– European Personalised Nutrition Strategy –

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1. Introduction

Food choices change with age and are influenced by many factors including changing taste, budget as well as lifestyle. Superimposed on food choice factors, are nutritional requirements; these also change with age.

This review gathers together evidence that may inform decision-making to support nutrition for older adults. It includes evidence on nutritional requirements for people over the age of 65 years were they are different from adults in general and considers whether or not these requirements are being met; the association between lower nutrient levels and health outcomes is considered for older adults, although because of the design of these studies, the evidence cannot imply that restoring a nutrient level that is deficient in older adults will improve health outcomes; and finally we consider the effects of diets that are supplemented with particular nutrients within intervention trials on age-associated health outcomes.

In undertaking the review, we considered nutritional evidence about people over the age of 65 years. Historically, the majority of studies have included people up to the age of 79 years. In 1960 1.4% of Europeans were over 80 and reached 4.1% in 2010. By 2060, 11.5% of Europeans are predicted to be above 80 years of age[1]. In 2012, healthy life-expectancy for European men was for 61.2 healthy years and for European women was 61.9 healthy years. There is a 10 year variance across Europe in healthy life years for men comparing Western Europe (64 years) with Eastern Europe (54 years). The numbers of and ages when older people require and receive care varies accordingly. Very few nutritional studies focus on the population over 80 years of age and on those living in care homes; we have identified the age-groups and whether they are independently living in the sections below.

2. Nutritional requirements change with age

It is difficult to generalise about the energy requirements of older adults because of the variation in health and mobility. Nevertheless, it the requirements are likely to be the same as younger adults during good general health and when mobility is maintained. However, in the oldest adults and for those who have much less mobility, it is highly likely that their physical activity levels will be lower; consequently their energy requirement will be lower. The Scientific Advisory Committee on nutrition in the UK has estimated energy requirements based on average age, size and mobility (Figure 1)[2]. The change in requirement is most striking over the age of 65 years and most likely relates to slower metabolism and loss of muscle.

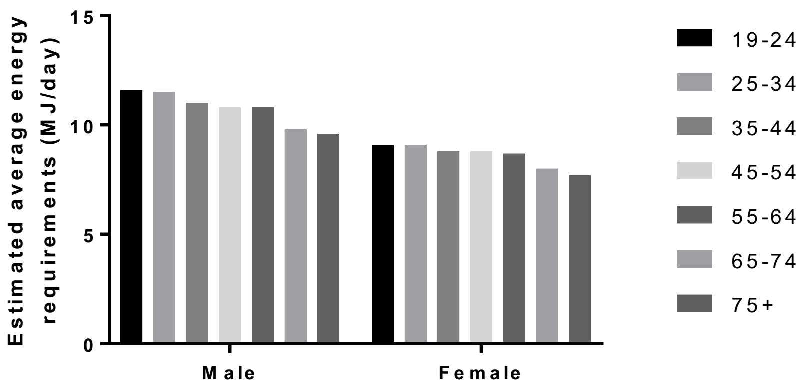

Figure 1. Gender and age effects on Estimated Average energy requirements at current mean height and BMI (22.5Kg/m2; 2)

[1] Eurostat. Extracted June 2017. Population structure and ageing
[2] Scientific Advisory Committee on Nutrition Dietary Reference Values for Energy 2011

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A similar picture is described by EFSA for the European population and septuagenarian men with a very physically active lifestyle could have an energy requirement up to 11.9MJ/d[3].

In the UK, total daily energy intake is estimated as 9.8MJ/d for the average man aged 65-74 or dropping to 9.6MJ/d for a man more than 75 years. For women, total daily energy intake is estimated as 9.86MJ/d dropping to 9.6MJ/d respectively.

If energy intake is maintained with reducing energy expenditure, body fat accumulates around the organs of the body, with much less in the subcutaneous fat deposits. Visceral body fat increases the risk for diseases like type 2 diabetes which increases in prevalence with older adults.

Macronutrient requirements in people over 65 years

The dietary protein intake that is needed by people of different ages to meet their nitrogen balance has been discussed extensively in the published literature. The safe limit for protein intake takes into account the studies that have looked at whether renal function is compromised by high protein intake in older adults and those that are concerned with delaying age-associated muscle-loss, sarcopenia, by increasing dietary protein to promote muscle synthesis.

The World Health Organisation recommends 0.75g protein per Kg body weight per day for older adults and is not higher than for adults under 65 years of age[4]. The population Reference Intakes for protein reported by EFSA are 0.83g/d for adults over the age of 60 years[3].

Some recent studies that use a different method to study protein requirement, have suggested that the recommendation could be increased by a further 25% in older adults and there are a number of studies that are investigating whether particular types of dietary protein are better to increase the rate of amino acid accretion into muscle.

Carbohydrates are a major energy source in the diet that are made up of the same constituents, carbon, hydrogen and oxygen, but can behave in very different ways in the body. The "free" sugars, mono- and di-saccharides, provide a ready burst of energy. High intake of free sugars has been associated with increased risk for obesity and type 2 diabetes. The WHO extended the definition of free sugars to include monosaccharides and disaccharides that are added to foods and beverages by the manufacturer, cook or consumer and include sugars that are naturally present in honey, syrup and fruit juices (WHO, 2015). The UK government commissioned a SACN report of carbohydrates and health that also reported in 2015[5].

The SACN concluded that the dietary reference value for total carbohydrate intake of an average adult should be 50% of total dietary energy and dietary intake of free sugars should not exceed 5% of total energy. The average population intake of dietary fibre[6] for adults should be 30g/day.

Fats are a major source of energy for the body and also are important to carry certain vitamins in the blood such as vitamin A, D, E and K, and some other nutrients such as carotenoids which are only soluble in fat. Dietary fats are found in three major types; triglycerides, sterols such as cholesterol and smaller amounts of phospholipid.

For adults, overall intake for dietary fat in all its forms should not exceed 35% of total energy intake.

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[3] https://www.efsa.europa.eu/sites/default/files/assets/DRV_Summary_tables_jan_17.pdf
[4] WHO/FAO. Report of a Joint Expert Consultation. Protein requirements of adults, including older people, and women during pregnancy and lactation. Geneva (Switzerland): WHO Press; 2007 (UNU report 05123054).
[5] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf
[6] Fibre = carbohydrates that are not digested and not absorbed in the small intestine and are polymers of three or more subunits; and lignin

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Fatty acids are the constituent of triglycerides and can be grouped into saturated, monounsaturated and polyunsaturated fatty acids. Many of these fatty acids can be synthesised by the body but two poly-unsaturated fatty acids (n-3 and n-6) cannot be made efficiently and are considered to be essential. The essential n-3 fatty acid is α-linolenic acid and the essential n-6 fatty acid is linoleic acid. The n-3 fatty acids are considered to be anti-inflammatory and have been the focus of many studies that have supplemented with other n-3 fatty acids such as eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA). Institute of Medicine Guidelines have defined adequate intakes of n-3 essential fatty acids and they do not differ for adults between age groups[7].

The Institute of Medicine state that insufficient information is available to establish a recommended daily intake for n-3 fatty acids but adequate Intake (AI) levels are considered to be 1.6g/d for men and 1.1g per day for women. EFSA report AIs of 4% and 0.5% of total energy for LA and ALA respectively[3].

Trans-fatty acids are produced during food processing and have been associated with negative health outcomes[8]. The UK Scientific Advisory Committee on Nutrition recommends that average intakes of trans fatty acids should not exceed 2% of food energy.

Micronutrient requirements in people over 65 years

The reference intakes for vitamins do not increase with age although for some e.g. for niacin, there is a minor reduction in requirements between young and older adults over the age of 50. Table 1 describes vitamin requirements for UK older adult populations. The data is was collated by the British Nutrition Foundation[9] in 2016. At the European level, information is available for adults in general over the age of 18 years but not for older adults.

