013–1023.
143. Miller JW, Harvey DJ, Beckett LA *et al.* (2015) Vitamin D status and rates of cognitive decline in a multiethnic cohort of older adults. *JAMA Neurol* **72**, 1295–1303.
144. Toffanello ED, Coin A, Perissinotto E *et al.* (2014) Vitamin D deficiency predicts cognitive decline in older men and women: the Pro. VA study. *Neurology* **83**, 2292–2298.
145. Hooshmand B, Lökk J, Solomon A *et al.* (2014) Vitamin D in relation to cognitive impairment, cerebrospinal fluid biomarkers, and brain volumes. *J Gerontol A Bio Sci Med Sci* **69**, 1132–1138.
146. Williams JA, Sink KM, Tooze JA *et al.* (2015) Low 25-hydroxyvitamin D concentrations predict incident depression in well-functioning older adults: the health, aging, and body composition study. *J Gerontol A Bio Sci Med Sci* **70**, 757–763.
147. Okereke OI & Singh A (2016) The role of vitamin D in the prevention of late-life depression. *J Affect Disord* **198**, 1–14.
148. Brouwer-Brolsma E, Dhonukshe-Rutten R, Van Wijngaarden J *et al.* (2016) Low vitamin D status is associated with more depressive symptoms in Dutch older adults. *Eur J Nutr* **55**, 1525–1534.
149. Briggs R, McCarroll K, O'Halloran A *et al.* (2019) Vitamin D deficiency is associated with an increased likelihood of incident depression in community-dwelling older adults. *J Am Med Dir Assoc* **20**, 517–523.
150. Mikola T, Marx W, Lane MM *et al.* (2022) The effect of vitamin D supplementation on depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr* **July 11**, 1–18.
151. Beauchet O, Cooper-Brown LA & Allali G (2021) Vitamin D supplementation and cognition in adults: a systematic review of randomized controlled trials. *CNS Drugs* **35**, 1249–1264.
152. Leoncini E, Nedovic D, Panic N *et al.* (2015) Carotenoid intake from natural sources and head and neck cancer: a systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol Biomarkers Prev* **24**, 1003–1011.
153. Hak AE, Stampfer MJ, Campos H *et al.* (2003) Plasma carotenoids and tocopherols and risk of myocardial infarction in a low-risk population of US male physicians. *Circulation* **108**, 802–807.
154. Hamer M & Chida Y (2007) Intake of fruit, vegetables, and antioxidants and risk of type 2 diabetes: systematic review and meta-analysis. *J Hypertens* **25**, 2361–2369.
155. Amadieu C, Lefevre-Arbogast S, Delcourt C *et al.* (2017) Nutrient biomarker patterns and long-term risk of dementia in older adults. *Alzheimers Dement* **13**, 1125–1132.

https://doi.org/10.1017/S0029665123002707 Published online by Cambridge University Press

