



**SACN Statement on
Diet, Cognitive Impairment and Dementias**

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Acronyms

AA	arachidonic acid
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale cognitive subscale
ALA	alpha-linolenic acid
ALSPAC	Avon Longitudinal Study of Parents and Children
APOE	apolipoprotein E
BMI	body mass index
CI	confidence interval
DASH	Dietary Approaches to Stop Hypertension
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
HR	hazard ratio
IQ	intelligence quotient
LCPUFA	long-chain polyunsaturated fatty acids
LDL	low-density lipoprotein
LOAD	late-onset Alzheimer's disease
MCI	mild cognitive impairment
MD	mean difference
MeDi score	Mediterranean Diet Score
MeSH	Medical Subject Headings
MIND	Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
OR	odds ratio
PCS	prospective cohort study
PAR	population attributable risk
PET-CT	positron emission tomography - computed tomography
PUFA	polyunsaturated fatty acids
RCT	randomised controlled trial
RR	relative risk
SACN	Scientific Advisory Committee on Nutrition
SMD	standardised mean difference
TICS	Telephone Interview for Cognitive Status
TICS-M	Telephone Interview for Cognitive Status - Modified
UK	United Kingdom
US	United States
WMD	weighted mean difference

1 Introduction

- 1.1 The purpose of this statement is to provide an overview of the currently available evidence on nutrition and cognitive impairment and dementias in adults. This statement considers evidence relevant to the prevention of cognitive impairment or dementias. This statement is not focused on evidence relevant to the treatment of cognitive impairment or dementias.
- 1.2 This statement considers evidence assessing the possible relationship between dietary patterns and individual nutrients and various forms of cognitive impairment and dementias, including Alzheimer's disease (AD). Such evidence has not previously been considered by the Scientific Advisory Committee on Nutrition (SACN). Throughout this statement the term dementia is used to refer to all forms of dementia collectively, unless otherwise stated.
- 1.3 This is a position statement rather than a full risk assessment; therefore it is not intended to be a comprehensive review of the evidence base. It provides an overview of the evidence base.
- 1.4 This position statement evaluates the evidence in terms of:
 - a) the overall diet and dietary pattern
 - b) specific nutrients (B vitamins, vitamins C and E and omega-3 fatty acids)
 - c) other dietary components (polyphenols, flavonoids and caffeine) where there has been sufficient research carried out in relation to cognitive impairment, AD or other kinds of dementia, to allow a preliminary assessment.

For iodine, iron, zinc, copper and protein the evidence was not sufficient to allow a preliminary assessment.

2 Background

United Kingdom (UK) prevalence and disease burden

- 2.1 In 2016, dementia (including AD) accounted for 12% of all registered deaths in England and Wales, making it the leading cause of death using WHO disease groupings, ahead of ischemic heart diseases (11%) (ONS, 2017). In Scotland and Northern Ireland dementias (including AD) accounted for 8.9% (NRS, 2017) and 11.3% (NISRA, 2015) (respectively) of all registered deaths in 2015.
- 2.2 Dementia is more prevalent among older adults. In 2014, the UK prevalence of dementia was estimated as 7.1% for those aged 65 years or older and 1.3% for the entire population (total 816,000) (AS [Alzheimer's Society]. 2014). Dementia is more prevalent among women than men. Age and sex specific estimates of dementia prevalence are provided in Table A below.

Table A - Estimates of population prevalence of dementia*

Age in years	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	85 to 89	90 to 94	95 +
women	0.9	1.8	3.0	6.6	11.7	20.2	33.0	44.2
men	0.9	1.5	3.1	5.3	10.3	15.1	22.6	28.8

*data from (AS, 2014)

- 2.3 Approximately 95% of dementia cases in the UK are among those over 65 years of age (AS, 2014). For those over age 65 years with dementia, it is estimated that, 55% have mild dementia, 32% moderate dementia and 13% severe dementia.
- 2.4 Of those affected by dementia, 65% are women. Women with dementia are more likely to have AD than men (AD accounts for 67% of all dementia cases in women compared to 55% of all cases in men). Conversely, men with dementia are more likely to have vascular dementia (accounting for 20% of all dementia cases in men compared to 15% of all cases in women). (AS, 2014).
- 2.5 Due to limited data it is not currently possible to estimate the prevalence of dementia (including AD) for black, Asian and minority ethnic groups (AS, 2007).
- 2.6 The average annual cost per dementia case in the UK has been estimated as £32,250 (based on 2013 costs). This figure includes costs for healthcare (16%), social care (39%) and the value of the work provided by unpaid carers (44%) (AS, 2014). Of those with dementia over 65 years of age, 39% are estimated to live in care homes and 61% in the community.
- 2.7 It is estimated that, compared with the UK, the dementia prevalence in other Western European countries is lower in 3 countries and higher in 9 countries, with 'no clear regional or cultural pattern' (AS, 2014).

UK government advice

2.8 Current UK government advice (NHS, 2016) to reduce the risk of developing dementia is to:

- eat a healthy diet (as depicted in the Eatwell Guide)
- maintain a healthy weight
- exercise regularly
- don't drink too much alcohol
- stop smoking (if you smoke)
- make sure to keep your blood pressure at a healthy level.

Advice and information on dementia is available on [NHS Choices](#).

Clinical presentation

2.9 Dementia describes a group of symptoms, including memory loss, confusion, mood changes and difficulty with day-to-day tasks. Although the overwhelming majority of people with dementia are elderly, dementia is not an inevitable part of ageing.

2.10 Mild cognitive impairment (MCI) causes a slight decline in cognitive abilities, including memory and thinking skills, but not to such an extent that it hinders activities of daily living. MCI is not a form of dementia. However, a person with MCI is at an increased risk of developing dementia (including Alzheimer's disease).

2.11 Dementia is caused by a variety of diseases and injuries that primarily or secondarily affect the brain. The most common types of dementia are:

- Alzheimer's disease (AD) (including early-onset AD)
- vascular dementia
- dementia with Lewy bodies
- frontotemporal dementia
- mixed dementia.

2.12 These differing forms of dementia are likely to have different aetiological variables and the effect of nutrients on the risk of developing dementia, or its progression, are likely to differ between them. However, there are very few studies that report data for sub-types of dementia other than AD.

Alzheimer's disease

- 2.13 Alzheimer's disease accounts for an estimated 60% of cases (Qiu et al., 2007). The aetiology of AD is unclear; however, key pathological processes appear to be the deposition of abnormal amyloid in the central nervous system (Hardy, 1991) as well as changes to intracellular proteins in brain cells. AD is characterised by a slow, progressive deterioration in cognitive function. Problems with day-to-day memory are often noticed first, but other symptoms may include difficulties with word finding, problem solving, decision making or visual perception.
- 2.14 The vast majority of AD cases are late-onset. Both early-onset AD (before age 65y) and late-onset AD (LOAD) (age 65y and above) have a genetic component and twin studies predict the heritability of LOAD to be as high as 80%. Apolipoprotein E (APOE)¹ genotype is recognized as the main genetic risk factor, with semi-dominant inheritance for LOAD (Yu et al., 2014). Large genome-wide association studies (GWAS) have identified additional loci for LOAD but the effects of these genes on AD risk are much smaller than those of APOE. In general terms, one allele of APOE-ε4 shifts the risk curve for the disease to be 5 years earlier, 2 copies of APOE-ε4 shift it 10 years earlier, and one copy of the APOE-ε2 allele shifts it 5 years later; these APOE effects also apply in amyloid precursor protein (APP) and presenilin mutation carriers (Yu et al., 2014).
- 2.15 Early-onset AD (before 65 years of age) is a relatively rare condition, with prevalence roughly doubling with every 5 years of age. UK prevalence (cases per 100,000) is 9 for ages 30-34y, rising to 30 for ages 45-49y and 137 for ages 55-59y (AS, 2014). Early-onset AD shows strong evidence of an autosomal-dominant inheritance due to mutations in presenilin or amyloid precursor protein genes. People with Down's syndrome have a greatly increased rate of AD, with up to 50% of those aged over 60 years affected (Zigman et al., 1996). This may be because people with Down's syndrome have an extra copy of chromosome 21, and hence an extra copy of the amyloid precursor protein gene.

Vascular dementia

- 2.16 Vascular dementia, which may account for around 5 to 20% of dementia cases (Rizzi et al., 2014) occurs as a consequence of decreased blood flow to the brain, caused by stroke, a series of small strokes, or damage to small blood vessels in the brain. It usually has a more sudden onset and stepwise progression than AD, and often has a patchy picture of cognitive deficits.

¹ The APOE gene is located on chromosome 19q13.2 and it contains several single nucleotide polymorphisms (SNPs). Two in particular – rs7412 (C/T) and rs429358 (C/T) – are responsible for the 3 major alleles: epsilon-2 (ε2), epsilon-3 (ε3), and epsilon-4 (ε4); resulting in 3 major protein isoforms, APOE-ε2, APOE-ε3, and APOE-ε4, which differ from each other by one or two amino acids at positions 112 and 158 which alter APOE structure and function (Giau et al., 2015).

However, symptoms are very variable and often overlap and coexist with those of AD.

Dementia with Lewy bodies

- 2.17 Dementia with Lewy bodies may account for around 4% of dementia cases (AS, 2007). This type of dementia is caused by abnormal deposits of the protein alpha-synuclein forming structures called Lewy bodies within brain cells. Symptoms differ from AD in that fluctuating alertness, visual hallucinations and difficulty judging distances tend to occur before memory loss. Symptoms of tremor and rigidity (Parkinsonism) are also present. In the early course of the condition it may be difficult to distinguish dementia with Lewy bodies from AD.

Frontotemporal dementia

- 2.18 Frontotemporal dementia is less common than other types of dementia and may account for around 2% of dementia cases (AS, 2007). It is characterised by the degeneration of nerve cells in the frontal and temporal lobes of the brain, which are generally involved in personality, behaviour and language. Early symptoms tend to involve changes in personality and behaviour and depending on where the damage is, a person may have difficulty with speech or forget the meaning of words or objects. Frontotemporal dementia has a known genetic element; 30% to 50% is familial with mutations in 2 genes, microtubule associated tau protein and progranulin (GRN) accounting for half of these cases (Seelaar et al., 2011).

Mixed dementia

- 2.19 Mixed dementia has been estimated to account for around 10% of dementia cases (AS, 2014). Mixed dementia involves 2 or more different causes contributing to the condition. This can be overlooked in the process of diagnosis, or may be difficult to establish, and therefore the prevalence may be underestimated. It is now thought that the majority of dementias in older age groups have more than one component which is responsible for the symptomatology of dementia.

Assessment

- 2.20 Assessing cognitive function is essential in detecting and diagnosing cognitive impairment and dementias. The various assessment methods used provide differing levels of sensitivity and specificity, and these vary depending on the type of cognitive impairment being assessed (for example, mild cognitive impairment (MCI), AD or other forms of dementia) (Cullen et al., 2007). Relatively short and simple assessments can be carried out by non-specialist health professionals as a method of screening. Longer and more in depth tools, while being more sensitive and/or specific, require specially trained staff.

- 2.21 The Mini-Mental State Examination (MMSE) is the best known and most widely used measure of cognition worldwide. MMSE is a short 30-point scale which can be easily administered by clinicians or researchers with minimal training, takes around 10 minutes, and assesses cognitive function in the areas of orientation, memory, attention and calculation, and language and visual construction; lower scores indicate worse function (Folstein et al., 1975). The MMSE, however, has some limitations in that it does not include executive function² which is commonly the first manifestation of vascular aetiologies.
- 2.22 The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) was designed to assess cognitive symptoms of AD. It is generally used for more detailed assessments, research evaluations and to measure cognition in clinical trials. It is a 70-point scale, with a 4 point difference between treatment groups considered clinically important (Rockwood et al., 2007).
- 2.23 The Telephone Interview for Cognitive Status (TICS) is a standardised test of cognitive functioning developed for use in situations where in-person cognitive screening is impractical or inefficient, although it may also be administered face-to-face. The Telephone Interview for Cognitive Status – Modified (TICS-M) is a widely used screening instrument for Alzheimer's disease.
- 2.24 In addition to tests of cognitive function, blood tests and brain imaging (CT, MRI or PET-CT (positron emission tomography - computed tomography)) are commonly used in clinical assessment for potential causes of dementia.
- 2.25 The diagnostic criteria for AD and other forms of dementia have evolved with time. As a consequence of this, published research studies have used different definitions for dementia and cognitive dysfunction. It is important to take this into account when considering the evidence relating to nutritional intake, cognitive function and dementia risk.

Non-dietary factors affecting risk

- 2.26 The risk of cognitive impairment and dementias is affected by a broad range of factors.
- 2.27 Reviews considering factors affecting the risk of cognitive impairment have found more and stronger evidence for some of the non-dietary factors than for dietary factors (Deckers et al., 2015; Cooper et al., 2015; Di Marco et al., 2014). An expert panel organised by Deckers et al. (2015) ranked the most important factors affecting dementia risk. A Mediterranean dietary pattern was in 6th position (as a beneficial factor), alongside a number of (detrimental) risk

² Executive function refers to higher order cognitive abilities relevant to the regulation of other cognitive processes. Executive functions include working memory, reasoning, task flexibility, problem solving, planning and execution.

factors potentially modifiable through dietary means such as diabetes (2nd position), hypertension (5th), midlife obesity (7th), and high cholesterol (10th).

- 2.28 The research evidence for the effect of alcohol on dementia is mixed. Some studies suggest that a light to moderate alcohol consumption may be associated with a decreased risk of AD or other forms of dementia, while other studies do not support such an association. Definitions of alcohol consumption vary widely across studies. Variability in findings may also occur because of differences in drinking patterns (which are not captured by the studies), individual differences, varying follow-up periods or possible interactions with other lifestyle-related factors such as smoking. Confounding by general cognitive ability and other uncontrolled factors is also possible. Therefore, the relationship between alcohol intake and dementia risk needs further investigation.
- 2.29 In some cases non-dietary factors may interact with dietary factors or may confound associations with dietary factors.
- 2.30 The evidence from studies that report on non-dietary determinants of dementia risk (including alcohol intake and physical activity) has been summarised in Annex 1.

Potential confounding

- 2.31 Cognitive decline occurs over decades and much of the evidence relating nutrition to cognitive decline and dementia is observational and therefore subject to confounding.
- 2.32 While a number of systematic reviews and meta-analyses report that the primary studies included appropriate adjustment for potential confounding by relevant dietary and lifestyle factors, much of the evidence on individual nutrients does not report whether the primary studies had included adjustments for confounding factors. Without clear evidence that relevant confounders were taken into account, any conclusions from these meta-analyses need to be treated with caution.
- 2.33 Most identified studies did not investigate differences in risk between people of different socio-economic position, race or ethnic origin, religion, gender, sexual orientation or disability.
- 2.34 Cognition in midlife and old age is strongly correlated with childhood cognitive ability even when controlling for the influence of educational attainment and parental and an individual's own socioeconomic position. However, it is not clear whether the level of cognitive ability in childhood influences the rate of decline in later life, or simply the level from which such decline begins

(Richards & Deary, 2014). Lower premorbid cognitive ability is a risk factor for certain types of dementia³ (McGurn et al., 2008) and childhood intelligence is a predictor of educational and occupational success, social mobility, and health (Deary, 2012). It is not known whether higher intelligence leads to better health and cognitive performance through improved lifestyle choices and life opportunities or whether there is a fundamental biological link between intelligence and cognitive decline. These associations complicate the interpretation of observational studies designed to investigate the role of diet and nutrition in cognitive decline.