Gender	Thiamin mg/d	Riboflavin mg/d	Niacin mg/d	Vit B6 mg/d	Vit B12 µg/d	Folate µg/d	Vit C mg/d	Vit A µg/d
Male	**0.9**	**1.3**	**16**	**1.4**	**1.5**	**200**	**40**	**700**
Female	**0.8**	**1.1**	**12**	**1.3**	**1.5**	**200**	**40**	**600**

Table 2 – European Food Safety Agency Population Reference Intakes (PRIs) and Adequate Intakes (AIs) for vitamins in adults

Gender	Thiamin mg/d	Biotin mg/d	Niacin mg/d	Vit B6 mg/d	Vit B12 µg/d	Folate µg/d	Vit C mg/d	Vit A µg/d
Male	**0.1**	**40**	**1.7**	**1.7**	**4**	**330**	**110**	**750**
Female	**0.1**	**40**	**1.7**	**1.6**	**4**	**330**	**95**	**650**

A comprehensive review of vitamin D intake in older adults was included in the UK SACN report on vitamin D and health[10] and concludes with a recommended intake of 10 **µg** daily intake for men and women in the UK over 50 years of age. Currently, in the UK the average intake from the diet alone is 3.3 µg i.e. 1/3 of the requirement. For those taking supplements, the mean daily intakes were 5.1 µg vitamin D for men and 5.2 µg for women. This is approximately 50% of the recommended intake for vitamin D. It is clear that those on lower incomes and people who are living in care homes also have lower intakes; in care homes, mean daily vitamin D intake for men was 3.9 µg and was 3.4 µg for women from all sources. Similar requirements are

[7] https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/#h2
Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: National Academy Press; 2005.
[8] https://www.bda.uk.com/foodfacts/TransFats.pdf
[9] https://www.nutrition.org.uk/attachments/article/234/Nutrition%20Requirements_Revised%20Oct%202016.pdf
[10] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf

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also anticipates for other Northern European countries, however, in France, vitamin D requirements are lower in anticipation of efficient production in the skin through UV exposure.

Population Reference Intakes (PRIs) and Adequate Intakes (AIs) for vitamins have been reported by the European Food Safety Agency for adults in general rather than for older adults specifically.

Table 3. Dietary reference values for vitamin D (µg/day) in European countries for older adults (adapted from Spiro and Buttriss[11])

Country	AU	BE	FR	IE	ES	CH	TU	NL	UK	EC	IOM	WHO
Vitamin D requirement	20	15	5	20	10	20	10	20	10	10	10-15	10-15

The NIH recommends an intake of 15mg (22.4 IU) vitamin E per day for adults but does not specify any age-dependency in requirements[12].

Apart from the many studies that have consistently shown that vitamin D intake tends to be low in older adults, other vitamin intake requirements appear to be adequately met through a healthy balanced diet.

Nutritional intake mineral requirements for older adults in the UK has been reported by the British Nutrition Foundation and are summarised in Table 3.

Table 4. UK Reference Nutrient Intakes for Minerals for older adults

gender	calcium	phosphorous	magnesium	sodium	potassium	iron	zinc	copper	selenium	iodine
Men 50+ years	700 mg/d	550 mg/d	300 mg/d	1600 mg/d	3500 mg/d	8.7 mg/d	9.5 mg/d	1.2 mg/d	75 µg/d	140 µg/d
Women 50+ years	700 mg/d	550 mg/d	270 mg/d	1600 mg/d	3500 mg/d	8.7 mg/d	7.0 mg/d	1.2 mg/d	60 µg/d	140 µg/d

Intakes for potassium and magnesium are significantly reduced in UK older adult populations who are living independently. Intakes of these two minerals are also lower in older adults who are living in care. The UK reference nutrient intake for iron is the same in older men and women, and this represents a reduction in the requirement for women who are post-menopausal.

Table 5. EFSA Population Reference Intakes (PRIs) and Adequate Intakes (AIs) for minerals

gender	calcium	phosphorous	magnesium	manganese	potassium	iron	Zinc*	copper	selenium	iodine
Men	950 mg/d	550 mg/d	350 mg/d	3 mg/d	3500 mg/d	11 mg/d	9.4-16.3 mg/d	1.6 mg/d	70 µg/d	150 µg/d
Women	950 mg/d	550 mg/d	300 mg/d	3 mg/d	3500 mg/d	11 mg/d	7.5-12.7 mg/d	1.3 mg/d	70 µg/d	150 µg/d

***Varies according to phytate**

[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288313/
[12] https://ods.od.nih.gov/factsheets/VitaminE-Consumer/

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In general, EFSA reference intakes for minerals are marginally higher than the specific UK data but these data represent adult populations as a whole and are not references for older adults.

Phytochemicals

The previous reviews have focussed on essential nutrients that are found within food and for which known functions have been ascribed. Food offers a benefit that goes beyond the individual nutrients because of interactions between different components and because the rates of nutrient release from different foods will vary. The consumption of phytochemicals such as carotenoids and polyphenols that are found within whole fruits and vegetables may also have beneficial effects on health. As these are not considered essential, reference intake levels are not required. A numbers of studies have considered the association between phytochemical intake and health outcomes, and there are a number of examples of dietary intervention studies that have included phytochemicals. Phytochemicals are important components in the Mediterranean diet and their contribution to overall nutritional quality of nuts is reviewed[13].

Food versus nutrient enrichment

Nutrients in the diet interact in the way that they are absorbed. For examples, foods that are rich in phytates will impede zinc absorption and for iron, absorption is also inhibited by vitamin C and calcium. Iron bioavailability for vegetarians is estimated at between 33-66% of that for non-vegetarians. Other nutrients act positively together for their physiological activity; for example B vitamins with folate for DNA synthesis; vitamin C and E for antioxidant function; and vitamin D and calcium for bone health. Indeed, one of the limits to the epidemiological association studies that we have reviewed in section 2 is that they tend to report the association between one nutrient and health outcomes but of course, this single nutrient is most likely to have been consumed as part of a mixed diet; other components in the diet acting either alone or in combination, may contribute to an overall improvement in health. Association studies are retrospective, therefore only indicative and can be highly variable. The strongest evidence for the value of a nutrient or diet for health outcomes is achieved by intervention studies that are designed to test the effect of nutrient or diet on a specifically defined health outcome in a prospective way.

Personalised nutrition for older adults

Moving forward from generalised nutrient requirements to personalised nutrition can involve many different variables. The older adult population is very heterogeneous and will be influenced in their personal choices by many different factors. The concept of convenience may outweigh nutritional value for example in one population whereas another maybe motivated to try protein-enriched, functional food products. Understanding consumer behaviour will be an important factor for the success of personalised nutrition.

A recent study has highlighted how personalising nutrition at an individual level, using foods that are readily available, can result in effective lifestyle changes that increase the intake of essential nutrients such as folate[14].

For active and healthy older adults, adequate energy intake and a balanced diet providing macronutrients within the recommended ranges will most likely meet the majority of their nutritional needs. There will be seasonality in requirements, for example vitamin C intake by diet is typically higher during the summer months when more fresh fruit and vegetables are available but correspondingly low in the winter.

[13] Br J Nutr. 2015 Apr;113 Suppl 2:S79-93. doi: 10.1017/S0007114514003250
[14] https://academic.oup.com/ije/article-abstract/46/2/578/2622850/Effect-of-personalized-nutrition-on-health-related

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Conversely, iron intake and protein is typically is typically lower during the summer as less red meat is consumed.

Geography and ethnicity also play an important part in the nutritional intake patterns of otherwise healthy older adults, with Pakistani men and women living in the UK typically consuming less calcium[15] and highlight a specific calcium requirement for health. The capacity to make vitamin D from sunlight is also affected by skin pigmentation. However, the prevalence of vitamin D deficiency in older adults living in Europe according to ethnicity is unclear, cases of rickets were recorded in much greater frequency in children of South Asian, Middle Eastern or sub-Saharan African background. Increasing vitamin D intake is being increasingly recognised as an important public health goal. The aforementioned evidence points to ethnicity as a factor in personalised nutrition.

People with long term conditions such as high blood pressure, high cholesterol and type 2 diabetes which increase in prevalence in older adults, have dietary requirements for foods that are lower in fat, salt and refined sugars. There are certain genotypes that increase risk for these metabolic diseases. In the near future, a risk calculation based on genotype for such long-term conditions is likely to emerge that would encourage a personalised nutrition approach to reduce disease risk. One of the first European studies that used genomic information to advise individuals on their personal risk profile and to develop an appropriate on nutritional programme has now concluded. The study identified that personalised nutrition advice resulted in participants selecting a much healthier diet, irrespective of whether the genomic information was used. This suggests that personalised nutrition could be a sustainable way to improve health[16].

An important consideration in foods for adults with poor oral health and dental problems is to minimise meals that require chewing while maintaining fibrous and protein content. Protein enriched foods have been successfully used in the hospital setting but cost, taste and scepticism from consumers has not helped with wider uptake.

Nutritional health may be affected by drug treatments that affect appetite, absorption and metabolism. Conversely, some foods also affect drug metabolism, most notably grapefruit that impairs the activity of a cytochrome p450 metabolising enzymes and so increases blood concentrations of drugs. These factors are addressed in drug safety notes that accompany medicines.

The aforementioned data assumes that absorption of nutrients is also unaffected although if an individual has physiological changes with ageing e.g. in gastric acid secretion, the absorption of B vitamins may be impaired hence intake requirements may be higher. In this case, the state of an individual's health will impact on their personal dietary requirements. The clinical practitioner will assess whether this is the case on a personalised basis if an individual presents with symptoms of B vitamin deficiency. In this case, the motivation to increase a specific nutrient would be health-related via a pharmacist rather than lifestyle choice dependent.