156. Sugiura M, Nakamura M, Ogawa K *et al.* (2012) High serum carotenoids associated with lower risk for bone loss and osteoporosis in post-menopausal Japanese female subjects: prospective cohort study. *PLoS ONE* **7**, e52643.
157. Perry A, Rasmussen H & Johnson EJ (2009) Xanthophyll (lutein, zeaxanthin) content in fruits, vegetables and corn and egg products. *J Food Compos Anal* **22**, 9–15.
158. Bohn T (2017) Carotenoids, chronic disease prevention and dietary recommendations. *Int J Vitam Nutr Res* **87**, 121–130.
159. Ben-Dor A, Steiner M, Gheber L *et al.* (2005) Carotenoids activate the antioxidant response element transcription system. *Mol Cancer Ther* **4**, 177–186.
160. Palozza P, Simone R, Catalano A *et al.* (2011) Lycopene prevention of oxysterol-induced proinflammatory cytokine cascade in human macrophages: inhibition of NF-kappaB nuclear binding and increase in PPARgamma expression. *J Nutr Biochem* **22**, 259–268.
161. Gruszecki WI & Strzalka K (2005) Carotenoids as modulators of lipid membrane physical properties. *Biochim Biophys Acta* **1740**, 108–115.
162. Rietman ML, Spijkerman AM, Wong A *et al.* (2019) Antioxidants linked with physical, cognitive and psychological frailty: analysis of candidate biomarkers and markers derived from the MARK-AGE study. *Mech Ageing Dev* **177**, 135–143.
163. Semba RD, Blaum C, Guralnik JM *et al.* (2003) Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clin Exp Res* **15**, 482–487.
164. Feeney J, O'Leary N, Moran R *et al.* (2017) Plasma lutein and zeaxanthin are associated with better cognitive function across multiple domains in a large population-based sample of older adults: findings from the Irish longitudinal study on aging. *J Gerontol A Biom Sci Med Sci* **72**, 1431–1436.
165. García-Romera M-C, Silva-Viguera M-C, López-Izquierdo I *et al.* (2022) Effect of macular pigment carotenoids on cognitive functions: a systematic review. *Physiol Behav* **254**, 113891.
166. Ng TP, Feng L, Nyunt MSZ *et al.* (2015) Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. *Am J Med* **128**, 1225–1236.e1.
167. Sofi F, Macchi C, Abbate R *et al.* (2014) Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* **17**, 2769–2782.
168. Psaltopoulou T, Sergentanis TN, Panagiotakos DB *et al.* (2013) Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. *Ann Neurol* **74**, 580–591.
169. Bollwein J, Diekmann R, Kaiser MJ *et al.* (2013) Dietary quality is related to frailty in community-dwelling older adults. *J Gerontol A Bio Sci Med Sci* **68**, 483–489.
170. Talegawkar SA, Bandinelli S, Bandeen-Roche K *et al.* (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**, 2161–2166.
171. León-Muñoz LM, Guallar-Castillón P, López-García E *et al.* (2014) Mediterranean diet and risk of frailty in community-dwelling older adults. *J Am Med Dir Assoc* **15**, 899–903.
172. Milaneschi Y, Bandinelli S, Corsi AM *et al.* (2011) Mediterranean diet and mobility decline in older persons. *Exp Gerontol* **46**, 303–308.
173. Veronese N, Stubbs B, Noale M *et al.* (2018) Adherence to a Mediterranean diet is associated with lower incidence of frailty: a longitudinal cohort study. *Clin Nutr* **37**, 1492–1497.
174. García-Esquinas E, Rahi B, Peres K *et al.* (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**, 132–142.
175. Yannakoulia M, Kontogianni M & Scarmeas N (2015) Cognitive health and Mediterranean diet: just diet or lifestyle pattern? *Ageing Res Rev* **20**, 74–78.
176. Kojima G, Avgerinou C, Iliffe S *et al.* (2018) Adherence to Mediterranean diet reduces incident frailty risk: systematic review and meta-analysis. *J Am Geriatr Soc* **66**, 783–788.
177. Lopez-Garcia E, Hagan KA, Fung TT *et al.* (2018) Mediterranean diet and risk of frailty syndrome among women with type 2 diabetes. *Am J Clin Nutr* **107**, 763–771.
178. Bach-Faig A, Berry EM, Lairon D *et al.* (2011) Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr* **14**, 2274–2284.
179. Fan Y, Zhang Y, Li J *et al.* (2021) Association between healthy eating index-2015 and physical frailty among the United States elderly adults: the national health and nutrition examination survey (NHANES) 2011–2014. *Aging Clin Exp Res* **33**, 3245–3255.
180. Laclaustra M, Rodriguez-Artalejo F, Guallar-Castillon P *et al.* (2020) The inflammatory potential of diet is related to incident frailty and slow walking in older adults. *Clin Nutr* **39**, 185–191.
181. Valls-Pedret C, Sala-Vila A, Serra-Mir M *et al.* (2015) Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med* **175**, 1094–1103.
182. Martínez-Lapiscina EH, Clavero P, Toledo E *et al.* (2013) Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry* **84**, 1318–1325.
183. Hu FB (2002) Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* **13**, 3–9.

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