- 2.35 Observational studies, including cohort and case-control studies are potentially subject to reverse causality and confounding by other lifestyle factors. Individuals with early cognitive decline may change their diet, or change how they report their diet on a questionnaire, several years before their dementia is diagnosed, leading to a spurious association between reported diet and dementia risk. The impact of this reverse causation bias on the results of epidemiological studies can be reduced if analyses are restricted to cases of dementia diagnosed at least 10 years after the measurement of diet, but few studies have reported results with such long follow-up and therefore the results of many of the available studies may be influenced by this bias. Randomised controlled trials (RCTs) can provide evidence for causal relationships but can also be subject to limitations including sample size, duration and compliance.
- 2.36 The interpretation of studies may also be complicated by genetic effects. Genetic variation within the APOE gene (OMIM 107741) has been linked to both intelligence and cognitive decline and dementia (Davies et al., 2014), and even postulated links between diet and cognitive decline (Whalley et al., 2008).
- 2.37 Many large UK longitudinal studies hold information that allows the effects of a number of potential confounders to be assessed. In some cases it is possible to adjust for these confounders. Such longitudinal studies are also useful in providing insights into early life factors thought to influence the cognitive trajectory across the life-course. More information is provided in Annex 2.

³ McGurn et al. (2008) reported that higher mental ability score at age 11 was associated with significantly lower odds of vascular dementia. The odds ratio was 0.62 (95% CI 0.41, 0.94) for a 10 point increase in mental ability score (0.7 standard deviations). The average mental ability scores for cases/controls were 34/41.

3 Review methodology

Literature search

- 3.1 Pubmed and the Cochrane Library were searched from inception to August 2016 for systematic reviews and meta-analyses that included evidence on dietary patterns or selected nutrients in relation to cognitive function or the risk of dementia or AD in adults. The 2 databases were searched for publications with the relevant search terms in the title, abstract or keywords. Pubmed was also searched for the respective Medical Subject Headings (MeSH) terms.
- 3.2 Searches did not include restrictions on the age of participants or the type of dementias.
- 3.3 The following key words were used to search for the literature considered in chapter 4 'Dietary patterns, cognitive impairment and dementias': *dietary pattern, Mediterranean diet, healthy diet, mild cognitive impairment, cognitive decline, dementia, Alzheimer's disease*.
- 3.4 The following key words were used to search for the literature considered in chapter 5 'Nutrients, cognitive impairment and dementias' and chapter 6 'Other dietary components: polyphenols, flavonoids and caffeine': *B vitamins, vitamin B6, vitamin B12, folic acid, folate, thiamin, vitamin C, ascorbic acid, vitamin E, omega-3 fatty acids, tryptophan, phytochemicals, flavonoids, polyphenols, caffeine, mild cognitive impairment, cognitive decline, dementia, Alzheimer's disease*.
- 3.5 The full search strategy is described in Annex 3: Search strategy.
- 3.6 In addition to the search outlined in Annex 3 one additional study that met the inclusion criteria was identified by an interested party commenting on a draft version of this position statement. This study (Lamport et al., 2012) is considered in chapter 6 'Other dietary components: polyphenols, flavonoids and caffeine'.

Study selection and reporting of study findings

- 3.7 The review of the evidence is limited to findings relevant to the reduction in risk of developing MCI or dementias (including AD). This position statement does not consider the treatment of MCI or dementias.
- 3.8 This review generally states the results of individual studies as they were reported in the systematic reviews and meta-analyses. The review of the evidence is focused primarily on the findings from RCTs and prospective cohort studies (PCS). In line with the SACN Framework for the Evaluation of Evidence,

more weight was given to good quality RCTs and less weight to observational studies (SACN, 2012). Relevant evidence from cross-sectional studies or case-control studies was considered where these were included in meta-analysis. While most of the available evidence on dietary patterns is based on cohort studies, most evidence in relation to individual nutrients is based on RCTs.

- 3.9 The assessment tests used in studies are reported where this information was available in systematic reviews (also reported in the evidence tables in Annex 4 to Annex 6). Where studies reported both the incidence of MCI or dementias *and* cognitive function tests, less weight was placed on the latter. Cohort studies mostly considered associations with the incidence of MCI or dementias, while RCTs mostly reported effects on performance in cognitive function tests. Much of the considered evidence in chapter 5 on individual nutrients is based on RCTs, which reported on cognitive function and cognitive decline, rather than on MCI dementias. Effect sizes (Relative Risks (RR) or Odds Ratios (OR)) for cognitive function and decline are reported where available (and are also reported in the tables summarising the evidence in Annex 4 to Annex 6).
- 3.10 Where participants' cognitive health at baseline was reported this information is provided. Where findings relate to populations with cognitive impairments (i.e. MCI, AD and other dementias) effort has been made to state what impairments the findings relate to, though this was not always possible when different types of cognitive impairments were grouped together.
- 3.11 The number of study subjects (n) is stated where this was reported in the reviewed meta-analysis or systematic review.
- 3.12 Throughout this statement the term 'significant' is used to indicate statistical significance ($p < 0.05$).

4 Dietary patterns, cognitive impairment and dementias

- 4.1 This chapter summarises the findings of meta-analyses and systematic reviews that consider the role of dietary patterns in the prevention of MCI, AD and other dementias in adults with or without diagnosed MCI. The meta-analyses and systematic reviews are further summarised in Annex 4.
- 4.2 Most of the identified evidence on dietary patterns relates to Mediterranean dietary patterns. Less evidence was available on other ‘healthy’ dietary patterns.
- 4.3 The mean population age in studies included in the identified systematic reviews and meta-analyses ranged from 62 to 80 years.

Mediterranean dietary patterns and ‘healthy’ dietary patterns: review of the evidence

Note regarding the Mediterranean diet score (MeDi score)

- 4.4 The Mediterranean diet adherence score (MeDi) (Trichopoulou et al. (1995) and Trichopoulou et al. (2003)) was used by many studies to assess participants’ adherence to a Mediterranean dietary pattern.
- 4.5 While different variations of the MeDi score are in use, the most commonly assessed components in calculating the MeDi score are: higher intakes of vegetables, fruit, legumes, cereals and fish; higher ratio of mono- to saturated fatty acid intake; lower intake of dairy products and meat; and a regular but moderate alcohol intake. While there is no single Mediterranean diet, the dietary components that are characteristic of Mediterranean dietary patterns broadly align with current UK healthy eating recommendations as depicted in the Eatwell Guide (PHE, 2016). However, there are currently no studies which provide evidence specifically on UK healthy eating recommendations and cognition.
- 4.6 The MeDi score combines the assessments of 9 different dietary components. A value of 0 or 1 is given to each component based on whether it is below or above the age-specific median intake. The MeDi score is then calculated as the sum of the 0 or 1 values given to each of the 9 dietary components. Maximal adherence to a Mediterranean dietary pattern is scored as 9. As the population median intake is used to produce the MeDi scores, the score of individual study subjects is relative to a specific population (Cheung et al., 2014). Therefore, a subject assigned a high score in one study population may be assigned a lower score if the same subject is placed within another study population, or vice versa. This limitation is of particular relevance when comparing the results of studies whose populations differ widely in their dietary intakes.

- 4.7 This position statement includes 5 meta-analyses on Mediterranean dietary patterns, which are based on data from 7 primary studies. In all 7 studies the MeDi scores assessed intakes of the following 6 dietary components: higher intakes of legumes, fruit, vegetables and fish; a higher ratio of monounsaturated to saturated fatty acids; and a moderate alcohol intake. However, the MeDi score of the primary 7 studies differed in 3 other dietary components. Five studies assessed higher intake of cereal products while the other 2 studies assessed higher intake of whole-grain products. Four studies assessed lower meat intake while 3 studies assessed lower intakes of red and processed meat. Six studies assessed lower dairy intake while one study instead assessed higher nut intake in one study group and higher olive oil intake in a second group.
- 4.8 None of the reviews included in this statement investigated which individual components of a Mediterranean dietary pattern may contribute towards any of the observed associations with cognitive impairment and dementias.

Yusufov et al. (2016)

- 4.9 Yusufov et al. (2016) completed a systematic review of dietary factors and the development of AD. The review included cross-sectional studies and longitudinal studies whose primary outcome was AD incidence and which were published between 1 January 1995 and 31 December 2015.
- 4.10 Eleven studies were identified which considered Mediterranean dietary patterns. A beneficial and significant association was reported for 4 out of 5 PCS, 4 out of 5 cross-sectional studies, and one case-control study. Yusufov et al. (2016) stated that ‘studies predominantly converge on the notion that a MeDi diet is associated with decreased odds of AD development and mortality’.
- 4.11 Yusufov et al. (2016) identified one PCS which considered ‘healthy’ dietary patterns (other than the Mediterranean diet): the MIND⁴ diet, a hybrid diet between a Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet (Morris et al., 2015). Those in the highest tertile of adherence to the MIND dietary pattern had a lower risk of AD (hazard ratio (HR)= 0.47, 95% CI 0.26, 0.76) compared to those in the lowest tertile⁵.

⁴ The MIND diet was developed with the aim ‘to identify the nutrients, foods and dietary patterns related to brain health and dementia’ (Morris et al., 2015). For the MIND diet a maximum score of 1 was allocated for each of the following 15 component servings: whole grain $\geq 3/d$; green leafy $\geq 6/wk$; other vegetable $\geq 1/d$; berries $\geq 2/wk$; red meats and products $< 4/wk$; fish $\geq 1/wk$; poultry $\geq 2/wk$; beans $> 3/wk$; nuts $\geq 5/wk$; fast/fried food $< 1/wk$; olive oil primary oil; butter; margarine $< 1 T/d$; cheese $< 1/wk$; pastries; sweets $< 5/wk$; alcohol/wine 1/d.

⁵ All effect sizes reported for Morris et al. (2015) are adjusted for age, sex, education, APOE- $\epsilon 4$, participation in cognitively stimulating activities, physical activity, and total energy intake.

4.12 Morris et al. (2015) also reported a beneficial association when the same cohort was evaluated for a Mediterranean dietary pattern⁶ (HR=0.46, 95%CI 0.26, 0.79) and for the DASH diet⁷ (HR=0.61, 95%CI 0.38, 0.97) (highest vs lowest tertile). A beneficial association was also found when comparing the middle tertile with the lowest tertile for the MIND diet (HR 0.65, 95%CI 0.44, 0.98), but not so for the Mediterranean (HR 0.81, 95%CI 0.54, 1.24) or the DASH diet (HR 0.98, 95%CI 0.66, 1.46). Morris et al. (2015) concluded that 'high' adherence to all 3 dietary patterns may reduce AD risk and that moderate adherence (middle tertile) to the MIND dietary pattern may also be protective.

Cao et al. (2016)

4.13 The systematic review and meta-analysis by Cao et al. (2016) considered PCS of dietary patterns and incidence of cognitive impairment (MCI or dementia), with at least one year of follow-up. Five PCS of Mediterranean dietary patterns were identified. The studies varied in the covariates adjusted for, however, all 5 studies adjusted for age, sex, education and APOE genotype.

4.14 Closer adherence to a Mediterranean dietary pattern was associated with a reduced risk of developing cognitive impairment (RR 0.69, 95%CI 0.57, 0.84)⁸.

4.15 Of the 5 PCS identified by Cao et al. (2016), 4 were also included in the meta-analyses by Singh et al. (2014) and Psaltopoulou et al. (2013) and 3 in the meta-analysis by Sofi et al. (2010).

Cooper et al. (2015)

4.16 Cooper et al. (2015) conducted a systematic review and meta-analysis of longitudinal studies reporting on potentially modifiable risk factors for progression from mild cognitive impairment to incident all-cause dementia (including AD). Cooper et al. (2015) identified one eligible PCS in relation to dietary patterns (Scarmeas et al., 2009b). The study assessed adherence to a Mediterranean dietary pattern in a multi-ethnic community in New York. The study showed that adherence to a Mediterranean dietary pattern was associated with a lower risk of progression from amnesic MCI (MCI with

⁶ For the Mediterranean dietary pattern a maximum score of 5 was allocated for each of the following 11 component servings: non-refined grains >4/d; vegetables >4/d; potatoes >2/d; fruits >3/d; full-fat dairy <10/wk; red meat <=1/wk; fish >6/wk; poultry <=3/wk; legumes, nuts & beans >6/wk; olive oil >=1/d; alcohol <300 but >0 ml/d.

⁷ For the DASH diet a maximum score of 1 was allocated for each of the following 10 component servings: The component servings of the DASH diet are: total grains >=7/d; vegetables >=4/d; fruits >=4/d; dairy >=2/d; meat, poultry and fish <=2d; nuts, seeds & legumes >=4/wk; total fat <=27% of kcal; saturated fat <= 6% of kcal; sweets <=5/wk; sodium <=2400 mg/d.

⁸ The statistical comparison made appears to be between the lowest and highest tertiles of MeDi score, however this does not seem to be stated explicitly in Cao et al. (2016).

objective memory impairment) to AD. Cooper et al. (2015) did not report an effect size.

Deckers et al. (2015)

- 4.17 Deckers et al. (2015) undertook a systematic literature review of modifiable risk factors for dementia prevention. The systematic literature review included PCS studies with more than 200 participants, aged over 45 years, with more than one year of follow-up and published between October 2009 and December 2012.
- 4.18 In relation to 'healthy' dietary patterns (other than Mediterranean patterns), 3 PCS were identified. No effect sizes were reported for these studies. Two of the PCS associated a 'healthy' dietary pattern with a lower dementia risk (Gu et al., 2010b; Shatenstein et al., 2012), while the third PCS showed no significant association (Gelber et al., 2012). The healthy dietary pattern in Gu et al. (2010b) was 'characterised by higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and a lower intake of high-fat dairy products, red meat, organ meat, and butter'. The healthy dietary pattern in Shatenstein et al. (2012) was based on the Canadian Healthy Eating Index which assesses the number of portions eaten from each of the 4 food groups (vegetables and fruit, meat and alternatives, grain products, milk and alternatives), total fat, saturated fat, sodium, cholesterol and dietary diversity. The 'healthy' dietary pattern in Gelber et al. (2012) was defined by higher intakes of fruit, vegetables, fish and cereals, a high ratio of monounsaturated to saturated fat intake, lower intakes of meat and dairy, and low to moderate alcohol consumption. These dietary components were largely the same as those assessed by the MeDi score, but did not include legumes.
- 4.19 In relation to Mediterranean diets, 2 PCS were identified, of which one showed a protective association with dementia risk (Gu et al., 2010a) and the other found no association (Cherbuin & Anstey, 2012). Also identified were the systematic reviews and meta-analyses by Lourida et al. (2013) and Psaltopoulou et al. (2013), both of which are discussed below. Deckers et al. (2015) concluded that further studies were needed, especially RCTs, to clarify the relationship between diet and dementia prevention.

van de Rest et al. (2015)

- 4.20 A systematic review by van de Rest et al. (2015) concluded that closer adherence to a Mediterranean dietary pattern 'is associated with less cognitive decline, dementia, or Alzheimer disease, as shown by 4 out of 6 cross-sectional studies, 6 out of 12 PCS, one RCT, and 3 meta-analyses'. The 3 included meta-analyses also included some of the primary studies identified by van de Rest et al. (2015).