Nevertheless, healthy older adults do experience an age-related decline in many physiological systems without the development of overt disease. The systems affected by age include the immune system, musculo-skeletal system, brain and metabolic system. The outcomes of declining function at the systems level include increased susceptibility to infection and to develop strong vaccination responses, increased risk of falls and fractures, declining cognition and weight gain. We have reviewed the evidence for whether adequate or enriched nutrition associates with better physiological systems functions in populations of

[15] http://onlinelibrary.wiley.com/doi/10.1046/j.1365-277X.2003.00461.x/epdf
[16] https://clinicaltrials.gov/show/NCT01530139

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healthy older adults (Section 3) and provide a state of the art review of evidence supporting dietary enrichment or supplementation on healthy older adults (section 2).

Overall, success in adopting personalised nutrition in an older adult population will be the result of integrating different approaches to improved dietary intake of nutrients. These should take into account any personal monitoring devices that an individual has for existing health conditions e.g. for blood sugar and blood pressure, wearables that monitor activity and mobile apps that offer coaching. Together these could help to integrate lifestyle and medical variables to improve the perceived importance of diet and compliance with healthy nutrition.

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Section 2

Systematic review of nutritional intervention studies in older adults

The following section describes a focussed systematic review of those clinical studies that have determined health outcome measures in older adults following nutrient or dietary enrichment or supplementation in order to understand any value of nutrition for general health and well-being. The review was conducted in July and August 2017. All data was reviewed by two people independently.

Search strategy

Bibliographic databases were searched for randomised, placebo-controlled trials investigating the effect of nutrients on health outcomes in older adults. The search was conducted by combination (using Boolean operators) of the search terms in table 2.1. The following databases were searched: PubMed, Cochrane Library, Web of Knowledge, Controlled-Trials website and Science Direct. The exclusion criteria were as follows: population age <65 years; animal studies; and studies of individuals with disease only and not of healthy controls.

Table 2.1. Search strategy for systematic reviews

Age category	Food	Outcome
older adult	vitamin A	frailty
elderly	thiamin	muscle strength
septuagenarian	riboflavin	immune response
octogenarian	niacin	lifespan
nonagenarian	folate	longevity
centenarian	dietary-protein	cognition
pension age,	omega 3 fatty acid	falls,
retirement age,	polyunsaturated fatty acid	fractures
Geriatric	monounsaturated fatty acid	dental health
senior citizen,	iron	infection
OAP,	calcium	body weight
old age	magnesium	
	potassium	
	vitamin B6	
	vitamin B12	
	vitamin C	
	vitamin D	
	vitamin E	
	fibre	
	zinc	
	MULTIVITAMINS	

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Data extraction

For investigation of the effects of nutrients on health outcomes, we focussed on measures of physiological systems that decline with age rather than effects on overt existing disease. The ageing systems that we included as outcomes in our searches are described in Table 1. We extracted measures of function at baseline and at the end of the nutritional intervention for both the control and treatment groups. The following participant characteristics were noted as possible confounders: nutrient form and amount or dose consumed, study duration, number of participants per group, participant age range. The methodological quality of studies was assessed to eliminate bias by dropout rate and compliance were possible. The threshold limits set for the critical appraisal were that studies should be randomised controlled trials, with a control group and single blinding. In addition both comparator groups must have been subjected to identical treatment analysis. Those studies meeting the inclusion criteria are listed in the Tables 2.2 etc.

Macronutrients

Fibre intervention studies; effects on older adult health outcomes

One study on fibre supplementation in older adults that met inclusion criteria was identified (Table 2.2). The reported intervention outcome was weight gain. The study noted that fibre treatments were effective and reported no increase in mean body weights following fibre intervention (Baghurst et al, 1985). **One study in healthy men showed that increased fibre intake maintained body weight.**

Protein intervention studies; effects on older adult health outcomes

Four studies that focused on dietary protein enrichment were identified; one of the studies recruited a male population only with all studies using age-groups greater than 65 years (Table 2.3). Intervention outcome of these studies include muscle loss, muscle gain and skeletal muscle hypertrophy, physical performance frailty. One study concluded that additional protein intake was required to allow muscle mass gain during exercise training in frail elderly people (Tieland et al, 2012b). Another study reported that timed protein supplementation immediately before and after exercise does not further augment the increase in skeletal muscle mass and strength after prolonged resistance-type exercise training in healthy elderly men who habitually consume adequate amounts of dietary protein (Verdijk et al, 2009). Dietary protein supplementation improved physical performance, but did not increase skeletal muscle mass in frail elderly people (Tieland et al, 2012a). Finally, a study on frailty reported that protein-energy supplementation administered to frail older adults with low socioeconomic status showed evidence of reducing the progression of functional decline (Kim and Lee, 2013). **In summary, three out of four studies showed positive outcomes of protein supplementation on functional muscle strength or muscle mass gain in frail older adults. One study in healthy mean showed no effect of protein supplementation on muscle mass strength.**

Omega-3 fatty acid intervention studies; effects on older adult health outcomes

Twelve studies involving omega-3 supplementation were identified as meeting inclusion criteria, one of which focused on a female population, two on male only populations and the remainder were mixed gender (Table 2.4). Six of the studies recruited patients from upwards of 50-64 years. The intervention outcomes relevant to our study were cognition and all-cause mortality. One study has yet to report. Six smaller studies (<100 people analysed in each study) of omega-3 fatty acid supplementation in older people were identified; three studies recruited people with MCI and all focused on cognition as the intervention outcome. The intervention had positive impacts on cognition including improved learning and memory in all cases (Bo et al 2015, Tokuda et al, 2015, Strike et al, 2010, Lee et al, 2011, Randanelli et al, 2012, Nilsonn et al 2012). One large study with

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485 participants, showed a benefit for cognitive performance for people of 55 years (Yurko-Mauro, 2011). However, in three other larger studies omega-3 fatty acid supplementation no significant effects on cognitive decline over 3 years in elderly people with or without memory complaints were observed (Andrieu et al, 2017, van de Rest et al, Dangour 2010). These findings are consistent with a systematic review by Jiao et al in 2014 and the Cochrane systematic review (Sydenham, Dangour et al. 2012) which concluded that the available trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people.

In a Norwegian population at risk for cardiovascular disease, a statistically significant reduction on all-cause mortality was observed following three years of omega-3 supplementation (Einvik et al, 2010).

In summary, in healthy older adults three of four large omega 3 intervention studies showed neither benefit nor risk on cognition and one large intervention study showed positive benefit. A reduction in all-cause mortality for men with cardiovascular disease risk was observed in one large omega-3 supplementation study.

Micronutrients

Vitamin B6, B12 and folate intervention studies; effects on older adult health outcomes

Eight vitamin B12 studies in elderly persons that met the inclusion criteria for this review were identified. One of the studies included vitamin B6, one study included omega-3 fatty acids and two included folate supplementation (Table 2.5). Seven of the studies were conducted on subject aged 65+, with one study recruiting participants from the age of 60; men and women participated in all studies. The intervention outcomes were cognition, brain atrophy, bone mineral density, fractures, immune function and physical performance. Two of the four studies focused on the impact of vitamin B12 on brain atrophy or cognition reported beneficial significant effects; and both also included omega-3 fatty acid supplements (Walker et al, 2012) and one also include vitamin B6 supplementation (Jerneren et al, 2015). A third large study of 2919 participants did not describe any cognitive improvement from vitamin B12 supplementation in healthy older adults (van der Zwaluw et al, 2014). Other studies concluded that vitamin B12 supplementation has no impact on bone mineral density, fractures, physical performance and immune function in older adults (Enneman et al, 2015, Wijngaarden et al, 2014, Swart et al, 2015, van Dijk et al, 2016). **In summary, in healthy older adults two of three large vitamin B12 combined with omega-3 fatty acid intervention studies showed benefit on cognition and one large intervention study showed no effect. No adverse outcomes were noted.**

Vitamin C intervention studies; effects on older adult health outcomes

Three vitamin C supplementation studies in elderly persons were identified as meeting the inclusion criteria focused on subjects aged more than 60 years (Table 2.6). One study recruited only male participants. The intervention outcomes measured were cognition, acute respiratory infections and physical performance. With regard to cognition, vitamin C intake did not enhance cognitive performance in elderly persons with mild cognitive impairment (Naeini et al, 2013). Vitamin C was shown to significantly improve respiratory function in the presence of acute respiratory infection in individuals with low vitamin C concentrations (Hunt et al, 1994). High dosage of vitamin C and E supplementation was shown to blunt certain muscle adaptations to strength training in elderly men (Bjornsen et al, 2015). **In summary, older adults with low plasma vitamin C showed benefit from supplementation whereas high dose supplementation with vitamin C and E had negative effects on muscle training.**