- 4.21 For cognitive performance, the authors reported that 6 out of 12 PCS observed a beneficial association after 3 to 7.6 years of follow-up. Of these studies, 5 were performed in the United States (US) and one in France. In the other 6 studies, of which 3 were performed in the United States and the others in France, Australia, and Greece, the association was not statistically significant after 2-3 years of follow-up (van de Rest et al., 2015). The PREDIMED-NAVARRA RCT (n=522, duration 6.5 years) investigated the effect of Mediterranean diets, rich either in olive oil or nuts in a population at high vascular risk⁹ (Martinez-Lapiscina et al., 2013a). Compared with control, significant effects in a beneficial direction were shown for both diets but observed effect sizes were small. The adjusted differences between intervention and control were 0.62 (95%CI 0.18, 1.05) for (olive oil) and 0.57 (95%CI 0.11, 1.03) (nuts) for the Mini-Mental State Examination (MMSE, 0 to 30 point scale). The adjusted differences for the clock drawing test (0 to 7 point scale) were 0.51 (95%CI 0.20, 0.82) (olive oil) and 0.33 (95%CI 0.003, 0.67) (nuts).
- 4.22 MCI was assessed in a subsample of the PREDIMED-NAVARRA RCT, (n=268; duration 6.5 years) (Martinez-Lapiscina et al., 2013b). The RCT was effectively a mixed method study design with the participants randomly chosen as a sub-cohort within the overall study cohort. The RCT showed a beneficial effect for a Mediterranean dietary pattern rich in olive oil (OR 0.34, 95%CI 0.12, 0.97) but not for a Mediterranean dietary pattern rich in nuts (OR 0.56, 95%CI 0.22, 1.43), when compared with the control. The study's primary outcomes were 16 cognitive function tests¹⁰. Of these, 4 tests¹¹ showed a significant beneficial effect in the olive oil group (12 tests were non-significant) and 1 test¹² showed a significant beneficial effect in the nut group (15 tests were non-significant), when compared with the control and after controlling for multiple comparisons. Both studies based on the PREDIMED-NAVARRA RCT (Martinez-Lapiscina et al., 2013a; Martinez-Lapiscina et al., 2013b) assessed cognitive outcomes only at the end of the follow-up period and it cannot be precluded that differences in cognitive outcomes observed at follow-up, may have already been present at baseline.
- 4.23 Of the 2 PCS which considered MCI and adherence to a Mediterranean dietary pattern, one showed a beneficial association (HR 0.85, 95%CI 0.72, 1.00; p=0.05) (Scarmeas et al., 2009b), while the second showed no significant

⁹ Study participants were men and women (55-80 years) classified as being at high vascular risk based on the presence of type-2 diabetes, or 3 or more of the following risk factors: current smoking, hypertension, dyslipidaemia, overweight or family history of premature CVD.

¹⁰ Mini-Mental State Examination; Clock Drawing Test; Rey Auditory Verbal Learning Test; Verbal Paired Associates; Rey-Osterrieth Complex Figure; Similarities; Trail Making Test A; Trail Making Test B; Digit (forward); Digit (backward); Semantic Verbal Fluency Test; Phonemic Verbal Fluency Test; Boston Naming Test.

¹¹ Digit (forward); Rey-Osterrieth Complex Figure (immediate); Rey-Osterrieth Complex Figure (delay); Phonemic Verbal Fluency Test.

¹² Digit (forward)

association (OR 1.41, 95%CI 0.95, 2.10) (Cherbuin & Anstey, 2012). A PCS which considered the combined incidence of MCI and dementia did not show a significant association (HR 0.75, 95% CI 0.46, 1.21) (Roberts et al., 2010).

- 4.24 Three of five PCS showed a beneficial association for Mediterranean diet adherence and AD (HR 0.87, 95%CI 0.78, 0.97) (HR 0.91, 95%CI 0.83, 0.98) (HR=0.60, 95%CI 0.42, 0.97) (Gu et al., 2010a; Scarmeas et al., 2009a; Scarmeas et al., 2006b). One PCS of participants diagnosed with MCI at baseline showed a beneficial association for Mediterranean diet adherence and slower progression from MCI to AD (HR 0.71, 95%CI 0.53, 0.95) (Scarmeas et al., 2009b). One PCS found no association between Mediterranean diet adherence and AD risk (HR 1.00, 95%CI 0.85, 1.19) (Feart et al., 2009).
- 4.25 For studies investigating 'healthy' dietary patterns (other than Mediterranean patterns) in relation to cognitive decline and/or dementia risk, van de Rest et al. (2015) concluded that these demonstrated a beneficial association, as shown by 6 cross-sectional studies and 6 of 8 PCS. Only one RCT was identified which investigated 'healthy' dietary patterns. In comparison with the control group subjects consuming a DASH diet for 4 months showed better performance on 1 of 9 cognitive function tests (psychomotor speed, $p=0.036$).
- 4.26 Of the PCS investigating 'healthy' dietary patterns (other than Mediterranean patterns), only 2 PCS reported results in relation to the risk of dementias or AD. A PCS located in Japan with 15 years of follow-up used reduced rank regression to identify 7 dietary patterns (Ozawa et al., 2013). The 'Japanese' dietary pattern was 'correlated with higher intakes of soybeans and soybean products, vegetables, algae, and milk and dairy products and a lower intake of rice' and showed a significant beneficial association with all-cause dementia and vascular dementia (respectively: HR 0.66, 95%CI 0.46, 0.95; HR 0.45, 95%CI 0.22, 0.91 respectively) but no significant association with AD (HR 0.65, 95%CI 0.40, 1.06). A PCS located in the US (follow-up 3.9 years) investigated a 'healthy' dietary pattern and found a beneficial association with AD (HR=0.62, 95%CI 0.43, 0.89 for highest vs lowest tertile) (Gu et al., 2010b). The 'healthy' dietary pattern was characterised by higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and a lower intake of high-fat dairy products, red meat, organ meat, and butter'. The same study was also included in the review by (Deckers et al., 2015).

Xu et al. (2015)

- 4.27 Xu et al. (2015) performed a systematic review and meta-analysis of PCS on 'healthy diets', which included studies on Mediterranean dietary patterns. Five PCS were identified ($n=385$ to 2258 , follow-up 4 to 14 years). The meta-analysis (total $n=9,774$; $I^2=60\%$) showed a beneficial and significant association of 'healthy diets' and reduced AD incidence (RR 0.46, 95%CI 0.23, 0.68). The authors noted the high heterogeneity in the meta-analysis ($I^2=60\%$).

- 4.28 A further meta-analysis (n=3,668; follow-up 4 and 4.1 years) was performed that included only the 2 PCS that were based on Mediterranean diet scores. The meta-analysis showed a beneficial and significant association with AD incidence (RR 0.62, 95%CI 0.41, 0.84; $I^2=0\%$). Both studies (Feart et al., 2009; Scarmeas et al., 2006a) were also included in other reviews considered in this position statement.

Di Marco et al. (2014)

- 4.29 Di Marco et al. (2014) carried out a systematic review of a broad range of lifestyle factors that may affect dementia. Three PCS were identified that considered Mediterranean dietary patterns and incident dementia and/or AD. For dementia, one PCS showed a beneficial association (HR=0.60, 95%CI 0.42, 0.87 for highest versus lowest tertile), while a second PCS did not show an association (HR 1.12, 95%CI 0.60, 2.10). For AD, one PCS showed a borderline significant association in a beneficial direction when comparing lowest versus highest tertile (HR=0.66, 95%CI 0.41, 1.04) with a significant p-value for trend ($p=0.04$). One PCS did not show an association between Mediterranean diet adherence and risk of AD (HR 0.86, 95%CI 0.39, 1.88).
- 4.30 Di Marco and colleagues conclude that 'conflicting results are reported on the putative role of healthy dietary habits (MeDi, dietary antioxidants, omega-3 fatty acids, regular fish consumption)'.

Singh et al. (2014)

- 4.31 A systematic review and meta-analysis by Singh et al. (2014) considered the association between a Mediterranean dietary pattern and MCI and AD. The study identified 5 eligible PCS with at least one year of follow-up. All 5 studies were adjusted for age, sex, education and APOE genotype.
- 4.32 Two PCS considered the incidence of participants who were cognitively normal at baseline developing MCI. A meta-analysis of the 2 studies showed that, compared with the lowest MeDi tertile, the risk of developing MCI score was significantly reduced in the highest MeDi tertile (HR 0.73, 95%CI 0.56, 0.96; $p=0.02$), but not the middle tertile (HR 0.82, 95%CI 0.64 1.05; $p=0.11$). As a continuous variable MeDi was not associated with MCI ($p=0.45$).
- 4.33 Two PCS which considered the development of AD in participants who were cognitively normal at baseline were included in a meta-analysis. Compared with the lowest MeDi tertile the risk of developing AD was significantly reduced in the highest MeDi tertile (HR 0.64, 95%CI 0.46, 0.89; $p=0.007$), but not the middle tertile (HR 0.87, 95%CI 0.66, 1.14; $p=0.31$). As a continuous variable MeDi was associated with AD (HR 0.92, 95%CI 0.85, 0.99; $p=0.03$).
- 4.34 One PCS considered the incidence of participants converting from MCI to AD. Compared with the lowest MeDi tertile the risk of MCI converting to AD was significantly reduced in the highest MeDi tertile (HR 0.52, 95%CI 0.30, 0.91;

p=0.02), and in the middle tertile (HR 0.55, 95%CI 0.34, 0.90; p=0.02). As a continuous variable MeDi was not significantly associated with AD (HR 0.89, 95%CI 0.78, 1.02; p=0.09).

- 4.35 A meta-analysis of all 5 PCS considered incident cognitive impairment by combining the 3 earlier outcomes, i.e. cognitively normal to MCI; cognitively normal to AD; and MCI to AD. Compared with the lowest MeDi tertile the risk of cognitive impairment was significantly reduced in the highest MeDi tertile (HR 0.67, 95%CI 0.55, 0.81; p<0.0001) and in the middle tertile (HR 0.80, 95%CI 0.67, 0.95; p=0.01). As a continuous variable MeDi was also associated with reduced risk of cognitive impairment (HR 0.92, 95%CI 0.88, 0.97; p=0.001). Singh et al. (2014) undertook a sensitivity analysis as 2 studies considered different outcomes (MCI or AD) in the same cohort. To avoid possible overrepresentation of this cohort, the smaller of the 2 studies was excluded from the sensitivity analysis. The pooled results of the remaining 4 PCS showed a significantly reduced risk for the highest tertile (HR 0.67, 95%CI 0.51, 0.88; p=0.004), but not so for the middle tertile (HR 0.85, 95%CI 0.67, 1.07; p=0.17) or MeDi as a continuous variable (HR 0.94, 95%CI 0.87, 1.02; p=0.12).
- 4.36 Singh et al. (2014) concluded that adherence to a Mediterranean dietary pattern is associated with a reduced risk of developing MCI or AD and with a reduced risk of conversion from MCI to AD.

Lourida et al. (2013)

- 4.37 A systematic review by Lourida et al. (2013) considered the association between a Mediterranean dietary pattern and cognitive function, MCI and dementia (including AD). While Lourida et al. (2013) also considered evidence in relation to cognitive function tests and evidence from cross-sectional studies, this was not included in the following consideration of evidence.
- 4.38 The evidence in relation to MCI and all-cause dementia was inconsistent and mostly non-significant. The evidence in relation to AD showed a consistent risk reduction.
- 4.39 For MCI, Lourida et al. (2013) identified 4 eligible PCS, 2 of which were also considered by Singh et al. (2014). Only 1 of the 4 cohorts showed a significant association (beneficial) and overall the evidence was inconsistent.
- 4.40 For all-cause dementia, the review identified 2 PCS, the results of which were inconsistent and non-significant.
- 4.41 Lourida et al. (2013) identified 4 eligible PCS which assessed AD risk, 3 of which were from the same cohort (Columbia Ageing Cohort) and were also considered in Singh et al. (2014). Comparing the lowest and highest MeDi tertiles of the 4 PCS, 3 showed a beneficial association (HR=0.60, 95%CI 0.42, 0.87; HR=0.60, 95%CI 0.42, 0.87; HR=0.52, 95%CI 0.30, 0.91) and the fourth

study showed a non-significant association in a beneficial direction (HR=0.66, 95%CI 0.41, 1.04). Of the 3 PCS that reported AD risk per unit increase in MeDi score, 2 studies reported a beneficial association and the third a non-significant association in a beneficial direction (HR 0.89, 95%CI 0.78, 1.02).

Psaltopoulou et al. (2013)

- 4.42 The meta-analyses by Psaltopoulou et al. (2013) assigned study participants into one of 3 groups for adherence to a Mediterranean dietary pattern: 'low' (MeDi score 0 to 3), 'moderate' (MeDi score 4 or 5) or 'high' (MeDi score 6 to 9).
- 4.43 A meta-analysis of 4 PCS showed that 'high' adherence to a Mediterranean dietary pattern was associated with a lower risk of cognitive impairment (MCI, AD or other dementia), compared to 'low' adherence (RR 0.72, 95%CI 0.58, 0.88). For 'moderate' adherence there was no association, compared to 'low' adherence (RR 0.90, 95%CI 0.75, 1.08). All 4 PCS (plus one additional study) were also included in the meta-analyses by Singh et al. (2014) (see above).
- 4.44 A further meta-analysis by Psaltopoulou et al. (2013) pooled the data from the 4 PCS with an additional 4 cross-sectional studies and one case-control study. 'High' and 'moderate' adherence to a Mediterranean dietary pattern was inversely associated with cognitive impairment (MCI, AD or other dementia), compared to 'low' adherence (RR 0.60, 95%CI 0.43, 0.83, $I^2=76%$ and RR 0.79, CI 96% 0.67, 0.94, $I^2=28%$ respectively). While the pooled analysis for the 'high' adherence group showed significant heterogeneity this was not the case for the 'moderate' adherence group.
- 4.45 A further subgroup analysis separately considered studies from Mediterranean and non-Mediterranean countries. The analysis for non-Mediterranean countries pooled the data from 3 PCS, 2 cross-sectional studies and one case-control study. 'High' and 'moderate' adherence to a Mediterranean dietary pattern was inversely associated with cognitive impairment (MCI, AD or other dementia), compared to 'low' adherence (RR 0.49, 95%CI 0.34, 0.70, $I^2=71%$ for 'high' adherence and RR 0.74, 95%CI 0.60, 0.91, $I^2=40%$ for 'moderate' adherence). The pooled analysis for the 'high' adherence group, but not 'moderate' adherence group, showed significant heterogeneity. The analysis for Mediterranean countries pooled the data from one PCS and 2 cross-sectional studies. 'High' and 'moderate' adherence to a Mediterranean pattern was not significantly associated with cognitive impairment, compared to 'low' adherence (RR 1.01, 95%CI 0.80, 1.28 and RR 1.02, 95%CI 0.73, 1.43 respectively).

Sofi et al. (2010)

- 4.46 Sofi et al. (2010) performed a systematic review and meta-analysis of PCS on Mediterranean dietary patterns and neurodegenerative disease (this included Parkinson's disease as well as AD, dementia & MCI). Four eligible PCS were

included in the meta-analysis. Of these studies, 3 were included in the latter meta-analysis of Singh et al. (2014) and 2 in the meta-analysis by Psaltopoulou et al. (2013) (see above). The 4th study related to Parkinson's disease. The MeDI score was inversely associated with the risk of neurodegenerative diseases (RR 0.87, 95%CI 0.81, 0.94 ($p < 0.00001$) per 2 point increase in MeDI score).

Summary – Dietary patterns

Mediterranean dietary patterns

- 4.47 In the considered evidence, Mediterranean dietary patterns were defined as: higher intakes of vegetables, fruit, legumes, cereals (or whole grain products) and fish; a higher ratio of mono- to saturated fatty acid intake; a lower intake of dairy products and meat (or red and processed meat); and a moderate alcohol intake. One study assessed higher intakes of either olive oil or nuts in place of lower dairy intake. While there is no single Mediterranean diet, the dietary components that are characteristic of Mediterranean dietary patterns broadly align with current UK healthy eating recommendations as depicted by the Eatwell Guide (PHE, 2016). However, there are currently no studies which provide evidence specifically on UK healthy eating recommendations and cognition.
- 4.48 The only identified RCT (Martinez-Lapiscina et al., 2013b) showed a significantly reduced risk of developing MCI for a Mediterranean dietary pattern rich in olive oil (OR 0.34, 95%CI 0.12, 0.97) but no significant effect for a Mediterranean dietary pattern rich in nuts (OR 0.56, 95%CI 0.22, 1.43) after 6.5 years of intervention. Of a total of 16 cognitive function tests, 4 tests showed a significant beneficial effect in the olive oil group (12 tests were non-significant) and 1 test showed a significant beneficial effect in the nut group (15 tests were non-significant), when compared with the control.
- 4.49 The reviews considered in this position statement identified 19 PCS on Mediterranean dietary patterns and cognitive impairment outcomes (MCI, AD and other dementias). The majority of these cohort studies provide evidence consistent with a beneficial association. While most cohort studies appear to have adjusted for known confounders (e.g. educational attainment, socio-economic status, smoking), the observed associations may be the result of residual confounding or reverse causality.
- 4.50 A meta-analysis (Singh et al., 2014) compared the highest and lowest tertiles for adherence to a Mediterranean dietary pattern. Subjects with the greatest adherence had a 27% reduced risk of developing MCI (2 PCS: HR 0.73, $p = 0.02$), a 36% reduced risk of developing AD (2 PCS: HR 0.64, $p = 0.007$) and a 33% reduced risk of developing either MCI or AD (4 PCS: HR 0.67, $p = 0.004$). A similar effect size was obtained by Cao et al. (2016), in a meta-analysis that

included 5 PCS (3 of which were also included in Singh et al. (2014)) and which showed a beneficial association between a Mediterranean dietary pattern and the risk of developing cognitive impairment (MCI or dementia) (RR 0.69, 95% CI 0.57, 0.84).

- 4.51 A meta-analysis by Psaltopoulou et al. (2013) pooled data from 4 PCS, 4 cross-sectional studies and one case-control study and found that high adherence to a Mediterranean dietary pattern (but not moderate adherence) was associated with less cognitive impairment (MCI, AD and other dementias). Sofi et al. (2010) performed a meta-analysis of 4 PCS which found that a two-point increase in the MeDi score was associated with lower risk of developing neurodegenerative diseases.

'Healthy' dietary patterns (other than Mediterranean pattern)

- 4.52 The evidence base is limited in relation to 'healthy' dietary patterns (other than Mediterranean patterns) and cognitive impairment outcomes (MCI, AD and other dementias). The considered reviews identified 5 PCS, none of which assessed the same dietary pattern. Four of the studies showed a significant beneficial association for the assessed 'healthy' dietary pattern with dementia risk, while one study showed no association. No meta-analyses were identified for cohort studies of 'healthy' dietary patterns.
- 4.53 The systematic review by van de Rest et al. (2015) identified 2 PCS that considered 'healthy' dietary patterns (other than Mediterranean patterns). A Japanese PCS (Ozawa et al., 2013) showed a significant beneficial association of a 'Japanese' dietary pattern with all-cause dementia and vascular dementia (HR 0.66, 95% CI 0.46, 0.95; HR 0.45, 95% CI 0.22, 0.91 respectively) and a non-significant beneficial association with AD (HR 0.65, 95% CI 0.40, 1.06). A US PCS (Gu et al., 2010b) showed a beneficial association of a 'healthy' dietary pattern with AD (HR=0.62, 95% CI 0.43, 0.89 for upper versus lower tertile).
- 4.54 A third PCS (Morris et al., 2015) was identified in the systematic review by Yusuf et al. (2016). The study showed a significant association of the MIND diet and the DASH diet with AD incidence (HR=0.47, 95% CI 0.26, 0.76; HR=0.61, 95% CI 0.38, 0.97 respectively, for upper versus lower tertile).
- 4.55 Two further PCS that considered 'healthy' dietary patterns (other than a 'Mediterranean' pattern), were identified in the systematic review by Deckers et al. (2015). One study showed that a 'healthy' dietary pattern was associated with lower risk of dementia (Gu et al., 2010b; Shatenstein et al., 2012), while the other study showed no significant association (Gelber et al., 2012) (no effect sizes were reported).
- 4.56 No trials were identified that considered 'healthy' dietary patterns (other than Mediterranean diet) and cognitive impairment outcomes (MCI, AD or other dementias).

Overall summary – Dietary patterns

- 4.57 The evidence obtained from meta-analyses of PCS indicates that greater adherence to a Mediterranean dietary pattern is associated with the lower risk of mild cognitive impairment and dementias, including AD. The only identified RCT with a Mediterranean diet intervention found a significantly lower MCI risk for a Mediterranean dietary pattern rich in olive oil but no significant effect for a Mediterranean dietary pattern rich in nuts. Within the considered reviews, no other studies provided evidence in relation to nut or olive oil consumption.
- 4.58 In relation to ‘healthy’ dietary patterns (other than Mediterranean patterns) and cognitive impairment outcomes the evidence is insufficient to draw any conclusions, as only 5 relevant cohorts were identified which differed considerably in the dietary patterns considered. No relevant meta-analyses were identified.
- 4.59 Besides the RCT considering Mediterranean dietary patterns with either nuts or olive oil, the reviewed evidence on dietary patterns does not allow consideration of specific dietary components that might be responsible for any observed associations with cognitive outcomes.

5 Nutrients, cognitive impairment and dementias

- 5.1 This chapter summarises the findings of 22 systematic reviews and meta-analyses identified in the literature search that consider the role of individual nutrients (B vitamins including folate/folic acid, vitamins C and E and omega-3 fatty acids) in cognitive function, cognitive decline and the risk of MCI, AD and dementia.
- 5.2 The identified publications consider cognitively healthy adults and older adults as well as those with MCI or diagnosed AD or other forms of dementia. The majority of studies included in the identified systematic reviews and meta-analyses enrolled participants over 45 years of age; however one review combined data on children with data on adults (Jiao et al., 2014). The systematic reviews and meta-analyses described below are further summarised in Annex 5.

B vitamins

- 5.3 Twelve systematic reviews were identified that consider B vitamins and cognitive function, cognitive decline and the risk of MCI, AD and other dementias. Of these, 4 reported on B vitamins in combination, one reported on vitamin B6, 2 reported on vitamin B12, 4 reported on folate/folic acid and one looked at thiamin. It should be noted that the systematic reviews considering vitamin B6 and thiamin were both published over 10 years ago, in 2003 and 2001 respectively. A search of the primary evidence was not performed for this position statement and it is possible that primary evidence considering vitamin B6 or thiamin and cognition or dementia risk has been published subsequent to these reviews.

B vitamins in combination

- 5.4 Forbes et al. (2015) conducted a systematic review and meta-analysis of RCTs investigating combinations of B vitamins and cognitive function. Seven RCTs were identified, employing various combinations and doses of folate (0.4 to 5 mg/d) and/or vitamins B6 (10 to 50mg/d) and/or B12 (0.1 to 1 mg/d). Intervention periods ranged from 12 weeks to 6.6 years and population sizes from 152 to 2009 subjects. Trial participants were adults aged 60 years and above who were healthy or had cardiovascular diseases at baseline. Various different cognitive outcomes were assessed in the included RCTs.
- 5.5 Forbes et al. (2015) report the results of the 7 identified RCTs to be inconsistent. While some RCTs reported benefits in at least one of the cognitive domains assessed when the intervention group was compared with the control group (4 RCTs), others did not (3RCTs).

- 5.6 A meta-analysis including 3 RCTs (n=789), which reported MMSE scores as a study outcome, was performed. Interventions consisted of combinations of folate/folic acid (0.8 to 2 mg/d), vitamin B6 (10 to 25 mg/d) and B12 (0.4 to 0.5 mg/d). There was no significant difference between the MMSE scores in the intervention group compared with the control group (mean difference [MD]=0.02, 95% CI -0.22, 0.25) (Forbes et al., 2015).
- 5.7 The systematic review by Cao et al. (2016) considered a range of dietary factors, including B vitamin intake, and dementia risk in adults aged 65 years and above. The authors of the meta-analysis, which included 4 PCS with between 1.5 and 9.3 years follow-up, reported a significant association between a greater intake of B vitamins and a reduced risk of dementia (RR 0.72, 95% CI 0.54, 0.96; $p=0.026$; $I^2=41.6\%$, $p=0.072$). This review has many limitations including the low number of identified cohort studies, high heterogeneity, no information on sample sizes and no consideration of confounding factors and no assessment of study quality.
- 5.8 The efficacy of B vitamin supplementation (folic acid alone and B vitamins in combination) on cognition in people with MCI and AD is considered in a systematic review by Li et al. (2014). Five RCTs, with samples sizes of 41 to 409 participants, and intervention periods ranging from 26 weeks to 24 months, were included in meta-analysis. Two of the RCTs included in the meta-analysis were also considered by Forbes et al. (2015).
- 5.9 In patients with MCI, meta-analysis showed no significant difference between B vitamins and placebo groups in memory (mean difference [MD]=0.60; 95% CI 0.20, 1.00; $p=0.03$; 2 RCTs; 361 participants), general cognitive function (weighted mean difference [WMD]=-0.10; 95% CI -0.80, 0.59; $p=0.77$; 2 RCTs; 361 participants), executive function (standardised mean difference (SMD)=0.05; 95% CI -0.11, 0.21; $p=0.54$; 2 RCTs; 361 participants) and attention (WMD=-0.03; 95% CI -1.20, 1.14; $p=0.96$; 1 RCT; 138).
- 5.10 In patients with AD, no significant cognitive benefits were observed for B vitamins supplementation compared with placebo, measured using the Alzheimer's Disease Assessment Scale (ADAS-cog) or MMSE (WMD=1.01; 95% CI -0.68, 2.70; $p=0.24$; 2 RCTs; 498 participants and WMD=-0.22; 95% CI -1.00, 0.57; $p=0.59$; 3 RCT; 539 participants respectively). The authors concluded that from the evidence considered, supplementation with B vitamins has no beneficial effect on cognition in people with MCI or AD.
- 5.11 Clarke et al. (2014) conducted a meta-analysis which considered the effect of B vitamins supplements on cognitive ageing in cognitively healthy adults (mean age: 60 to 82 years). Eleven RCTs were identified which compared the effects of folic acid (dose: 0.4 to 2.5mg/d) and/or vitamin B12 (dose: 0.02 to 1.00mg/d) with a placebo or 5-methyltetrahydrofolate. Three of the 11 RCTs were also included in the review by Forbes et al. (2015).

- 5.12 Four RCTs assessed the effects of B vitamin supplements on specific cognitive domains (memory, speed, executive function and their sum i.e. domain-composite score) measured using a range of tests. Mean treatment duration ranged from 3.5 months to 3 years and the 4 RCTs reported on a total of 1423 participants. The other 7 RCTs assessed effects of B vitamins supplementation on cognitive function measured using the MMSE, TICS, or TICS-M. These 7 RCTs reported on a total of 20431 participants with mean treatment durations ranging from 1 to 7 years (overall mean 5 years).
- 5.13 Allocation to B vitamins had no significant effect on changes in domain-specific scores for memory, speed, executive function or domain-composite score. B vitamins compared with placebo also had no significant effect on MMSE, TICS or TICS-M scores. The effect remained non-significant when analysed by age at randomisation, sex, smoking status, history of stroke, folic acid fortification, treatment duration, presence of cognitive impairment at baseline (in this meta-analysis individuals were defined as having cognitive impairment at baseline if they had a MMSE score <24 or a TICS score <31 or a TICS-M score <22), pre-treatment concentrations of folate, vitamin B12 and homocysteine. The authors of this meta-analysis concluded that B vitamins supplements had no significant effect on cognition in cognitively healthy adults after 5 years.

Summary – B vitamins in combination

- 5.14 Only one meta-analysis was identified that considered the association between the risk of incident dementia and the intake of B vitamins (Cao et al., 2016). The authors of the meta-analysis, which included 4 PCS, reported that a greater intake of B vitamins was associated with a reduced risk of dementia. However, given the study limitations it is not possible to draw a conclusion based on this evidence.
- 5.15 The 2 meta-analyses of RCTs, which reported on cognitive function, indicate no effect of B vitamins supplements on cognition when measured using domain specific (i.e. memory, speed, executive function) and global cognitive function (i.e. MMSE, TICS, TICS-M) tests (Clarke et al., 2014; Forbes et al., 2015).
- 5.16 One of the identified meta-analyses of RCTs reported on people with MCI and AD (Li et al., 2014). In this population, supplementation with B vitamins was reported to have no effect on cognition. However, due to the limited number of RCTs and participants included in the meta-analyses there is insufficient evidence to draw a conclusion.

Vitamin B6

- 5.17 The effect of vitamin B6 supplementation on cognition in cognitively healthy people is considered in a Cochrane Collaboration review (Malouf & Grimley Evans, 2003). Of the 2 RCTs identified, one enrolled 211 healthy women into a

five-week study. Twelve women, aged 65 to 92 years, received 75 mg vitamin B6 orally per day and were compared with 21 women who were allocated to receive a placebo. The remaining women were allocated to receive either folic acid or vitamin B12; the results for these arms were not reported in the review. No statistically significant benefits of vitamin B6 supplementation (75 mg/d for 5 weeks) were observed for cognition measured using a range of different tests (see Table 6).

- 5.18 The other RCT recruited 76 healthy men, aged 70 to 79 years, who were divided into 38 matched pairs. One member of each pair was randomly allocated to receive 20 mg of vitamin B6 per day for 12 weeks, the other to a placebo. No statistically significant differences in cognition, measured using the Associated Recognition Task (WMD=-1.02, 95%CI -2.40, 0.36) and Forget Scores (WMD=0.79, 95%CI -0.34, 1.92), were observed between treatment and placebo groups. The authors concluded that short-term vitamin B6 supplementation has no beneficial effects on mood or cognition in cognitively healthy adults.

Summary – Vitamin B6

- 5.19 Neither of the RCTs included in the only review to report on supplementation of vitamin B6 alone found any effect of this nutrient on cognition (Malouf & Grimley Evans, 2003). However, given that only 2 RCTs were included in the review, both of which had short durations and a limited number of participants; it is not possible to draw any conclusions on the effect of vitamin B6 on cognition.

Vitamin B12

- 5.20 Doets et al. (2013) considered the relationship between dietary intakes of vitamin B12, vitamin B12 supplementation, cognitive function and risk of AD and dementia.
- 5.21 Eight primary studies were identified, 2 RCTs and 6 PCS. Three of the PCS were also considered by Cao et al. (2016) and one of the RCTs was considered by Clarke et al. (2014).
- 5.22 Three of the PCS, involving 5254 older adults with mean ages of 70 to 75 years, were included in a meta-analysis. The relative risk for incidence of AD, during 3.9 to 9.3 years of follow-up, per 1 µg increase in vitamin B12 intake at baseline was calculated; no association was found (RR 0.99, 95%CI 0.99, 1.00; $I^2=0\%$; $p=0.92$). The one PCS to consider dementia risk found no association with vitamin B12 intake after a 9 year follow-up (HR 0.87; 95% CI 0.52, 1.44; 3634 participants, 352 cases).

- 5.23 One RCT and 2 PCS considered the relationship between cognitive domains (executive function, memory, speed and/or language) and vitamin B12 intake or supplementation. The 2 PCS, involving 443 older adults with mean ages of 67 and 72 years, found that higher baseline dietary vitamin B12 intakes were associated with better executive function after 3 and 6 years. However, the RCT involving 110 older adults with a mean age of 82 years did not find an effect of vitamin B12 supplementation (1 mg/d for 24 weeks) on executive function. The findings for memory were inconsistent and the single study that presented findings on speed and language reported no significant effect or association respectively. RCTs and PCS reported no significant effect/association between vitamin B12 intake and global cognition assessed by MMSE (1 RCT, 1 PCS) or compound z score (1 PCS).
- 5.24 The effect of vitamin B12 supplements on cognitive function in people with low vitamin B12 status and dementia is examined in a Cochrane Collaboration review (Malouf & Areosa Sastre, 2003). Three RCTs which included 182 participants in total, with a mean age range of 74 to 81 years, met the inclusion criteria. One of the identified RCTs was also included in the review by Doets et al. (2013). All the RCTs compared vitamin B12 supplements with a placebo. In one trial participants received a 1 mg vitamin B12 injection every day for 5 days then one injection per month for 5 months. In the second they received a 1 mg cyanocobalamin supplement per week for 4 weeks. The third RCT comprised of 3 arms; the 2 intervention groups received an oral cyanocobalamin supplement for a month at doses of 0.01 mg and 0.05 mg per day.
- 5.25 Compared with placebo, vitamin B12 supplementation at any dose, administered orally or by injection, had no benefit on cognitive function in people with low serum vitamin B12 levels and dementia (see Table 7). Malouf & Areosa Sastre (2003) concluded that there was no evidence that vitamin B12 supplementation has a beneficial effect on cognitive function in adults with low vitamin B12 levels and dementia.