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Vitamin D intervention studies; effects on older adult health outcomes

Thirteen vitamin D supplementation studies in elderly persons were identified (Table 2.7). Twelve of the thirteen studies used subjects aged 65+ and one recruited people older than 60 years of age. Three of the studies recruited woman only and one studied men only. The intervention outcomes relevant to this study were cognition, falls, muscle strength and fractures. Of the four studies focused on vitamin D intake and falls, two suggested such intervention was effective at reducing falls (Imaoka et al, 2016, Flicker et al, 2005) and two studies suggest vitamin D supplementation was not effective (Burleigh et al, 2007, Latham et al, 2003). All four studies focused on vitamin D intake and the incidence of fractures; this did not demonstrate any positive improvements (Law et al , 2006, Salovaara et al, 2010, Meyer et al, 2002, RECORD trial group, 2005). Of the four studies focused on the impact of vitamin D supplementation on muscle strength, two studies suggested it was insufficient for improving muscle strength (Kenny et al, 2003, Janssen et al, 2009), whereas two studies suggested a positive response (Moreira-Pfrimer et al, 2009, Pfeifer et al, 2008). One study found no association between vitamin D treatment and the incidence of cognitive impairment (Rossom et al, 2012). **In summary, four out of fourteen vitamin D intervention studies in older adults showed positive benefit on health outcomes and ten other studies showed no benefit and no increased risk.**

Vitamin E intervention studies; effects on older adult health outcomes

Four vitamin E supplementation studies in elderly person were identified (Table 2.8). Three of the four studies used subjects 65+ years old, one study was conducted on male subjects only and one study focused on females only. The intervention outcomes included cognition and immune function. In the presence of fish oil, vitamin E was shown to improve immune function (Wu et al, 2006), whereas another study reported that there was no clear indication of improved immune responses (Park et al, 2002). A study on risk for pneumonia concluded that although the evidence for the benefit from vitamin E to reduce risk of pneumonia is strong, the overall findings are complex (Hemila, 2016). Another study reported that vitamin E did not provide cognitive benefits in healthy older woman after four years of follow-up (Kang et al, 2006). **In summary, two out of four vitamin E intervention studies in older adults showed positive benefit on immune function and two other studies showed no benefit and no increased risk for health outcomes.**

Multivitamin intervention studies; effects on older adult health outcomes

Five studies that focused on multivitamin supplementation in healthy older adults were identified as meeting the study inclusion criteria (Table 2.9). Two studies recruited females only. Intervention outcomes measured include cognition, nutrition and bone density and immune function. Two studies on cognition concluded that multivitamin supplementation had no impact on cognitive performance (Wolters et al, 2005, Harris et al, 2015) whereas another study suggested that combined multivitamins, mineral and herbal formula may benefit working memory in elderly woman at risk of cognitive decline (Macphearson et al, 2012). A study focused on bone mineral density concluded that supplementation had a positive effect on bone density (Grieger et al, 2009). A study to investigate immune function effects of multivitamin and multi-mineral supplementation of older people living at home did not show any improvement in self-reported infection related morbidity (Avenell et al, 2005). **In summary, three out of five multi-vitamin intervention studies in older adults did not show benefits or risks from supplementation. Other studies suggests improved memory and bone density in at risk population.**

Calcium intervention studies; effects on older adult health outcomes

Nine calcium supplementation studies in elderly persons were identified as meeting the study criteria, four of which were combined with vitamin D supplementation (Table 2.10). Six of the nine studies used subjects aged 65+ and three of the nine were conducted on female participants only. The intervention outcomes were

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concerned with bone mineral density (BMD), dementia, dental health and fractures. Two of the studies suggest that calcium supplementation may have a positive impact on BMD (Dawson-Hughes and Harris, 2002, Nakamura et al, 2012). Three studies investigating the impact of combined calcium and vitamin D supplementation on dental health generally found positive outcomes regarding tooth loss, dental plaque and periodontal health (Krall et al, 2001, Adegboye et al, 2013, Garcia et al, 2011). The impact of calcium intake on fractures was less consistent. No evidence of reduced risk of fractures was reported in one study focused on calcium/vitamin D intake, a reduction in fracture risk was observed in another investigation, whereas the third study stated that the relationship between calcium intake and fracture susceptibility is complex (Porthouse et al, 2005, Bischoff-Ferrari et al, 2008, Cho et al, 2008). Finally, one study concluded that calcium supplementation may increase the risk of developing dementia in elderly woman (Kern et al, 2016). **In summary, six out of nine studies showed positive outcomes of calcium supplementation for a variety of health measures; one study suggested a complex effect; another study described no benefit; and one study suggested risk.**

Potassium intervention studies; effects on older adult health outcomes

Three studies focused on potassium supplementation in elderly persons were identified as meeting the study criteria, two of which were based on a female cohort only (Table 2.11). Only one study recruited an age-group of 65+ while the other two selected participants over 55 years of age. The intervention outcome of these studies were bone metabolism and calcium balance. One study reported that treatment with potassium citrate for three months in an all-female cohort reduced bone resorption (Marangello et al, 2004), whereas another two-year study, also with a group of woman consisting of 276 participants aged between 55-65 did not find evidence that potassium citrate reduced bone turnover or increased bone mineral density (MacDonald et al, 2008). The third study focused on calcium balance concluded that potassium citrate has the potential to improve skeletal health (Mosely et al, 2013). **In summary, the effects of potassium supplementation on bone health on older adults is varied but there was no evidence for negative effects.**

Magnesium intervention studies; effects on older adult health outcomes

Three studies on magnesium supplementation in elderly persons were identified as meeting the study criteria (Table 2.12). Two of the three studies were conducted on participants aged 65+ and one recruited people between 51 and 85 years. One study recruited only females. Outcomes measures relevant to this report were bone mineral density, muscle performance, glucose handling and immune function. Daily magnesium oxide supplementation improved physical performance in healthy elderly woman (Veronese et al, 2014). In another study, correction of a low erythrocyte magnesium concentration associated with improvement of glucose handling (Paolisso et al, 1992). Finally, magnesium supplementation was shown to reduce inflammation (Nielson et al, 2010). **In summary, magnesium supplementation in healthy older adults improved the health outcomes studied here.**

Iron intervention studies; effects on older adult health outcomes

One study which investigated iron supplementation in elderly persons was identified as meeting the study criteria, which was in combination with 5-aminolevulinic acid (Table 2.13). Combined iron and 5-aminolevulinic acid intake augmented exercise efficiency and thereby improved interval-walking training (Masuki et al, 2015). **In summary, magnesium supplementation in healthy older adults improved physical health.**

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Selenium intervention studies; effects on older adult health outcomes

Seven studies focused on selenium supplementation were identified in older adults were identified as meeting the report criteria, with only two studies using age groups 65+; all studies recruited participants over 50 years of age (Table 2.14). Intervention outcomes measured included immune function, mood, thyroid function and mortality. Regarding thyroid function, one study reported that selenium intake does not improve thyroid function in an elderly UK population (Rayman et al, 2008) and another study suggests that selenium intake only minimally and dose dependently affects thyroid function (Winther et al, 2015). A study focused on immunity found that selenium intake can have both beneficial and detrimental effects on cellular immunity to flu that was affected by the form of selenium, supplemental dose and delivery matrix (Ivory et al, 2017). Another study suggests that intake of selenium-enriched yeast results in an immunostimulatory response in elderly humans (Peretz et al, 1991). A five-year long supplementation study reported no impact on plasma cholesterol concentrations in an elderly population consisting of 492 participants aged between 60 and 74 (Cold et al, 2015). In another study consisting of 501 individuals aged between 60-74 years, no evidence was found to suggest that selenium treatment improves mood or quality of life (Rayman et al, 2006). Supplementation with Selenium and Coenzyme Q10 was shown to reduce cardiovascular mortality in elderly with low selenium status (Alehagen et al, 2016). **In summary, selenium supplementation in healthy older adults does not exert consistent effects and attention should be paid to the form in which selenium is available.**

Zinc intervention studies; effects on older adult health outcomes

One study on zinc supplementation conducted on a group of 50 55-87-year-old men and woman for 12 months (Table 2.15). It reported that the incidence of infection was significantly lower following supplementation suggesting an improvement in immune function (Prasad et al, 2007).

Diet enrichment interventions

The search strategy was designed to investigate specific dietary nutrient effects in older adults. Some previous studies have considered a wider context of diet and dietary enrichment in older adults. The most significant of these studies is the PREDIMED study; in a healthy older adult population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function, immune function, bone and health (Valls-Pedret, Sala-Vila et al. 2015, Casas, Sacanella et al. 2016, Savanelli, Barrea et al. 2017). A Mediterranean diet is considered to deliver the nutrient balance that promotes good health outlined in Section 1 and points to the importance of diet for positive health outcomes.

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Retrospective, epidemiological studies of the effects of

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SECTION 3

Systematic review of epidemiological studies of nutrients and health outcomes in older adults

The following section describes a focussed systematic review of those epidemiological studies that have determined health outcome measures in older adults living independently and without disease in order to understand any associations between nutrition and general health and well-being. The review was conducted in July and August 2017. All data was reviewed by two people independently.

Search strategy

Bibliographic databases were searched for studied reporting the relationships between nutrients and health outcomes in independent-living, healthy older adults. The search was conducted by combination (using Boolean operators) of the search terms in table 2.1. The following databases were searched: PubMed, Cochrane Library, Web of Knowledge and Science Direct. The exclusion criteria were as follows: population age >65 years; animal studies; and studies of individuals with disease only and not of healthy controls.

Table 3.1. Search strategy for systematic reviews

Age category	Food	Outcome
older adult	vitamin A	frailty
elderly	thiamin	muscle strength
septuagenarian	riboflavin	immune response
octogenarian	niacin	lifespan
nonagenarian	folate	longevity
centenarian	dietary-protein	cognition
pension age,	omega 3 fatty acid	falls,
retirement age,	polyunsaturated fatty acid	fractures
Geriatric	monounsaturated fatty acid	dental health
senior citizen,	iron	infection
OAP,	calcium	body weight
old age	magnesium	
	potassium	
	vitamin B6	
	vitamin B12	
	vitamin C	
	vitamin D	
	vitamin E	
	fibre	
	zinc	
	MULTIVITAMINS	

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Data extraction

For investigation any association between nutrients and health outcomes, we focussed on measures of physiological systems that decline with age rather than effects on overt existing disease. The ageing systems that we included as outcomes in our searches are described in Table 3.1. The following participant characteristics were noted as possible confounders: follow-up duration, number of participants per group, participant age range and gender. Those studies meeting the inclusion criteria are listed in the Tables 3.2 etc.

Macronutrients

Fibre

Two studies on dietary fibre were identified as meeting the inclusion criteria for this review, one of which was studied with protein intake. These two studies focused on frailty and dental health. One study concluded that carbohydrate, fat, protein, and dietary fibre showed no consistent associations with frailty status (Shikany et al, 2013). The other study reported that only fruits that were good to excellent sources of fibre were associated with lower risk of progression of ABL, probing pocket depth, and tooth loss (Schwartz et al, 2012). The last study highlights the difficulty in interpreting retrospective studies; it is possible that poor dental health may have contributed to older people selected fewer "hard" or fibrous foods to eat rather than the fibre itself offering any benefit for progression of periodontitis.

Limited epidemiological studies of fibre intake have been reported for older adults. A possible benefit exists for dental health and no risks were identified.

Protein

Sixteen studies were identified which focused on the relationship between dietary protein intake and health outcomes. Normal protein intake varies between 15-35% of the energy intake. Nine of the studies used populations >65yrs and 6 studied all-female cohorts. Outcome measures included fractures, bodyweight, protein intake, bone mineral density, infection, frailty, muscle mass/strength. The five studies focused on the relationship between protein intake and fracture incidence all agreed that a correlation existed between low protein intake and fracture occurrence (Wengreen et al, 2004, Misra et al, 2011, Munger et al, 1999, Martinez-Ramirez et al, 2011, Frassetto et al, 2000). One study reported that each 20% increase in protein intake was associated with a significantly higher bone mineral density (BMD), for total body and hip (Beasley et al, 2014), whereas another study concluded that bone mineral density was not significantly associated with the ratio of animal to vegetable protein intake (Sellmeyer et al, 2001). Investigating any relationship between protein intake and body weight, one study reported that in the total population, protein intake was associated with higher percent body fat, but in the subgroup with intermediate BMI and stable weight, there was no association between protein intake and percent body fat (Vinknes et al, 2011). Another study reported that a 1% increase in carbohydrate and protein consumption was associated with a 14% and 16% lower likelihood of being obese (Tyrovovlas et al, 2011).

With regard to the relationship between protein intake and frailty, one study reported that subjects with higher protein intake had lower risk of frailty (Kobayashi et al, 2013). In support of this, another study reported that a 20% increase in uncalibrated protein intake (%kcal) was associated with a 12% lower risk of frailty, while a 20% increase in calibrated protein was associated with a 32% lower risk of frailty (Beasley et al, 2010). Similarly, a further study concluded that diet with a combination of high protein and high total antioxidant capacity is strongly associated with low prevalence of frailty among old Japanese women (Kobayashi et al, 2017).

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Investigating muscle strength/mass, one study reported that not meeting the recommended dietary protein intake was associated with significantly lower appendicular lean mass at baseline (Scott et al, 2010) and another reported that greater protein intake was associated with less age-related decrease in grip strength (McLean et al, 2015). It was reported that malnutrition and inadequate protein intake were very common and associated with poor dental health among older people with multiple disabilities in assisted living facilities (Saarela et al, 2014). Finally, a study on infection incidence concluded that a lower protein intake was independently associated with hospitalisation due to infection (Wham et al, 2015).

In summary, higher protein intake was associated with lower risk for frailty, improved bone density and strength but there was no consistent relationship between protein intake and body mass. Lower protein intake was associated with negative health outcomes.

N-3 fatty acids and PUFA

Cognition

Sixteen studies were identified that focused on N-3 fatty acid/PUFA intake and met the inclusion criteria of this review. Eleven were conducted on 65+ years or used a mean group age greater than 65 years. All studies except one (male only) were of mixed gender populations. Health outcome measures were cognition (9), fracture risk (3), dental health (2) muscle strength (2).

Higher omega-3 fatty acid/PUFA intake was associated with positive health outcomes in several studies. Seafood consumption was associated with slower decline in semantic memory and perceptual speed (Van de Rest et al, 2016). Another study reported that consumption of lean fried fish had no protective effect but consumption of fatty fish more than twice per week was associated with a reduction in risk of dementia by 28% and Alzheimer's disease by 41% in comparison to those who ate fish less than once per month (Huang et al, 2005). Fish consumers had significantly less cognitive decline over five years than did non-consumers (Van Gelder et al, 2007). Another study reported that low intake of EPA and DHA were predictors of cognitive impairment and were negatively associated with cognitive function, assessed by the Mini Mental State Examination (Gonzalez et al, 2010). Higher global cognitive function was also reported to be associated with higher levels of serum EPA and DHA + EPA after controlling for confounders (Nishihira et al, 2016). Plasma EPA has also been associated with a slower decline in the Benton Visual Retention Test in ApoEe4 carriers and depressive subjects (Samieri et al, 2011). A further study concluded that Montreal Cognitive Assessment test scores were related to fish servings (Brutto et al, 2015). Finally, there was significant association between reported fish consumption and a verbal language score (Dangour et al, 2009). High fish consumption associated with less cognitive impairment and slower cognitive decline.

Fractures

In a study of associations between fish-oil consumption in early life, midlife, and late life with osteoporotic fracture risk, in the highest tertile of omega–3 fatty acid consumers (daily) a decreased fracture risk was observed in men that almost reached significance in women (Harris et al, 2015). One study reported inverse associations with vegetable consumption, fish consumption and polyunsaturated lipid intake with hip fracture, whereas saturated lipid intake was positively associated with hip fracture risk (Benetou et al, 2011). A third study reported no statistically significant association between intakes of total PUFA, total n-3 PUFA, total n-6 PUFA, n-6/n-3 PUFA ratio or individual PUFAs and hip fracture risk; however, women with low intakes of total PUFA, n-6 PUFA and linoleic acid were at increased risk of fractures (Virtanen et al, 2012).

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Dental health

Two relevant studies were retrieved. They reported that a high dietary n-6:n-3 PUFA intake ratio was associated with a greater number of periodontal disease events (Iwasaki et al, 2011); similarly a low DHA intake was associated with more periodontal disease events (Iwasaki et al, 2010).

Muscle strength

Two relevant studies were retrieved. One study concluded that higher concentrations of total PUFAs were associated with larger muscle size and with greater knee extension strength (Reinders et al, 2014). A second study concluded that the most important dietary factor in relation to grip strength was fatty fish consumption (Robinson et al, 2008).

In summary, fish consumption (particularly oily fish rich in omega-3 fatty acids) associated positively with muscle strength, dental health and cognitive function. In addition, two of three studies suggest that daily fish consumption associates with reduced fracture risk, particularly in men.