Summary – Vitamin B12

- 5.26 The considered evidence indicated no association between intake of vitamin B12 (through diet or supplements) and risk of AD or dementia in older adults (Doets et al., 2013). However, the limited number of PCS are insufficient to base a conclusion on the relationship between vitamin B12 and AD or dementia risk.
- 5.27 Doets et al. (2013) also reported inconsistent results from 2 PCS and one RCT on B12 and cognitive function. It is therefore not possible to draw a conclusion on the relationship between vitamin B12 and cognitive function based on the evidence considered.
- 5.28 Only one review was identified that reported on cognitive function and vitamin B12 supplementation in people with dementia. The 3 RCTs included in the review provided insufficient evidence to draw a conclusion on the effect of

vitamin B12 supplementation on cognition in this population (Malouf & Areosa Sastre, 2003).

Folate/Folic acid

- 5.29 The term folate describes a family of B-group vitamins. There are large numbers of naturally occurring folates that are found in a wide variety of foods. Folic acid is a synthetic form of folate. It is widely used for food fortification and in supplements because it is more stable in foods than natural folates and is better absorbed.
- 5.30 SACN considered evidence on the benefits and risks of folate/folic acid in 2006, 2009 and 2017 (SACN, 2006; SACN, 2009; SACN, 2017). In 2006, SACN concluded that there were 'indications of possible benefit, but overall, the evidence for either beneficial or deleterious effects of folic acid ... on cognitive function in older people' was 'inconclusive'. In 2017, SACN's *Update on folic acid* (SACN, 2017) concluded that intervention studies showed no significant effect on cognitive decline in older individuals. Similarly, observational studies showed no significant relationship with higher folate status.
- 5.31 Xu et al. (2015) performed a systematic review and meta-analysis of PCS on folate intake and AD incidence. Four PCS were identified (n=6219 participants, follow-up 3.9 to 9.3 years). The meta-analysis showed a significant association between high folate intake and reduced AD incidence (RR 0.51, 95%CI 0.29, 0.73; $I^2 < 50%$).
- 5.32 Dangour et al. (2010) considered the relationship between dietary intake (including supplementation) of folate/folic acid with other B vitamins, fatty acids and change in cognitive performance or incident AD or dementia in a systematic review, which did not include a meta-analysis. Only findings relating to intakes of folate/folic acid with other B vitamins are reported here. Findings relating to intakes of fatty acids are reported later in this position statement.
- 5.33 Ten RCTs and 3 PCS that reported on folate/folic acid intake were included in the systematic review (Dangour et al., 2010). The 3 PCS were also considered by Xu et al. (2015). Five of the RCTs were included in the review by Clarke et al. (2014) (discussed earlier). Doets et al. (2013) (discussed earlier) considered one of the RCTs and 2 of the cohort studies.
- 5.34 The 3 PCS considered dietary intakes of folate, vitamin B6 and vitamin B12, assessed using a 7-day food record or food frequency questionnaire (FFQ), and their relationship with risk of AD. The follow-ups across the studies ranged from 3.9 years (mean) to 9.3 years (median) with sample sizes ranging from 579 to 1041 participants. Two of the 3 PCS reported a significantly decreased risk of incident AD with higher folate intake. One PCS also observed a significant association between higher intake of vitamin B6 and decreased risk

of AD, but no significant association was found between vitamin B12 intake and incident AD in any of the studies. Although all participants were free of AD or dementia at baseline, some studies did include people with poor cognitive performance and cognitive impairment.

- 5.35 Of the 10 RCTs identified, 4 considered the effect of folic acid supplementation alone (dose: 0.75 mg to 20 mg/d for 35 days to 3 years) and 6 investigated the effect of supplementation with folic acid in combination with other B vitamins on cognitive function (dose: 0.4 mg to 2.5 mg/d folic acid for 45 days to 2 years). The participants, aged 20 to 92 years, included a mixture of cognitively healthy people, people with mild to moderate cognitive impairment and diagnosed dementia.
- 5.36 Of the four RCTs which supplemented with folic acid alone, sample sizes ranged from 7 to 818 participants. Two RCTs included community dwelling participants with no reported cases of AD or other forms of dementia, one included participants with mild to moderate cognitive impairment (MMSE scores 16-24) and the other involved participants with diagnosed dementia. The 3 RCTs, which considered subjects without diagnosed AD or other forms of dementia, reported statistically significant improvements in some of the memory and cognitive function tests studied with folic acid supplementation. Two of the RCTs also reported statistically significant declines in some cognitive function tests, although in one, declines were observed in both the control and intervention groups, with less of a decline in the folic acid group. No significant difference was found in the change in test scores between the folic acid and placebo groups in subjects with diagnosed dementia.
- 5.37 Sample sizes ranged from 69 to 253 participants in the 6 RCTs that supplemented with folic acid in combination with other B vitamins. None of the RCTs reported improvements in cognitive performance with folic acid and other B vitamins supplements. Three reported a trend for improved cognitive performance or slower decline in the placebo compared with the folic acid and other B vitamins group. The authors of the systematic review concluded that there is insufficient evidence to draw conclusions on the association between intakes of folate/folic acid with or without other B vitamins and cognitive performance or incident AD or dementia in healthy older people or people with mild to moderate cognitive impairment or dementia.
- 5.38 Wald et al. (2010) conducted a meta-analysis with the aim of quantifying the effect of folic acid supplementation on the prevention of cognitive decline in adults without dementia. The meta-analysis included data from 9 RCTs, 7 of which were also considered by Dangour et al. (2010) and 5 by Clarke et al. (2014). Sample sizes ranged from 24 to 910 participants (2835 participants in total) aged 60 to 83 years. Across the RCTs, folic acid supplementation ranged from 0.2 to 15 mg/d and in 4 RCTs was combined with other B vitamins (vitamin B2, B6 or B12). Trial duration ranged from 1.2 months to 3 years.

- 5.39 Folic acid, with or without other B vitamins, had no significant effect on cognitive function in cognitively healthy adults (SMD=0.01, 95%CI -0.08, 0.10). The results were similar within each of the 4 categories of cognitive function; memory (SMD=0.01, 95%CI -0.08, 0.09), speed (SMD=0.01, 95%CI -0.10, 0.13), language (SMD=-0.05, 95%CI -0.15, 0.04), and executive function (SMD=0.03, 95%CI -0.13, 0.19). There was no evidence of heterogeneity across the RCTs. The authors concluded that folic acid supplementation, with or without other B vitamins, for up to 3 years had no effect on cognitive function in adults without dementia.
- 5.40 Malouf & Grimley Evans (2008) conducted a Cochrane review which evaluated the effect of folic acid supplementation (dose: 400 µg/d – 15 mg/d), with or without vitamin B12, on cognitive function in cognitively healthy adults and adults with dementia (age 50 to 92 years). Eight RCTs, which ranged in duration from 35 days to 3 years, were identified and included in the review. One of these RCTs was also considered in the review by Li et al. (2014), 2 by Clarke et al. (2014), one by Doets et al. (2013), 6 by Dangour et al. (2010) and 5 by Wald et al. (2010). Half of the RCTs enrolled healthy adults while the other half enrolled adults with mild to moderate cognitive impairment or dementia. Due to heterogeneity in sample selections, outcomes, trial duration and supplement dosage, pooling of the data was not possible. The authors concluded that the evidence considered provides ‘no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of healthy or cognitively impaired older people’.

Summary – Folate/folic acid

- 5.41 Two of the identified reviews (Dangour et al., 2010; Xu et al., 2015) considered the association between folate intake and incident AD risk. The most recent review, which also included a meta-analysis, found an association between higher intakes of folate and a reduced risk of AD (Xu et al., 2015). However, Dangour et al. (2010), based on data from 3 PCS (all of which were included in the meta-analysis by Xu et al. (2015)), concluded that there was insufficient evidence to draw a conclusion on the association between intakes of folate/folic acid with or without other B vitamins and risk of AD.
- 5.42 The effect of folic acid supplementation on cognition in cognitively healthy participants was considered in 3 of the identified reviews (Malouf & Grimley Evans, 2008; Wald et al., 2010; Dangour et al., 2010). Of the 3 reviews, which all included evidence from RCTs, one included a meta-analysis (Wald et al., 2010). No effect of folic acid supplementation in combination with vitamin B6 and B12 on cognition was found.
- 5.43 The 2 reviews to consider cognition in people with AD or other forms of dementia found no effect of folic acid supplementation (Malouf & Grimley Evans, 2008; Dangour et al., 2010). There was an insufficient number of participants (265 participants) included in the 4 RCTs which are reported in the

identified systematic narrative reviews to draw a conclusion on the effect of folic acid on cognition in this population.

Thiamin

- 5.44 A Cochrane Collaboration review evaluated the effect of thiamin supplementation on cognition in adults with mild to moderate AD (Rodriguez-Martin et al., 2001). Three RCTs were identified that met the inclusion criteria, however, the authors were unable to combine the data in meta-analysis due to insufficient detail in the results and the small number of participants included in the trials ($n < 50$). Two RCTs compared 3 mg/d thiamin hydrochloride with a placebo and one compared 3 mg/d thiamin hydrochloride with 750 mg/d niacinamide.
- 5.45 One study found no evidence of an effect on MMSE score at 3, 6, 9 and 12 months for thiamin compared with placebo. Another noted that 38% of participants receiving thiamin, compared with 67% in the control group, were worse as measured on the ADAS-Cog at 3 months compared with baseline, but the difference was not statistically significant. The authors concluded that it was not possible to draw any conclusions from the evidence considered in the review due to the limited number of participants.

Summary – Thiamin

- 5.46 The sole systematic review identified, which included data on only 3 RCTs that reported on less than 50 participants in total, provides insufficient evidence to draw a conclusion on the effect of thiamin on cognition in people with AD (Rodriguez-Martin et al., 2001).

Vitamins C and E

- 5.47 Seven systematic reviews and meta-analyses were identified that considered the relationship between dietary or supplemental vitamins C and E intake and cognitive function, cognitive decline and the risk of MCI, AD and dementia. Many of the identified publications report on a range of antioxidant nutrients and other dietary and lifestyle factors. Where the data are available, findings are reported for vitamin C and E intakes separately as well as combined intakes of vitamins C and E. One of the identified reviews only reported on combined intakes of a range of antioxidant nutrients including vitamins C, E and β -carotene (Beydoun et al., 2014).
- 5.48 Forbes et al. (2015) conducted a systematic review of RCTs that supplemented subjects with vitamin E. Three RCTs, with intervention periods ranging from 3 to 9.6 years, were identified. Doses of vitamin E ranged from 200 to 1300 mg/d

with one RCT also supplementing with vitamin C and β -carotene. Trial participants were adults aged 65 years and above with no diagnosed cases of dementia at baseline. While the study participants of one RCT were healthy (n=6377), the participants in the second RCT had amnestic MCI (n=769) and the participants in the third RCT had 3 or more coronary risk factors (n=2824). None of the 3 RCTs showed a significant effect of vitamin E supplementation on any of the assessed cognitive outcomes.

- 5.49 Xu et al. (2015) performed a systematic review and meta-analysis of PCS which reported on vitamin C and/or E intake and the risk of AD. Six PCS, with a mean follow-up of 3.9 to 9.3 years, were identified that considered vitamin E or vitamin C separately. The meta-analysis ($I^2 < 50\%$) showed a significant association between high intake of vitamin E or C and reduced AD incidence (RR 0.73, 95%CI 0.62, 0.84, n=12,014; RR 0.74, 95%CI 0.55, 0.93, n=11788 respectively).
- 5.50 Xu et al. (2015) also identified four PCS, with a mean follow-up of 3 to 5.5 years, that considered vitamin E and C in combination. The meta-analysis showed no significant association of combined vitamin E and C intake and AD incidence (RR 0.82, 95%CI 0.60, 1.04; n=10588; $I^2 < 50\%$). While the result of the meta-analysis was non-significant, the direction of the association was consistent with the meta-analyses that considered vitamin C and vitamin E separately (see paragraph 5.49). The meta-analysis on combined intakes of vitamins C and E was largely based on different study populations than the meta-analyses that considered vitamin C and vitamin E separately.
- 5.51 Cao et al. (2016) reported on the relationship between dietary intakes of vitamins C and E, and the risk of dementia in adults aged 45 years and above. Ten PCS with follow-ups of 3 to 30 years met the inclusion criteria. Five of the 10 studies were also included in the review by Xu et al. (2015).
- 5.52 When considered separately, greater dietary vitamin E intake was associated with a reduced risk of dementia (RR 0.80, 95%CI 0.65, 0.98; p=0.034; $I^2 = 33.6\%$, p=0.14) but vitamin C intake was not (RR 0.89, 95%CI 0.74, 1.06; p=0.192; $I^2 = 24.0\%$, p=0.24). Data on dietary intakes of vitamins C and E as well as flavonoids was also combined in meta-analysis; greater intake was associated with a reduced risk of dementia (RR 0.87, 95%CI 0.77, 0.98; p=0.026; $I^2 = 36.2\%$, p=0.051). Cao et al. (2016) concluded that antioxidants may reduce the risk of dementia, however, these findings should be treated with caution as no information on sample sizes or consideration of the quality of included studies was reported in the review.
- 5.53 In a review of modifiable factors associated with cognition and dementia, 21 PCS in adults aged 45 years and above were identified that reported on dietary intakes and supplementation of antioxidant nutrients including vitamins C and E and β -carotene (Beydoun et al., 2014). The sample sizes of studies ranged from 526 to 16010 participants. Six of the 21 PCS identified were also included in reviews by Xu et al. (2015) and Cao et al. (2016).

- 5.54 The results of PCS that examined the association between antioxidants (i.e. vitamin C, vitamin E and β -carotene) and risk of dementia and AD were conflicting. Of the 8 PCS that looked at antioxidant supplementation, 4 reported an association between antioxidants and reduced risk of dementia and AD and 4 reported no association. Only 3 PCS were identified that evaluated dietary intakes of antioxidant nutrients. Two of these PCS found an association between dietary antioxidants and a reduced risk of dementia and AD while one cohort found no association.
- 5.55 The findings of the 10 PCS that assessed cognitive function using a range of tests were more consistent. Four PCS looked at antioxidant supplementation, of these, 3 found a reduced risk of cognitive decline with supplement use while one found no association. Dietary intakes of antioxidant nutrients were associated with a reduced risk of cognitive decline in the other 6 PCS. This review provides no information on supplement doses or dietary intakes, study duration or study quality and so the findings should be treated with caution.
- 5.56 The relationship between vitamins C and E and cognitive decline in older adults aged 60 years and above is considered in a systematic review by Rafnsson et al. (2013). Ten PCS met the inclusion criteria; 4 looked at vitamin C intake or supplementation and 5 looked at vitamin E intake or supplementation. Of the 5 PCS that considered vitamins C and E, one was included in the review by Xu et al. (2015) and 2 were included in the reviews by Cao et al. (2016) and Beydoun et al. (2014).
- 5.57 The PCS, which had follow-ups of 8.5 months to 7 years, estimated vitamin C and E intake using food intake data in 4 studies and self-reported use of vitamin supplements in one study. The methodological heterogeneity observed across the identified studies prevented a quantitative meta-analysis of the results.
- 5.58 Vitamin C intake was not significantly associated with cognitive function in 2 PCS. However one study found that participants with higher intakes of vitamin C had slower rates of cognitive decline than those with lower intakes, when measured at the 3 year follow-up but not at the 7 year follow-up. The study that looked at vitamin C supplementation found no significant association with cognitive function.
- 5.59 Greater vitamin E intake was associated with slower cognitive decline in 2 PCS. In one of these, the association was observed at the 3 year follow-up but not at the 7 year follow-up. The 3 remaining PCS, 2 of which considered dietary intakes and one of which looked at supplementation, found no significant association between vitamin E and cognitive decline.
- 5.60 The evidence on antioxidants, cognitive function and risk of dementia was also considered in a systematic review by Crichton et al. (2013). The review considered epidemiological and longitudinal evidence which assessed the association between dietary intakes of antioxidant nutrients including vitamins

C and E, flavonoids, carotenoids, and cognition in cognitively healthy adults aged 50 years and above. Only the evidence on vitamin C and E intake from cohort studies is reported below. Evidence on flavonoids is discussed in chapter 6.

- 5.61 The literature search identified 12 PCS which were reported in 13 publications. The PCS had follow-ups of 3 to 30 years and sample sizes of 117 to 5395 subjects. In these studies dietary intakes were mostly assessed using FFQs; however other methods used included twenty-four hour dietary recall, three- or seven-day food records and an interview method to ascertain usual food consumption. Four of the identified PCS were included in the review by Xu et al. (2015), 8 in the review by Cao et al. (2016), 5 in the review by Beydoun et al. (2014) and 3 in the review by Rafnsson et al. (2013).
- 5.62 Nine PCS reported in 10 publications were identified that looked at vitamin C intake, cognitive performance and dementia and AD risk. Two out of the 3 cohorts which looked at cognitive performance found no significant association with vitamin C intake. One of these PCS involved 117 participants and had a follow-up of 4 years; the other included 476 participants with a follow-up of 3 years. The third PCS, which had a follow-up of 20 years, found that cognitive function was poorest in those with lowest vitamin C intakes at baseline (n=921). The 6 PCS that considered AD and dementia risk found no association with vitamin C intake (follow-up=4 to 30 years; n= 579 to 5395 participants).
- 5.63 Six PCS were identified that reported on vitamin E intake, cognitive decline and risk of dementia and AD. Vitamin E intake was positively associated with better cognitive performance measured using visuospatial recall and abstraction tests at 6 years in one PCS involving 137 participants. Three PCS with follow-ups of 4 to 10 years, found that higher vitamin E intakes were associated with a slower rate of cognitive decline and a reduced risk of AD and dementia (n=815 to 5397 participants). In contrast, no association was found between vitamin E intake and dementia or AD risk in 2 PCS with follow-ups of 4 and 30 years involving 980 and 2459 participants. Crichton et al. (2013) concluded that the findings do not consistently show that intakes of vitamin C and E are associated with better cognitive performance or reduced risk of dementia or AD and that more research is needed.
- 5.64 Li et al. (2012) conducted a meta-analysis which evaluated the association between dietary intakes of vitamins C, E and β -carotene and the risk of AD in adults aged 45 years and above. Seven PCS, with follow-ups of 4 to 30 years involving 197 to 5395 participants, were identified and included in the meta-analysis. Six of the PCS included data on vitamin C intake, 7 on vitamin E intake and 5 on β -carotene intake. All of the identified cohort studies were also included in the review by Cao et al. (2016), 5 were included in the reviews by Xu et al. (2015) and Beydoun et al. (2014), one in the review by Rafnsson et al. (2013) and 6 in the review by Crichton et al. (2013). Only findings relating to vitamin C and E intake are reported below.

- 5.65 The results of the meta-analysis indicate that higher intakes of vitamins C (RR 0.83, 95%CI 0.72, 0.94; $I^2=0\%$, $p=0.657$) and E (RR 0.76, 95%CI 0.67, 0.84; $I^2=43\%$, $p=0.103$) are associated with a reduced risk of AD, with vitamin E exhibiting the most pronounced association.

Summary – Vitamins C and E

- 5.66 Five of the identified reviews, all of which considered evidence from PCS, reported on the association between dietary intake or supplementation of vitamins C and/or E and risk of AD and dementia (Li et al., 2012; Crichton et al., 2013; Beydoun et al., 2014; Cao et al., 2016; Xu et al., 2015). Three of the reviews included meta-analyses (Li et al., 2012; Cao et al., 2016; Xu et al., 2015). The meta-analyses in the most recent review (Xu et al., 2015) showed associations between higher intakes of vitamin C and vitamin E (respectively) and reduced AD incidence. The meta-analysis on combined intakes of vitamins C and E, which was largely based on different study populations, showed no significant association. The most recent meta-analysis to consider dementia risk, Cao et al. (2016), found an association between greater vitamin E intake and a reduced risk of dementia, but there was no association between vitamin C and dementia risk. Given that Cao et al. (2015) did not report on sample sizes in the included studies, it is not possible to draw a conclusion on the association between dementia and the intake of vitamins C and E.
- 5.67 The relationship between cognition and intake or supplementation of vitamins C and/or E was considered in 3 of the identified systematic narrative reviews (Crichton et al., 2013; Rafnsson et al., 2013; Forbes et al., 2015). Only one of the reviews reported on evidence from RCTs (Forbes et al., 2015); no significant effect of vitamin E intake on cognition was found in the 3 RCTs included in this review. The results of the studies included in the most up-to-date review to report on cohort studies were mixed (Rafnsson et al., 2013). Three of 4 PCS reporting on vitamin C intake or supplementation and 3 of 5 PCS reporting on vitamin E intake or supplementation found no association with cognition.

Omega-3 fatty acids

- 5.68 Eleven systematic reviews and meta-analyses were identified that considered the relationship between dietary or supplemental intakes of omega-3 fatty acids and cognitive function, cognitive decline and the risk of MCI, AD and dementia. Some of the identified reviews considered evidence in relation to the specific long-chain polyunsaturated omega-3 fatty acids (LCPUFA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA). One review considered the association between the ratio of omega-6/omega-3 fatty acid intake and cognitive outcomes.

- 5.69 A number of the identified reviews also consider fish consumption; where they did, the results are reported below, however, it should be noted that the literature search did not specifically look for reviews considering fish intake and cognitive function, cognitive decline and the risk of MCI, AD and dementia. None of the reviews which considered fish intake, differentiated between intakes of white and oily fish.
- 5.70 Zhang et al. (2016) investigated the relationship between omega-3 fatty acids, fish intake, and the risk of AD and dementia in older adults aged 52 years and above. Fifteen publications reporting 10 individual PCS and 3 case-control studies were identified.
- 5.71 Three PCS, with between 4 to 6 years follow-up, considered AD risk in adults 55 years and above at baseline, and intake of omega-3 fatty acids. Intake of omega-3 fatty acids was not associated with AD risk (RR 0.99, 95%CI 0.85, 1.12; 6900 participants, 391 cases).
- 5.72 Three publications (2 PCS and one case control study) evaluated DHA intake and risk of AD and dementia. A 0.1 g/d increment of DHA was associated with lower risks of both AD (RR 0.63, 95%CI 0.51, 0.76; $I^2=94.5\%$, $p < 0.001$) and dementia (RR 0.86, 95%CI 0.76, 0.96; $I^2=92.7\%$, $p < 0.001$); however, there was significant heterogeneity between studies. In contrast, a 0.05 g/d increment of EPA was not associated with AD risk (RR 1.04, 95%CI 0.85, 1.23).
- 5.73 Five PCS including 21941 participants considered fish intake and risk of AD and dementia (two of which also considered intakes of omega-3 fatty acid). A one serving per week increment of fish was associated with a lower risk of AD (RR 0.93, 95%CI 0.90, 0.95; $I^2=74.8\%$, $p=0.003$) and dementia (RR 0.95, 95%CI 0.90, 0.99; $I^2=63.4\%$, $p=0.042$). Again there was significant heterogeneity between studies.
- 5.74 Forbes et al. (2015) conducted a systematic review and meta-analysis of RCTs that supplemented subjects with omega-3 fatty acids. Intervention periods of the 6 RCTs included in the review ranged from 5 to 40 months. Participants were supplemented with DHA on its own (900 mg/d), combinations of EPA and DHA (400 to 2200 mg/d) and in one study a combination of EPA, DHA and alpha-linolenic acid (ALA) at doses of 240, 160 and 2000 mg/d respectively. The number of participants included in the RCTs ranged from 36 to 2911 and they were aged 55 years and above.
- 5.75 The relationship between cognitive function and omega-3 supplementation was assessed in a meta-analysis of 4 RCTs that reported on MMSE scores ($n=2713$), and a second meta-analysis of 3 RCTs that reported on digit span forward results ($n=1053$). No significant difference between the intervention and control groups was found in MMSE scores or digit span forward (summary mean difference=0.06, 95%CI -0.08, 0.19 and -0.02, 95%CI -0.30, 0.25, respectively). Data on memory and executive function was not combined in a

meta-analysis. Three RCTs reported a beneficial effect on memory and/or executive function and 3 did not.

- 5.76 Wu et al. (2015) conducted a systematic review and meta-analysis of PCS investigating the association between the intake of omega-3 fatty acids and fish consumption and the incidence of dementia and AD. Six PCS were identified, 3 reported on omega-3 fatty acids and fish intake and 3 reported on fish intake only. Follow-ups ranged from 2 to 14 years and sample sizes from 488 to 8085 subjects.
- 5.77 Two PCS reported on intakes of omega-3 fatty acids and the risk of dementia. No association was found between omega-3 fatty acids intake and dementia risk when the highest intake was compared with the lowest.
- 5.78 Data from 3 PCS, which reported on the risk of AD, was also combined in a meta-analysis. There was no significant association between the intake of omega-3 fatty acids and AD risk when the highest intake was compared with the lowest.
- 5.79 The 6 PCS that reported on fish intake were combined in meta-analyses. No association was found between fish intake and dementia risk (RR 0.84, 95% CI 0.71, 1.01; 5 PCS) when the highest category of consumption was compared with the lowest. A significant association was found between higher consumption of fish and a reduced risk of AD (RR 0.64, 95% CI 0.44, 0.92; 6 PCS), however, there was significant heterogeneity between studies ($I^2=59.0\%$, $p=0.023$).
- 5.80 Xu et al. (2015) performed a systematic review and meta-analysis of PCS which evaluated the association between intakes of DHA, EPA, omega-3 fatty acids, fish consumption, and AD incidence.
- 5.81 Four PCS reported on dietary intake of DHA (n=663 to 5395, follow-up 3.9 to 9.6 years). No association between DHA intake and AD incidence was found (RR 0.70, 95% CI 0.37, 1.03; n = 7,772; $I^2=68\%$).
- 5.82 Three PCS reported on EPA intake (n=663 to 5395, follow-up 3.9 to 9.6 years). Again no association between EPA intake and AD incidence was found (RR 0.96, 95% CI 0.75, 1.16, n=6,873; $I^2<50\%$).
- 5.83 Three PCS reported on the intake of omega-3 fatty acids (n=663 to 5395, follow-up 3.9 to 9.6 years). No association between omega-3 fatty acids intake and AD incidence was found (RR 0.81, 95% CI 0.39, 1.23, n=6,873). The authors noted high heterogeneity ($I^2=70\%$).
- 5.84 Six PCS reported on fish intake (n=815 to 8085, follow-up 2.1 to 9.6 years) (2 of the 6 studies also reported of the intake of omega-3 fatty acids, DHA and EPA). A significant inverse association between fish intake and AD incidence was found (RR 0.66, 95% CI 0.43, 0.90, n = 23,510). However, the authors noted high heterogeneity ($I^2=60\%$). The frequency of fish consumption was

considered in 4 PCS (n=815 to 8085, follow-up 3.5 to 7 years). A significant inverse association for fish consumption frequency and AD incidence was found (RR 0.64, 95%CI 0.46, 0.82, n=12,549; $I^2 < 50\%$).

- 5.85 Jiao et al. (2014) considered the effect of omega-3 fatty acid supplementation on cognitive development, function and decline throughout the life course. Findings were reported according to 3 life stages; infants, children and adults (data on these 2 life stages were grouped together) and older adults. In total 34 RCTs were identified; 7 in infants, 15 in children and adults and 12 in older adults. As this position statement focuses on cognitive function, cognitive decline and dementias, only the findings in children and adults and older adults are reported below.
- 5.86 The 15 RCTs in children and adults aged 9 to 30 years included a total of 5174 subjects. Interventions ranged from 4 to 8 months and omega-3 fatty acid doses ranged from 0.6 to 1.5 g/d. The 12 RCTs in older adults included 6794 subjects aged 68 to 74 years, had interventions of 6 to 20 months and supplemented with 0.9 to 1.8 g omega-3 fatty acids per day. Five of the RCTs identified by Jiao et al. (2014) were also included in the review by Forbes et al. (2015).
- 5.87 Jiao et al. (2014) evaluated cognitive performance using data on 4 cognitive domains: composite memory, executive function, attention and processing speed, as well as a range of cognition tests. When data on children and adults, and older adults was combined, supplementation with omega-3 fatty acids significantly improved 'attention' (SMD 0.13, 95%CI 0.01, 0.25; $I^2 = 59.0\%$, $p = 0.032$); however significant heterogeneity was observed. When considered separately, the effect remained for older adults (SMD 0.29, 95%CI 0.10, 0.47; $I^2 = 68.5\%$, $p = 0.042$) but not for children and adults (SMD 0.02, 95%CI -0.14, 0.18; $I^2 = 0.0\%$, $p = 0.526$).
- 5.88 Compared with control, omega-3 fatty acid supplementation significantly improved Stroop Test¹³ scores in children and adults (SMD 0.22, 95%CI 0.04, 0.40) but not in older adults (SMD -0.01, 95%CI -0.20, 0.18). No significant improvements were observed for any of the other cognitive domains or cognition tests in both children and adults and older adults.
- 5.89 To evaluate cognitive decline in older adults, Jiao et al. (2014) considered MMSE scores. Compared with placebo, omega-3 fatty acid supplementation did not significantly affect MMSE scores (SMD 0.04, 95%CI -0.02, 0.10; $I^2 = 0\%$, $p = 0.882$). The authors concluded that supplementation with omega-3 fatty

¹³ The Stroop Test, which can be used to measure executive function, is based on the finding that it takes longer to call out a colour name than to read a word and even longer to read printed colour names printed in a colour different from that named by the word. There are many variations of the Stroop Test but generally it involves timing how long it takes participants to read words or name the printed colours on a sheet of paper or participants are asked to read words or name the printed colours as quickly as possible within a time limit.

acids does not improve cognitive performance or reduce cognitive decline in children, adults or older adults.

- 5.90 Beydoun et al. (2014) reviewed a range of modifiable factors associated with cognition and risk of dementia and AD. Thirteen PCS in adults aged 55 years and above were identified that considered dietary intakes and supplementation of omega-3 fatty acids. Seven of the 13 PCS identified were also considered in the review by Zhang et al. (2016) and 4 in the review by Wu et al. (2015).
- 5.91 Findings for cognitive function and risk of MCI, dementia and AD were mixed. Higher omega-3 fatty acid intakes and supplementation doses were found to be associated with reduced risk of MCI, dementia and AD in 4 PCS (sample size 805 to 8085 participants). However, no significant association was observed between omega-3 fatty acid and risk of dementia and AD in 2 PCS (sample size 5395 and 5395 participants). Five PCS observed a protective association between cognitive function and decline and omega-3 fatty acids (sample size 1475 to 7814 participants). In contrast, 3 PCS observed no significant association (sample size 476 to 3718).
- 5.92 Abubakari et al. (2014) conducted a meta-analysis examining the effect of omega-3 fatty acid supplementation on cognitive function and decline measured using a range of tests. Twelve RCTs were identified, 7 in general or healthy populations and 5 in clinical or special populations including people with schizophrenia, various degrees of memory problems, depression and pregnant women. Three of the RCTs were also included in the review by Forbes et al. (2015) and 8 in the review by Jiao et al. (2014).
- 5.93 The number of participants included in the RCTs ranged from 53 to 867 (total $n=2831$), and the mean age of participants ranged from 21 to 75 years. The RCTs supplemented with any omega-3 fatty acids (ALA, EPA, DHA, and DPA) or fish/fish oil for 4 weeks to 24 months.
- 5.94 No significant change in cognitive function following supplementation with omega-3 fatty acids was observed (SMD -0.04, 95%CI -0.09, 0.01). When pooled analyses were stratified by follow-up duration ([short-term <6 months SMD -0.08, 95%CI -0.16, 0.01]; [long-term ≥ 6 months SMD -0.03, 95%CI -0.09, 0.03]); and type of participants ([general/healthy population SMD -0.04, 95%CI -0.10, 0.01]; [clinical/special population SMD 0.00, 95%CI -0.10, 0.09]) no significant differences in cognitive function between the omega-3 fatty acid supplemented group and the placebo group were found. A significant difference in cognitive decline was found when stratified by dose. Low doses of omega-3 fatty acids ($\leq 1.73\text{g/d}$) were found to significantly reduce rates of cognitive decline compared with placebo (-0.07, 95%CI -0.13, -0.02). No difference in cognitive decline was found between groups with higher doses of omega-3 fatty acids. There was no significant heterogeneity in any of the stratified analyses. The authors concluded 'that omega-3 fatty acids may be beneficial in preventing memory decline at lower doses'.