MUFA

Four studies were identified that met the inclusion criteria of this review and evaluated the relationship between monounsaturated fatty acids (MUFA) and health outcomes. Two of the four studies were conducted with older people of 65+ years and one focused on females. Measured health outcomes included cognition, fracture risk, and longevity. One study reported that MUFA intake was inversely associated with cognitive decline (Naqvi et al, 2011); a second study reported that the odds ratio for mild cognitive impairment was reduced in those with high vegetable intake and with high mono- plus polyunsaturated fatty acid to saturated fatty acid ratio (Roberts et al, 2010). A study on fractures reported that a dose-dependent increase in risk of hip fractures was associated with higher intakes of total fat, animal fat, saturated fatty acids and MUFA (Zeng et al, 2015). Higher MUFA intake was associated with an increased chance of survival in older adults (Solfrizzi et al, 2005).

In summary, MUFA intake was associated with positive health outcomes in three of four studies.

Vitamin A

Three studies on vitamin A were identified that met the inclusion criteria of this review; two included an all-female population and looked at relationships in people over 50 years of age. Health outcomes measured were fracture incidence and dental health. In relation to fracture incidence, one study concluded that there was no significant association between vitamin A intake and the risk of fracture but that those with in highest quintile for vitamin A intake and with low vitamin D intake were more likely to have increased fracture risk (Caire-Juvera et al, 2009). A second study reported that users of supplements containing vitamin A had a 1.18-fold increased risk of incident hip fracture compared with non-users, but there was no evidence for an increased risk of all fractures among supplement users (Lim et al, 2004). Regarding oral health, those with lower Healthy Eating Index scores and significantly lower vitamin A intake were more likely to have poor oral health (Bailey et al, 2004).

In summary, highest vitamin A intake was associated with increased risk for fracture, particularly when combine with low vitamin D in two of three studies. Poor oral health associated with low vitamin A intake.

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Vitamin B12

Eight studies that focused on vitamin B12 and met the inclusion criteria of this review were identified. Five of these studies were conducted on cohorts older than 65 years and all studied mixed gender populations. Outcomes assessed were cognition, fractures and mortality. Regarding cognition, one study reported that people over 50 with mild cognitive impairment and with low-normal vitamin B12 showed a significantly poorer learning ability and recognition performance than those with high-normal vitamin B12 concentration in the blood (Kobe et al, 2016). Similarly, it was also concluded that cognitive impairment was related to low blood vitamin B12 in a Brazilian population (Martinho, Tinoco and Ribeiro, 2015). Low vitamin B12 concentrations were identified in 13% of older people and were associated with memory impairment and depression (Hin et al, 2006). Another study concluded that the rates of dementia or decline associated with homocysteine for those in the lowest and highest tertiles of vitamin B12, respectively, were significantly higher and lower than the risk for those in the middle tertile (Haan et al, 2007). However, a further study found no evidence for a vitamin B12-related memory deficit although cognitive processing speed was lower (Jelicic, Jonker and Deeg, 2010).

Regarding fractures, one study reported that plasma vitamin B12 and B6 concentrations were inversely associated with hip fracture risk (McLean et al, 2008), with a second study reporting that osteoporosis occurred more among women whose B12 status was marginal or deficient than in women with a normal status (Dhonukshe-Rutten et al, 2002).

In relation to mortality, findings suggested that in patients at nutritional risk who were admitted to hospital and given supplements, those with high vitamin B12 had increased mortality and a longer length of stay (LOS) than those with normal concentrations (median 25 days) versus 23 days, and elevated vitamin B12 was an independent predictor of LOS (Cappello et al, 2017).

In summary, low vitamin B12 in the blood associated with poor cognitive performance and increased fracture risk. These studies did not consider vitamin B12 intake; absorption from the diet may be impaired with age.

Vitamin C

Four studies were identified which investigated vitamin C and met the inclusion criteria of this review. Health outcomes related to cognition, infection and muscle strength. All studies were conducted on subjects greater than 65 years of age, with two studies being undertaken on female populations. Investigating cognition, one study concluded that consumption of vitamin C supplements was associated with a lower prevalence of more severe cognitive impairment (Paleologous, Cumming and Lazarus, 1998), with another study suggesting that overall, long-term vitamin C intakes were not consistently related to cognition (Devore et al, 2012). With regard to infection, it was concluded that serum vitamin C (measured as ascorbate) concentration was strongly inversely related to fibrinogen, factor VIIC and acute phase proteins but not to self-reported respiratory symptoms (Khaw and Woodhouse, 1995). Plasma vitamin C concentration was also reported to be positively correlated with handgrip strength, length of time standing on one leg with eyes open and walking speed, and inversely correlated with body mass index (Saito et al, 2011).

In summary, vitamin C intake and blood concentrations were not associated with health risks and 50% of studies showed benefit; one on strength and the other on cognition.

Vitamin D

A total of one hundred studies that focused on vitamin D and met the inclusion criteria of this review were identified. Seventy-one studies specifically examined data from those above 65 years. Thirty-two of these

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studies were conducted on females only and eleven were undertaken on a male-only cohort. Health outcome were comprised of fractures (30), cognition (15), frailty (16), muscle strength (14), body weight (6), falls (6) longevity (6), vitamin D levels (2) dental health (2) and infection (2).

Fractures: Twenty-four out of thirty studies reported an inverse association between vitamin D and fracture incidence. Either subjects with higher levels of vitamin D had reduced incidence of fractures or more often, a correlation between low vitamin D levels and increase fracture occurrence was evident (see Table). Three studies reported no obvious correlation between vitamin D levels and fracture risk (Garnero et al, 2007, Shinkov et al, 2016, Steingrimsdottir et al, 2014). Conclusions from five other studies were more complex. A study combined with vitamin K1 reported that a 50 % higher risk of hip fracture was observed in subjects with both low vitamin K1 and vitamin D, but no increased risk was observed in the groups low in one vitamin only (Finnes et al, 2016). The same finding was reported by Dahl et al (2015). Similarly, looking at fracture incidence, low vitamin K1 and 25(OH)D were independently and synergistically associated with the risk of hip fracture (Torbergsen et al, 2015). Another report showed that serum vitamin D was a linear predictor of major osteoporotic fracture and significant quadratic predictor of hip fracture in the total sample and among those with <10 years of follow-up, but it was not related to risk of fracture among those with >10 years of follow-up (Looker et al, 2013). Cauley et al (2010) concluded that vitamin D levels were unrelated to non-spine fractures but a decrease in vitamin D was associated with increased risk of hip fracture. Age, height, weight, body mass index, fat mass, lean body mass, waist circumference, serum vitamin D, parathyroid hormone, and exercise were also reported to be related to bone mineral density (Yang and Kim, 2015). Finally, the relationship between baseline vitamin D and fracture risk was described as being U-shaped, with increased fracture risk in men with either low or high serum vitamin D levels (Bleicher et al, 2014).

Cognition: Fourteen of the fifteen studies reported an association between vitamin D levels and cognitive performance. Either subjects with higher levels of vitamin D were less likely to have cognitive impairment or with low vitamin D level were associated with increased cognitive impairment (Wilkins et al, 2006, Annweiler et al, 2012, Milman et al, 2014, Bartali et al, 2014, Perna et al, 2014, Jorde et al, 2015, Breitling et al, 2012, Llewellyn et al, 2011, Llewellyn et al, 2010, Wilkins et al, 2009, Annweiler et al, 2016, Chei et al, 2014, Seamans et al, 2010, Miller et al, 2010). One study reported that those in the lowest and highest vitamin D quartiles had an increased risk of impaired prevalent but not incident global cognitive functioning or decline in functioning compared with those in the middle quartiles (Granic et al, 2015).

Frailty: Sixteen of the seventeen studies reported an inverse correlation between vitamin D levels and frailty, with low vitamin D levels being associated with frailty (Shardell et al, 2012, Pabst et al, 2015, Gutierrez-Robledo et al, 2015, Shardell et al, 2009, Hirani et al, 2013, Alvarez-Rios et al, 2015, Trevisan et al, 2017, Wong et al, 2013, Vogt et al, 2015, Tajar et al, 2012, Buta et al, 2016, Smit et al, 2012, Wilhelm-Leen et al, 2010, Chang et al, 2010, Schottker et al, 2014). Less able patients reportedly had significantly lower vitamin D levels in another study (Skalska, Galas and Grodzicki, 2012). One study reported a U-shaped association at baseline was seen between 25(OH)D level and odds of frailty, with the lowest risk among those with mid-range plasma vitamin D levels 20.0–29.9ng/ml (Ensrud et al, 2010).