- 5.95 Loef & Walach (2013) performed a systematic review that considered the association between omega-6 / omega-3 ratio and risk of dementia or cognitive decline. Loef & Walach (2013) reviewed the evidence on both dietary intakes and blood levels of omega-3 and omega-6 fatty acids. Only findings relating to dietary intakes of omega-3 and omega-6 fatty acids are reported here.
- 5.96 A small controlled trial with a short duration (n=21, duration 90 days) was identified which showed significant improvements (compared with baseline) in immediate memory and attention score in those receiving a combined supplemented of DHA (omega-3) and arachidonic acid (omega-6), but not in those supplemented with olive oil.
- 5.97 In relation to the intake of omega-6 and omega-3 fatty acids 2 PCS were identified. One PCS (n=8085; follow-up 3.5y) found that for APOE-ε4 non-carriers, increased omega-6 intake that was not complemented by consumption of omega-3 rich foods was significantly associated with increased AD incidence (HR 2.12, 95% CI 1.30, 3.46). No significant association was shown for APOE-ε4 carriers. A second PCS (n=4809; follow-up 13y) showed an increased ratio of omega-6/omega-3 intake to be significantly associated with increased cognitive decline (OR=1.25, 95% CI 1.01, 1.55).
- 5.98 The effect of omega-3 fatty acids on cognitive function in cognitively healthy older adults is considered in a Cochrane collaboration review by Sydenham et al. (2012). Three RCTs were identified which ranged in duration from 24 weeks to 3.3 years, and considered data on a total of 4080 older adults aged 60 years and above. Participants received supplements containing a mixture of omega-3 fatty acids; EPA dose ranged from 200 to 1093 mg/d, DHA dose ranged from 176 to 847 mg/d and one RCT also supplemented with 2 g/d ALA. Two of the identified RCTs were also considered by Forbes et al. (2015), Jiao et al. (2014) and Abubakari et al. (2014).
- 5.99 In 2 of the identified studies, involving 3221 participants, MMSE was completed at baseline and follow-up. When combined in meta-analysis, no difference in MMSE score was found between the omega-3 fatty acid supplemented group and placebo group (MD: -0.07, 95% CI -0.25, 0.10). There was evidence of moderate heterogeneity which was not investigated further.
- 5.100 No difference between the treatment and placebo groups were found for immediate word recall (SMD 0.01, 95% CI -0.11, 0.14), delayed word recall (SMD -0.04, 95% CI -0.16, 0.09), word recognition (SMD 0.04, 95% CI -0.08, 0.16), verbal fluency (SMD: 0.06, 95% CI -0.06, 0.18), digit span forward (MD 0.03, 95% CI -0.25, 0.31) and digit span backwards (MD 0.12, 95% CI -0.12, 0.36) when data from 2 studies, involving 2058 participants, were combined in meta-analysis. No evidence of heterogeneity was observed in any of the analyses except for digit span backwards, where moderate heterogeneity was found which was not investigated further. Sydenham et al. (2012) concluded that

supplementation with omega-3 fatty acids provides no benefit to cognitive function in cognitively healthy older people.

- 5.101 Mazereeuw et al. (2012) also looked at the effect of omega-3 fatty acids on cognitive function in cognitively healthy people as well as people with MCI and diagnosed AD. Ten RCTs were identified; 3 in cognitively healthy individuals, 4 involving people with MCI and 3 in people diagnosed with AD. Two of the identified RCTs were also considered by Forbes et al. (2015), 7 by Jiao et al. (2014) and Abubakari et al. (2014) and 2 by Sydenham et al. (2012).
- 5.102 Study sizes ranged from 21 to 867 participants and trial duration ranged from 13 weeks to around 2 years. Supplementation involved a combination of, and individual, omega-3 fatty acids; DHA supplementation ranged from 40 to 1550 mg/d, EPA supplementation ranged from 20 to 1670 mg/d and one RCT supplemented with 40 mg/d of arachidonic acid.
- 5.103 Omega-3 fatty acid supplementation had a beneficial effect on immediate recall (Hedge's g 0.16, 95%CI 0.01, 0.32; 4 studies, $n=676$) and attention and processing speed (0.32 g , 95%CI 0.03, 0.61; 3 studies, $n=193$) in people with MCI but not those who were cognitively healthy. No statistically significant benefit in composite memory, delayed recall, recognition, working memory and executive function was observed with omega-3 supplementation in cognitively healthy people or those with MCI. Omega-3 fatty acid supplementation had no significant effect on MMSE score and ADAS-Cog score in those with MCI and diagnosed AD. This meta-analysis provides no evidence of a beneficial effect on cognitive performance in cognitively healthy individuals or those diagnosed with AD and only limited evidence of a benefit for those with MCI.
- 5.104 The systematic review by Dangour et al. (2010) which reported on folic acid intake, cognition and incident dementia and AD, discussed earlier in this position statement, also examined the association between omega-3 fatty acids or fish consumption and the incidence of dementia and AD. Six PCS were identified. Of these, 2 reported only on omega-3 fatty acids, 2 reported only on fish consumption, and the remaining 2 reported on both. Study duration ranged from 3.9 years to 21 years. Participants were aged 50 years and above and all were free of dementia at baseline. All six of the identified PCS were included in the review by Zhang et al. (2016), 3 in the review by Wu et al. (2015), and 2 in the review by Beydoun et al. (2014).
- 5.105 In 2 PCS, higher consumption of fish, DHA and total omega-3 fatty acids was associated with a reduced risk of dementia and AD. The remaining 4 PCS reported no association between fish and omega-3 fatty acid intakes and dementia and/or AD. The authors concluded that findings from PCS looking at intakes and blood levels of omega-3 fatty acids are inconsistent and therefore insufficient to draw conclusions.

Summary – Omega-3 fatty acids

- 5.106 Six of the 11 reviews identified considered cohort studies that looked at the relationship between intake of omega-3 fatty acids and risk of dementia or AD (Dangour et al., 2010; Loef & Walach, 2013; Beydoun et al., 2014; Xu et al., 2015; Wu et al., 2015; Zhang et al., 2016). The most up-to-date review which included a meta-analysis of 3 PCS with data on 6900 participants, found no association between intake of omega-3 fatty acids and AD incidence (Zhang et al., 2016). The most recent review to report on dementia incidence included 2 PCS in a meta-analysis; no association was found between omega-3 fatty acids intake and the risk of incident dementia (Wu et al., 2015).
- 5.107 Five reviews considered evidence from RCTs which studied the relationship between omega-3 fatty acids supplementation and cognitive function (Mazereeuw et al., 2012; Sydenham et al., 2012; Abubakari et al., 2014; Jiao et al., 2014; Forbes et al., 2015). The 5 reviews showed that some measures of cognitive function improved when participants received omega-3 fatty acid supplements, however, many did not. Overall evidence from RCTs failed to show an effect of omega-3 fatty acids on cognitive function or cognitive decline in healthy adults.
- 5.108 Fish intake and risk of AD and dementia was considered in 4 of the identified reviews (Dangour et al., 2010; Xu et al., 2015; Wu et al., 2015; Zhang et al., 2016). The most up-to-date review which included a meta-analysis (Zhang et al., 2016), included data from 5 PCS and 21941 participants. A significant association between higher fish consumption and a reduced risk of AD and dementia was found. The findings for AD were supported by the results of the meta-analyses by Xu et al. (2015) and Wu et al. (2015), however Wu et al. (2015) found no association between fish intake and dementia. Any possible effect of fish consumption on dementias may be mediated by nutrients other than omega-3 fatty acids.

Tryptophan

- 5.109 No systematic reviews or meta-analyses were identified that considered tryptophan.

Overall summary – Nutrients

- 5.110 The findings of systematic reviews and meta-analyses which considered the intake of individual nutrients and the risk of dementia and AD are inconsistent. In some cases the available data provide insufficient evidence of an effect/association and in others the data provide evidence favouring no effect/association between the intake of individual nutrients (B vitamins,

vitamins C and E, omega-3 fatty acids) and cognitive function and decline in people with or without cognitive impairment, AD or dementia. Overall, there was insufficient evidence that higher intakes of individual nutrients (from diet or supplements) protect against cognitive decline, MCI or dementias, including AD.

- 5.111 A number of the identified reviews which reported on omega-3 fatty acids also reported on fish consumption. About half of the primary studies that reported on fish consumption also reported on omega-3 fatty acid intakes. The evidence considered in this statement indicates a significant association between higher fish consumption and a reduced risk of AD and dementia. However, this may not reflect the totality of the evidence as the literature search did not specifically look for reviews considering fish intake and the risk of AD and dementia.

6 Other dietary components: polyphenols, flavonoids and caffeine

6.1 There was sufficient evidence on polyphenols, flavonoids and caffeine in relation to cognitive impairment and dementia to warrant an assessment within this statement. As these dietary components are not nutrients in the strict sense, they are considered in this separate chapter.

Polyphenols

6.2 One systematic review reported on the relationship between polyphenols and cognitive function in healthy adults, and adults reported as being 'mildly cognitively impaired' (Lampert et al., 2012). The authors did not consider the risk of MCI, AD or dementia as part of their review.

6.3 The review included four trials studies reporting on the consumption of polyphenols in berry juice, one RCT on resveratrol supplements and one PCS. The review also considered studies on flavonoids, which are reported in the section below (p.49).

6.4 Two of the four trials (n=9 and 12) that evaluated the consumption of polyphenols in berry juice reported significantly better cognition (immediate verbal recall) in the berry juice groups compared with control groups after 12 weeks. The other two trials had shorter durations (1 day and 6 weeks; n=35 and 50) and reported no significant effect of berry juice consumption on any measure of cognition.

6.5 The RCT that reported on resveratrol supplements reported no significant effect on cognition measured 45 minutes after consumption (n=24 participants).

6.6 A PCS (n=2574) with 13 years of follow-up reported that higher polyphenol intake was associated with better language and memory performance and worse executive function. A cross-sectional study (n=2031) reported on the consumption of polyphenol rich foods. Of 5 cognitive function tests, wine consumption showed a beneficial association with 4 tests, tea consumption with 3 tests and chocolate consumption with 1 test.

Summary – Polyphenols

6.7 Two trials with very few participants (n=9 and 12) reported better cognitive function after 12 weeks of berry juice consumption, while two larger trials (n=35 and 50) reported no associations after 1 day and 6 weeks of berry juice consumption. An RCT with resveratrol reported no acute effects 45 minutes after supplement consumption. A PCS with 13 years of follow-up reported higher polyphenol intake to be associated with better language and memory

performance and worse executive function. Based on this limited and inconsistent evidence it is not possible to draw conclusions on the relationship between polyphenols and cognition.

Flavonoids

- 6.8 Five systematic reviews and meta-analyses were identified that considered the relationship between flavonoids and cognitive function, cognitive decline and the risk of MCI, AD and dementia.
- 6.9 A systematic review by Cao et al. (2016) identified 2 PCS with follow-ups of 5 and 6 years that looked at flavonoids intake (measured using 24-hour dietary recall and FFQ) and dementia risk in adults aged 55 years and above. A meta-analysis showed no significant association between flavonoids intake and dementia risk (RR 0.97, 95%CI 0.65, 1.46; $I^2=59.6\%$). The review has many limitations including the low number of identified cohort studies, no information on sample sizes, and no assessment of study quality.
- 6.10 Crichton et al. (2013) conducted a systematic review of the role of antioxidants in cognitive performance and dementia risk. The review, which considered cross-sectional and longitudinal evidence in mostly cognitively healthy populations, identified 5 PCS(6 publications) and one cross-sectional study which looked at flavonoids intake and cognition.
- 6.11 One cross-sectional study in 70 year olds, considered the association between 5 classes of flavonoids and 7 cognitive assessments. The only significant association shown was between flavanones and the National Adult Reading Test (NART), when potential confounders were controlled for (age, gender, energy intake, socio-economic group, smoking, education, APOE e4, childhood IQ).
- 6.12 In 3 PCS (duration: 6, 9 and 30 years) flavonoid intake was not associated with the risk of dementia or AD. One PCS found flavonoid intakes of more than 11.5 mg/d were associated with a reduced risk of dementia over 5 years. In the same cohort, high flavonoid intake (>13.6 mg/d) was associated with a reduced rate of cognitive decline over 10 years. Both of these findings were adjusted for age, gender, education, weight, vitamin C intake, smoking and body mass index (BMI). A further PCS (duration: 3 years) showed no association between flavonoid intake and cognitive impairment or decline. The authors concluded that flavonoids do not appear to be associated with a reduced risk of dementia or AD.
- 6.13 A systematic review by Rafnsson et al. (2013) considered flavonoid intake and cognitive decline and identified 2 PCS both of which were included in the review by Crichton et al. (2013) (see above). One of these cohorts showed high flavonoid intake (3rd and 4th quartile) to be associated with a slower rate of

cognitive decline over 10 years, while the second PCS showed no association over 3 years.

- 6.14 The systematic review by Lamport et al. (2012) included 4 RCTs that reported on the consumption of flavonoids in cocoa, 2 RCTs with flavonoid supplements, 13 RCTs with isoflavone supplements, 1 PCS and 1 cross-sectional study.
- 6.15 Four RCTs considered the effects of flavonoids in cocoa. Two RCTs (n=30 for both) that assessed cognition 1.5 and 2 hours after consuming cocoa, reported significantly better cognition in the cocoa groups compared with the control groups. The other two RCTs on the consumption of flavonoids in cocoa, reported no significant effect on cognition after 5 days and 6 weeks (n = 16 and 101).
- 6.16 Both RCTs on flavonoid supplements, reported that those taking supplements had better cognition compared with the control group after 5 weeks and 3 months (n = 42 and 101).
- 6.17 Of the 13 isoflavone supplement RCTs, six reported significantly better cognition or greater improvements in cognition in the isoflavone groups compared with the control groups after 6 weeks to 6 months (n=27 – 78 participants). Five of these RCTs only included women. The results of one RCT involving 30 participants were mixed; after 6 months the isoflavone group scored significantly better than the control group in some cognitive function tests while the control group scored significantly better than the isoflavone group in other tests measuring cognitive function. The remaining six RCTs reported no significant effect of isoflavone supplements on cognition (after 1.75 hours – 1 year; n=28 – 175 participants).
- 6.18 The review identified one PCS which is already considered in the reviews by (Rafnsson et al., 2013; Crichton et al., 2013) above.
- 6.19 A systematic review by Clement et al. (2011) identified 8 RCTs that reported on isoflavone supplementation, all of which were also identified in the review by Lamport et al. (2012). Clement et al. (2011) concluded that the identified RCTs had failed to conclusively demonstrate a beneficial effect of isoflavone supplementation on cognition in postmenopausal women.

Summary – Flavonoids

- 6.20 Of the 5 reviews identified, 2 considered the relationship between flavonoids and the risk of dementia (Cao et al) and AD (Crichton et al., 2013; Cao et al., 2016). Only one of the reviews combined data from PCS in a meta-analysis (Cao et al., 2016). No association between the intake of flavonoids and risk of incident dementia was found. This meta-analysis included a limited number of cohort studies, provided no information on the size of the included studies, and did not assess study quality. The systematic review by Crichton et al. (2013) concluded that flavonoids appear not to be associated with a reduced

risk of dementia or AD. Based on this evidence, it is not possible to draw a conclusion on the association between flavonoids intake and risk of incident dementia or AD.