Muscle strength and falls: Ten of the fifteen studies showed a significant correlation between low vitamin D levels and muscle strength, with lower levels associating with poor strength (Gerdhem et al, 2005, Houston et al, 2007, Mastaglia et al, 2011, Iolascon et al, 2015, Zamboni et al, 2002, Bird et al, 2013, Inderjeeth et al, 2007, Gumieiro et al, 2015, Salminen et al, 2015, Pramyothin et al, 2009). Five studies reported no association. One such study concluded that few subjects had 25-hydroxyvitamin D concentrations <30 nmol/L and that above this concentration, there was no dose effect relation with physical performance except for single-leg stands (Chuang et al, 2016). A second study reported that there were no differences in the GCS Composite Scale, a global measure of physical function, between those with higher and lower 25(OH)D concentrations (Haslam

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et al, 2014). A further study reported that no significant relationship between balance, gait speed and grip strength, and serum 25-OHD was detected (Mathei et al, 2013). A fourth study concluded that although physical performance declined over time, this was not associated with baseline vitamin D (Houston et al, 2012). This was echoed by Chan et al (2012) who reported that serum 25OHD levels were not associated with baseline or 4-year change in physical performance measures and skeletal muscle mass. Five out of the six studies examining association between vitamin D and falls incidence reported an inverse correlation (Stein et al, 1999, Lloyd et al, 2009, Rothenbacher et al, 2014, Shimizu et al, 2015 and Flicker et al, 2003). One study however reported that use of vitamin D supplements was not associated with any measures of neuromuscular function, change in neuromuscular function, or fall rates (Faulkner et al, 2006).

Longevity: Four of the six studies identified a correlation between low serum vitamin D and increased mortality (Buchebner et al, 2016, Semba et al, 2009, Kim et al, 2015, Samefors et al, 2014). Two further studies reported no association between vitamin D levels and all-cause mortality (Cawthon et al, 2010, Eaton et al, 2011).

Body Weight: Five out of the six studies reported a correlation between low vitamin D levels and increased body weight, with three of these studies including a relationship to sarcopenia (Seo et al, 2012, Hwang et al, 2012, Huo et al, 2016, Oh et al, 2016, Sohl et al, 2015). Only one study concluded that vitamin D levels were not associated with overall weight change or body fat loss (Vogt et al, 2016).

Dental Health: Of the two studies identified, one reported that men with more severe periodontal disease have lower vitamin D levels and that vitamin D levels across all periodontitis groups are considered to be low (Schulze-Spate et al, 2015). The second study concluded that there were no statistically significant associations found between baseline vitamin D levels and change in periodontal disease measures, overall or in a subset (n=442) of women with stable vitamin D concentrations (change of <±20 nmol/L) (Millen et al, 2014).

Infection: Of the two studies identified, one reported that after multivariable adjustments, the subjects in the lowest serum vitamin D tertile (8.9-33.8nmol/L) had a 2.6-fold higher risk of developing pneumonia compared with the subjects in the highest tertile (50.8-112.8nmol/L) (Aregbesola et al, 2013). The second study concluded that in multivariable analyses, a serum vitamin D level of <15ng/mL was associated with a higher risk of hospitalization with an infection but not of hospitalization without an infection (Kempker et al, 2016).

In summary, 70% of 100 studies reported benefits of higher vitamin D levels for health outcomes (or lower vitamin and poor health outcomes). The highest concentrations of vitamin D may associate with increased prevalence of cognitive impairment, fractures and frailty. Vitamin K and vitamin D associate synergistically with bone health.

Vitamin E

Four studies on vitamin E that met the inclusion criteria of this review were identified. All studied people older than 65 years and one was an all-female population. Health outcomes measured were cognition, dental health and fractures. With regard to cognition, one study concluded that participants with plasma vitamin E levels in the bottom tertile (<26umol/L) had a significantly higher probability of being demented and suffering from cognitive impairment compared to those in the highest vitamin E tertile (>32.93umol/L) (Cherubini et al, 2005). Another cognition study reported that lower risk of cognitive impairment was observed in people with higher levels of y-tocopherol, B-tocotrienol and total tocotrienols (Mangialasche et al, 2013). With regard to dental health higher intake of vitamin E associated with reduced periodontal disease severity in community-dwelling older Japanese (Iwasaki et al, 2012). A report on fracture recovery identified higher vitamin E concentrations

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in people who were recovering from hip fractures than in controls, but they were had higher cognitive and physical function than the control group (D'Adamo et al, 2011).

In summary, low vitamin E intake/blood concentration was related to poor health outcomes in older adults.

Thiamin

One study that focused on thiamin was identified as meeting the inclusion criteria for this review; the average age of those studied was 83 years. Cognitive status did not differ according to thiamin status but thiamine-deficient subjects represented a larger proportion of Alzheimer's patients (Pepersack et al, 1998).

In summary, in healthy older adults thiamine status was not associated with cognitive function

Riboflavin

Two studies that focused on riboflavin were identified as meeting the inclusion criteria for this review; the health outcome was fracture risk. Low riboflavin intake alone was not associated with fracture risk and bone mineral density (Yazdanpanah et al, 2007 but a small, but significant association was found between vitamin B6 and riboflavin intake and baseline BMD of the femoral neck (Yazdanpanah et al, 2007).

In summary, there is a weak link between bone health and riboflavin with vitamin B6 intake.

Calcium

Nineteen epidemiological studies that focused on calcium were identified as meeting the inclusion criteria for this review; one study investigated calcium combined with zinc and another with protein. Further studies with vitamin D and calcium have been considered previously. Five of the studies used age groups of 65+ years, fourteen studies included people over 50 years and one study include people aged 41-79 years. Ten studies were conducted on female populations only and one study recruited an all-male cohort. Outcomes assessed included sarcopenia, cognitive function, bone mineral density, fractures, periodontitis, osteoporosis and mortality.

Two studies investigated the relationship between calcium intake and cognition; one study reported that cognitive decline was associated with elevated serum calcium (>1.29 mmol/L; Tilvis et al, 2004) whereas another study concluded that cognition increased with calcium up to a point (data could not be extracted from the source) and then cognition decreased as calcium further increased (Emsley et al, 2000). Another study reported that daily calcium intake was significantly lower in subjects with sarcopenia than in those without (Seo et al, 2013).

Fourteen studies investigated the association between calcium and outcomes related to bone mineral density (BMD), fractures and osteoporosis. One study concluded that bone disease was associated with a lack of dairy products or calcium supplementation (Wang et al, 2017), whilst another study reported that calcium intake was not associated with osteoporosis diagnosis or fracture (Fardellone et al, 2009). Four studies reported a positive correlation between BMD and calcium intake where lower calcium intakes were linked to fractures (Formosa and Xuereb-Anastasi, 2016, Wlodarek et al, 2012, Radavelli-Bagatini et al, 2014, Cauley et al, 2004). Two reports suggested that daily dairy calcium intake is not associated with BMD; in femoral neck BMD (Van den Berg et al, 2014) and people who were generally osteoporotic and osteopenic (Lee et al, 2007). Urinary calcium was reported to be negatively associated with trochanter, total femur and spine BMD (Ilich et al, 2009).

Considering the relation between calcium and bone fractures, one study reported that calcium intake was not related to the risk of fracture in women, however, daily calcium intakes above 1g associated with lower risks

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in men (Cooper, Barker and Wickham, 1988). Khan et al (2015) concluded that for older men and women, calcium intakes of up to 1348mg/d from food were associated with decreased risks for fracture, non-fatal CVD, stroke and all-cause mortality.

Finally, a study on periodontitis concluded that intakes of total dairy calcium, calcium from milk and fermented foods were inversely associated with periodontitis but non-dairy calcium, calcium from cheese and other dairy food intakes were not (Adegboye et al, 2012).

In summary, 75% of studies showed an association between higher calcium intake and bone health. One study showed that low calcium intake associated with age-related muscle loss. Two studies reported that higher blood ionised calcium was associated with poor cognition although it is not clear whether this was related to higher intake or other pathology.

Calcium and Vitamin D

Five studies that focused on calcium and vitamin D were identified as meeting the inclusion criteria for this review, four studied an all-female cohort. Health outcomes included BMD, fractures and cognition. One study reported that low vitamin D intake was associated with a more pronounced rate of fracture and that higher levels of calcium intake did not further reduce the risk of fractures of any type, or of osteoporosis (Warensjo et al, 2011). Another study reported that higher calcium and vitamin D intakes significantly reduced the odds of osteoporosis but not the 3-year risk of fracture in Caucasian women (Nieves et al, 2008). Other investigations concluded that women consuming vitamin D ≥12.5g/d from food/supplements had a 37% lower risk of hip fracture than did women consuming <3.5g/d, but total calcium intake was not associated with hip fracture risk (Feskanich, Willett and Colditz, 2003). A further study reported that no dose–response association between calcium intake and fracture risk was found and that vitamin D intake was not associated with fracture risk (Michaelsson et al, 2003).

Regarding cognition, neither serum ionized calcium nor 25-hydroxyvitamin D was reported to be associated with cognitive function (Tolppanen, Williams and Lawlor, 2011).

In summary, four of five studies did not observe any association between poor health outcomes ascribed to low vitamin D when calcium was increased.

Folate

Five studies that focused on folate were identified as meeting the inclusion criteria for this review, one of which also investigated vitamin D. All studied people over 65 years. Outcome measures were cognition, falls and dental health. All three studies of the relationship between folate and cognition reported positive associations with cognition. One of these studies reported that cognitive impairment and dementia decreased with increasing RBC folate concentration (Ramos et al, 2005), another that higher plasma folate concentrations are associated with better global cognitive function (Lau et al, 2007) and the third concluded that men had increased cognitive impairment and this was associated with lower serum folate (Lee, Shahar and Rajab, 2009). Regarding falls it was reported that serum folate was negatively associated with the number of falls and in those with prescribed medications it was the only protective factor against falls (Shahar et al, 2008). A study on dental health concluded that a low serum folate level was independently associated with periodontal disease in older adults (Yu et al, 2007).

In summary, all studies showed associations between low folate and poor health outcomes or higher folate and improved health outcomes.

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Folate and Vitamin B12

Twelve studies that focused on folate and vitamin B12 were identified as meeting the inclusion criteria for this review. Ten of the twelve studied people older than 65 years, two studied all-female populations and one studied males only. Health outcomes measured included cognition (11) and fracture incidence (1). Five studies on cognition reported that folate was significantly correlated with cognition, but vitamin B12 was not (Ravaglia et al, 2005, Tettamanti et al, 2006, Agnew-Blais et al, 2015, Feng et al, 2006, Mooijaart et al, 2005). One study reported that subjects in the lowest folate tertile had significantly higher adjusted odds ratios for mild cognitive impairment and dementia (Quadri et al, 2004) and another that dietary folate was a protective against a decline in verbal fluency (Tucker et al, 2005). Only plasma folate level was positively associated with the MMSE-KC and Boston Naming Test in another study (Kim et al, 2002). One study reported that higher vitamin levels were not associated with either initial cognitive performance or subsequent cognitive decline (Kang, Irizarry and Grodstein, 2006). Another study concluded that high folate intake was associated with faster rate of cognitive decline (Morris et al, 2005). Similarly, when serum folate was low, increasing the folate concentration associated with better cognitive performance especially when vitamin B12 levels were low, however, when folate was high and vitamin B12 was high, further increasing folate was associated with increased the risk for impaired cognitive function (Castillo-Lancellotti et al, 2014).

A single study focused on fracture incidence reported that participants in the lowest serum folate quartile (~9.3 nmol/L) had an increased risk of fracture than did those in higher quartiles but no dose-related protective effect for increasing serum folate levels was found (Ravaglia et al, 2005). This same study also concluded that no independent association was found for serum vitamin B12.

In summary, low folate but not B12 associated with poor health outcomes but that increasing folate in those with already high folate and B12 levels associated with poor health outcomes.

Iron

Six studies that focused on iron were identified as meeting the inclusion criteria for this review; health outcomes related to immunity, anaemia, cognition and body weight were identified. Regarding body weight, it was reported that lower serum Fe levels were related to the inflammation linked with higher BMI (Oldewage-Theron, Egal, Grobler, 2014). Also, serum ferritin was significantly correlated with the various indexes of adiposity, such as the hepatic fat content (negative association), visceral and subcutaneous fat (Iwasaki et al, 2005). Another study reported that the influence of high storage-iron levels impaired immunity and increased the prevalence of obesity and abdominal fatness (Kouris-Blazos et al, 1996). It was concluded in another study that vegetarians' low serum ferritin level may reduce the risk of metabolic syndrome in postmenopausal women (Kim and Bae, 2012). A study on cognition concluded that Mini-Mental State Examination scores were moderately and significantly correlated with iron levels and transferrin saturation (Yavuz et al, 2012). A study related to anaemia reported that iron deficiency anaemia was associated with positive urine culture for bacteriuria (Butta et al, 2014).

In summary, high iron concentrations related to poor health outcomes in older adults but that low iron also related to poor immune function and cognition.

Magnesium

Three studies that focused on magnesium were identified as meeting the inclusion criteria for this review; health outcomes were metabolism, BMD and fracture incidence. A strong inverse relationship between serum magnesium and the presence of metabolic syndrome was reported and as the number of components of metabolic syndrome increased, magnesium levels decreased (Evangelopoulos et al, 2008). In relation to

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fracture incidence, it was reported that BMI, serum magnesium, calcium and albumin were significantly lower in females when BMD was lower (Saito et al, 2004). Risk of lower-arm or wrist fractures was reported to increase with higher magnesium intake, however it was noted that these women were more active and at a higher risk of falls (Orchard et al, 2014).

In summary, in two of three studies, low magnesium associated with poor health.

Mixed vitamin/nutrient intake

Fifteen studies were identified which investigated multi-vitamin intake or nutrient-rich diets, with ten studying age groups of 65+ years and two studying all-female populations. Health outcomes were frailty, body weight, obesity, fracture risk, dental health and cognition. With regard to dental health, one study reported that intake of non-starch polysaccharides, protein, calcium, non-haem iron, niacin, and vitamin C intake were significantly lower in edentate subjects compared with dentate subjects (Sheiham et al, 2001). In another study, it was also reported that subjects who had at least 5 teeth had higher carbohydrate and vitamin B1 intake than those who had 4 or less teeth (Suzuki et al, 2006).

Cognition: differences in cognitive functioning were related to specific nutrient intakes; protein, fibre, eicosapentaenoic acid, niacin and vitamin B6 (Guligowska et al, 2016). Another study concluded that associations between lifestyle and cognition existed, including PUFA and vitamin B2, with fat intake, vitamins A, B2, B3, C, fibre and vegetables being associated with depression (Woo et al, 2006). A third study reported that female subjects with poor cognitive function had significantly lower intakes of cereals, vegetables, fruits, milk, spices and also, protein, fat, calcium, iron, vitamin A, thiamin, riboflavin and niacin than those of a normal cognition (Lee et al, 2001). Male subjects in the same study with poor cognitive function had significantly lower intake of fruits, fibre, and vitamin C than normal subjects. A fourth study concluded that the prevalence of low vitamins B12, B6, folate and niacin were 6.7%, 5.3%, 1.3% and 26.7% respectively and that there was no significant difference among grouped into tertiles of cognition (Paulionis, Kane and Meckling, 2005).

Fracture incidence: after adjustment, dose-dependent inverse associations were observed between the dietary intake of vitamin C, vitamin E, β-carotene, and Se and antioxidant score and the risk of hip fracture (Sun et al, 2014) but no significant association was observed between dietary Zn or animal-derived vitamin A intake and hip fracture risk. A second study concluded that a "nutrient-dense" pattern rich in calcium and phosphorous, iron, vitamins B including B12, vitamins C and E, alcohol, proteins, and unsaturated fats was associated with a 19 % lower risk of wrist fractures (Samieri et al, 2013). The same study reported that a "south-western French" dietary pattern rich in calcium, phosphorous, vitamins D and B12, retinol, alcohol, proteins, and fats-including unsaturated fats; poor in vitamins C, E, and K, carotenes, folates, and fibres; was related to a 33 % lower risk of hip fractures.

Frailty: one study concluded that daily energy intake ≤21 kcal/kg was significantly associated with frailty and after adjusting for energy intake, a low intake of protein; vitamins D, E, C, and folate; and having a low intake of more than three nutrients were significantly and independently related to frailty (Bartali et al, 2006). A second study reported that women in the lowest quartile of serum carotenoids, a-tocopherol, and 25(OH)D had an increased risk of becoming frail and that the number of nutritional deficiencies was associated with an increased risk of becoming frail, after adjustment (Semba et al, 2006). A third study concluded that frail women were more likely to have at least 2 deficiencies and that the odds ratios of being frail were significantly higher for those participants whose concentrations were in the lowest quartile for total carotenoids, a-tocopherol, 25(OH)D, and vitamin B6 (Michelon et al, 2006). One study focused on a Mediterranean diet and frailty on a mixed-sex population aged 60 years and greater concluded that the risk of frailty was inversely associated with fish and fruit consumption (Leon-Munoz et al, 2014).

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Body mass: With regard to body weight, it was reported that low intake of protein, vitamin D, calcium and vitamin C was significantly associated with loss of muscle in men, but not women (Oh et al, 2015). A further study concluded that no overall association was seen between patterns of nutrient intake and abdominal obesity in both genders (Kosaka et al, 2013).

In summary, protein and micronutrient-low diets associate with poor health outcomes and higher protein and micronutrient intakes associate with good health outcomes.

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