6.21 Four of the identified reviews reported on the relationship between flavonoids and cognitive performance. None of the reviews included a meta-analysis. A review by Lamport et al. (2012) identified two RCTs that reported on flavonoid supplementation, with both RCTs showing a significant association with better cognition. Four RCT's reported on the consumption of flavonoids in cocoa. Two RCT's showed significantly better cognition 1.5 and 2 hours after cocoa consumption, while the two longer-term RCTs showed no association after 5 days and 6 weeks. Of 13 RCTs that reported on isoflavone supplementation 6 showed significantly better cognition in the intervention group, while 6 RCTs reported no association and 1 RCT reported mixed results. Two reviews identified the same two PCS which consider flavonoid intake and cognitive decline (Rafnsson et al., 2013; Crichton et al., 2013). Only one of the two PCS showed a significant association. Based on this evidence, it is not possible to draw a conclusion on the relationship between flavonoids intake and cognitive performance.

Caffeine

6.22 Five reviews were identified that considered caffeine intake and cognition. Of these, 2 included a meta-analysis (Kim et al., 2015; Santos et al., 2010a) and 3 were narrative systematic reviews (Panza et al., 2015; Beydoun et al., 2014; Arab et al., 2013). Where reviews on caffeine intake also considered tea or coffee consumption, the results on tea and coffee are also reported.

6.23 Kim et al. (2015) conducted a meta-analysis of 9 PCS with follow-up periods between 1.3 and 6.3 years for 7 of the studies; the other 2 had follow-ups at 21 and 28 years. Participants were aged 55 years and above in all studies. No association was found between caffeine intake and cognitive disorders combined (AD, dementia, and cognitive decline) (RR 0.96, 95%CI 0.73, 1.28) and neither coffee nor tea intake alone was significantly associated with cognitive disorders. The highest and lowest categories from each PCS were compared in the meta-analyses, however, there was large variability between studies, for example, the highest category of coffee and tea intake ranged from 'ever' drunk tea to >8 cups/d, and the lowest category ranged from 'none' to 0-2 cups/d. Participants with identical intakes could, therefore, have been classified as being in either the lowest or highest category, depending on the study.

6.24 Santos et al. (2010a) conducted a meta-analysis of 9 PCS, 5 of which are also included in the meta-analysis by Kim et al. (2015). The 9 studies had follow-up periods ranging from 1.3 years to 28 years and contributed 18,088 participants to the meta-analysis. No significant association was found between caffeine

intake and a combined measure of cognitive impairment, decline, and dementia (RR 0.93, 95%CI 0.83, 1.04; $I^2=0\%$).

- 6.25 Panza et al. (2015) systematically reviewed 16 PCS with caffeine intake (5 studies), coffee intake (8 studies), or tea intake (8 studies) as an exposure measured. Nine of the 12 studies included in either of the meta-analyses (Kim et al., 2015; Santos et al., 2010a) were also included by Panza et al. (2015). Definitions of high and low intakes of caffeine, coffee, or tea are not reported for each study. Mean intakes ranged from 32 to 550 mg of caffeine per day, or for studies reporting coffee and/or tea intake, mean intakes were <1 to 5.4 cups per day for coffee and < 1 cup per day for tea.
- 6.26 Eleven of the 16 PCS assessed cognitive impairment or decline as an outcome. Higher intakes of caffeine, coffee, or tea were significantly associated with less cognitive decline or impairment in 8 of the 11 PCS. Of these studies, one was a male-only PCS, 2 were female-only PCS and another 2 only found a significant association in female participants. An additional all-male PCS found a significant association between cognitive decline and intakes of coffee with a J-shaped curve, where the lowest level of decline was found for 3 cups of coffee per day. Two PCS found no association between caffeine or coffee intake and cognitive impairment or decline.
- 6.27 Seven of the 16 PCS assessed dementia or AD as an outcome. Of these, 5 studies found no association between caffeine (1 study), coffee (3 studies), or tea (3 studies) intake and incident risk of dementia or AD. In 2 PCS, lower incidence of AD was associated with higher intakes of coffee but not tea. The authors conclude that some evidence suggests a protective effect of caffeine, coffee, or tea consumption against cognitive impairment, decline and dementia, with a stronger association in women than men. However, there was no distinct dose-response relationship.
- 6.28 Beydoun et al. (2014) conducted a systematic review with 11 PCS included, only one of which was not included in Panza et al. (2015). The authors judged there was not enough comparable data between studies on the exposure (caffeine, coffee, or tea intake) for a meta-analysis to be performed. The one additional study not already discussed in Panza et al. (2015) included 923 adults with mean baseline age of 70 years. The authors stated that higher intake of coffee was associated with higher cognitive function, but higher intake of tea was associated with lower cognitive function. Beydoun et al. (2014) do not draw any conclusion on the association between caffeine intake and cognitive outcomes, commenting that the evidence is too limited.
- 6.29 Arab et al. (2013) conducted a systematic review of tea, coffee, or caffeine consumption on cognitive decline. The review included 6 PCS, 5 of which were included in the review by Panza et al. (2015) and the 6th included in the meta-analysis by Kim et al. (2015). Arab et al. (2013) concluded that although there is no dose-response relationship, cognitive decline tended to be lower in

caffeine, coffee, and/or tea consumers, with a stronger association in women than men.

Limitations of evidence base on caffeine

- 6.30 Caffeine intake was measured through coffee and tea intake in the majority of studies, with foods containing caffeine such as chocolate, or other caffeinated drinks not included in the analysis. There are also concerns around whether studies considered caffeinated versus decaffeinated coffee intake, and the type of tea consumed. The caffeine content is different, for example, between green tea and black tea and therefore will affect any conversions to caffeine intake and the comparability between studies. Any observed effect may not be due to caffeine, but due to other substances contained within caffeinated drinks.
- 6.31 The reviews mostly did not report how the primary studies defined and quantified high and low intake categories of caffeine, tea or coffee. Where it was reported, there appeared to be high variability between different studies. While some studies converted intakes to standard cups of coffee, others reported caffeine intake in milligrams/day, or simply 'regular' versus 'non-regular' coffee and tea intake, or 'drinks tea/coffee' versus 'non-drinker'. Therefore, participants with identical intakes could have been categorised in either a high or low intake category depending on the study. These methodological variabilities between studies make it difficult to compare their results and to summarise their findings in valid conclusions.

Summary – Caffeine

- 6.32 In total, 5 reviews considered caffeine intake, two of which included meta-analysis. These 5 reviews included 19 primary PCS (20 publications), 14 of which were included in one or both of the 2 meta-analyses.
- 6.33 The 2 meta-analyses did not provide evidence of a significant association between caffeine intake and cognitive outcomes. One of these 2 meta-analyses also considered coffee and tea consumption, and found no significant associations with cognitive outcomes.
- 6.34 Of the 3 systematic reviews that did not include meta-analysis, two concluded that there was some evidence that the consumption of caffeine, coffee or tea was associated with better cognitive outcomes and that this association was stronger in women than men, however there was little evidence of a dose-response relationship. The third systematic review did not provide a conclusion due to the scarcity of available evidence.
- 6.35 The available evidence is limited in that the exposure definitions used by different studies are highly variable. In addition to the usual caveats around residual confounding in observational studies there are also specific concerns

around how caffeine intake was estimated, as the assumed caffeine content of coffee and tea varied between studies.

- 6.36 Overall, the evidence from the 2 meta-analyses is limited and indicates that over the longer term there is no association between caffeine intake and cognition.

Overall summary – Polyphenols, flavonoids and caffeine

- 6.37 For polyphenols, evidence from trials was inconsistent and there was insufficient evidence from epidemiological studies to draw a conclusion on the association between polyphenols intake and cognition.
- 6.38 For flavonoids, the reviewed literature provided insufficient evidence to draw any conclusions on the association between flavonoids intake and cognition.
- 6.39 For caffeine, the evidence from the reviewed literature is limited and indicates that there is no association between caffeine intake and cognition.

7 Limitations of the evidence base

- 7.1 RCTs identified in systematic reviews and meta-analyses were generally of short duration with many lasting only a few weeks. Dementia, including AD, develops over many years and supplementation with individual nutrients for a few weeks is unlikely to be long enough to show an effect on cognitive function or decline. Due to small sample sizes many RCTs also lacked the statistical power to detect an effect of an intervention, for example the systematic review by Rodriguez-Martin et al. (2001) identified 3 RCTs which together provided data on fewer than 50 participants.
- 7.2 Observational studies make up the bulk of the available evidence in this field. Compared with RCTs, the observational studies identified in systematic reviews and meta-analyses were generally of longer duration - some with follow-up periods of more than 20 years - and included greater numbers of participants. However these types of studies are potentially subject to bias, confounding and reverse causality because of the links between cognitive ability, cognitive decline, and a wide range of behaviours and exposures relevant to cognitive decline; for example, IQ and socio-economic position are considered to have an impact on the development of MCI, dementia and AD, and are also associated with dietary choices. These complex associations make it difficult to infer links between diet and cognitive decline. Furthermore, while a number of systematic reviews and meta-analyses report that the primary studies included appropriate adjustment for potential confounding by dietary and lifestyle factors, much of the evidence on individual nutrients and cognitive impairment, cognitive decline and risk of dementia and AD comes from meta-analyses which did not specify whether the primary studies had included adjustment for confounding factors.
- 7.3 Many of the systematic reviews and meta-analyses identified and discussed in this position statement included publications which considered a combination of cognitively healthy adults and adults with MCI, dementia and/or AD. The findings relating to cognitively healthy and cognitively impaired adults were reported separately in most publications. Findings relating to those with MCI, dementia and AD were often reported together. Many studies did not differentiate between the most prevalent types of dementia (AD, vascular dementia) or considered just AD. It may be important for research to differentiate between dementia types, as a nutrient's effect in preventing dementia may differ, depending on the dementia type.
- 7.4 Primary studies used a wide variety of tests to measure cognitive function with only some studies looking at risk of dementia or AD. This made it difficult to compare findings from different studies, and many authors of the meta-analyses and systematic reviews concluded it was not possible to combine data using a variety of tests in meta-analyses.

Supplementation doses of individual nutrients varied widely and in some cases were combined with other nutrients making it hard to interpret findings. In most studies supplements were taken orally however in some they were administered via injection; whether this would make a difference to the findings is not clear.

8 Overall summary and conclusion

- 8.1 Much of the available evidence on nutrition and cognitive impairment and dementias is based on observational studies. Whilst many of these studies adjust for a range of potential confounders, the possibility of residual confounding or reverse causality remains. To provide reliable evidence, cohorts need to be well controlled for confounding factors, including childhood cognitive ability. While evidence from birth-cohorts is especially valuable in this respect, little evidence of this kind is available. Few studies assessed cognition at intermediate time points to allow for internal validation or for the estimation of time periods before associations are observed. The considered systematic reviews and meta-analysis did not report whether included cohort studies assessed the potential impact of reverse causation by excluding the first years of follow-up.
- 8.2 The reviewed literature suggests that adherence to a Mediterranean dietary pattern is associated with a reduced risk of mild cognitive impairment and dementias, including Alzheimer's disease. However, most of the evidence was observational (only one RCT was identified) and potentially subject to residual confounding and reverse causality. Further evidence is required to establish whether this association signifies a protective effect of a Mediterranean dietary pattern, or of specific dietary components of such a pattern. There was no evidence of protective effects for any of the individual nutrients thought to account for the health benefits of Mediterranean dietary patterns.
- 8.3 There was insufficient evidence to draw any conclusions on the association between 'healthy' dietary patterns, other than Mediterranean diets, and risk of cognitive impairment.
- 8.4 There was insufficient evidence to draw any conclusions on the association between individual nutrients (B vitamins, vitamins C and E and omega-3 fatty acids) and risk of cognitive decline or cognitive impairment.
- 8.5 There was insufficient evidence to draw any conclusions on the association between polyphenols (including flavonoids) and cognition. For caffeine, the evidence provided by the reviewed literature is limited and indicates that there is no association between caffeine intake and cognition over the longer term.
- 8.6 Further risk assessment will only be warranted when more high quality evidence becomes available.

9 Research recommendations

- 9.1 In relation to dietary patterns more evidence is needed from RCTs and from longer follow-up PCS. Research on dietary patterns that meet UK dietary recommendations would be particularly helpful in informing dietary advice and policy.
- 9.2 Cohorts need to be well controlled for relevant confounding factors, including childhood cognitive ability. Evidence from birth-cohorts would be especially valuable in this respect. RCTs and PCS should be designed in a way that allows for more definitive conclusions to be drawn regarding potentially effective components of the diet.
- 9.3 Cognitive assessments at intermediate time points would allow for internal validation and better identification of the time period required before 'effects' may be observed.
- 9.4 There is an increasing focus on multi-domain interventions in this field and there is a need to strengthen methodological and statistical approaches to help identify the specific role of diet and nutrition.
- 9.5 Research is needed to establish the role of individual nutrients in diets which confer protection, whether whole dietary interventions are needed to provide benefit, and the role of specific nutrient interactions.
- 9.6 More research is needed to establish which non-dietary factors (including alcohol) may confound the relationship between nutrition and cognitive decline.
- 9.7 While some cohort studies do report on the association between early nutrition and early cognitive outcomes, more research is needed on the long-term effects of early nutrition on risk of later life cognitive impairments.
- 9.8 The various dementia types differ in their underlying pathologies. It may therefore be important for studies to consider different types of dementia (e.g. vascular, non-vascular and AD) separately as diet and nutrition could influence their development in different ways.
- 9.9 Research is needed to establish the prevalence of cognitive impairment among UK black, Asian and minority ethnic groups. Research is also needed to establish if the relationship between diet, cognition and dementias differs between ethnic groups in the UK.

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Annex 1:

Studies reporting on non-dietary factors affecting risk of cognitive impairment and dementias

A1.1 This annex reports on the evidence from studies which report on non-dietary factors that may affect risk of cognitive impairment and dementias. The evidence from these studies may help policy makers consider which dietary or non-dietary interventions may be most efficient to reduce the incidence of cognitive impairment and dementias. The evidence may also be relevant to the interpretation of the dietary evidence. A summary of this evidence is provided in the chapter 'Non-dietary factors affecting risk' (p.10).

Modifiable factors per se

A1.2 **Cooper et al. (2015)** conducted a systematic review and meta-analysis of longitudinal studies reporting on potentially modifiable factors affecting conversion from mild cognitive impairment to incident all-cause dementia (including AD). Where data from 3 or more studies were available the unadjusted results were pooled in the meta-analyses.

A1.3 For a history of ever having smoked, a pooled analysis of 3 studies found a significant association (unadjusted OR 0.45, 95%CI 0.24, 0.84). However, none of the 3 studies showed significant results after adjustment for age (results adjusted for other factors are not stated). Taking account of additional studies not included in meta-analysis, the authors concluded that there was consistent evidence from 'higher-quality' studies that smoking was not associated with conversion from mild cognitive impairment (MCI) to dementia.

A1.4 The evidence on conversion from MCI to dementia was reviewed for a number of neuropsychiatric symptoms. A pooled analysis of 4 clinical studies showed a significant association of having neuropsychiatric symptoms¹⁴ and conversion from MCI to dementia (unadjusted OR 3.11, 95%CI 1.38, 7.02). For individuals with depression, a pooled analysis of 13 studies did not show a significant association of having depressive symptoms and conversion from any-type MCI to all-cause dementia. (unadjusted OR 1.35, 95%CI 0.89, 2.06). However, on the basis of 2 large studies not included in the pooled analysis (reasons for exclusion not stated) the authors concluded that there was consistent evidence from higher-quality studies in non-clinical settings that more depressive symptoms predicted conversion from MCI to dementia. For apathy,

¹⁴ Study participants were assessed with a least one symptom on the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). The NPI assesses the following 12 neuropsychiatric symptoms: delusions; hallucinations; agitation; dysphoria; anxiety; apathy; irritability; euphoria; disinhibition; aberrant motor behaviour; night-time behaviour disturbances; and appetite and eating abnormalities.

a pooled analysis of 5 studies showed no significant association of apathy symptoms and conversion from MCI to dementia (unadjusted OR 1.62, 95%CI 0.63, 4.17). For anxiety, a pooled analysis of 3 clinical studies showed no significant association of anxiety scores and conversion from MCI to dementia (standardised effect size -0.11, 95%CI -0.34, 0.11).

- A1.5 A pooled analysis of 12 studies showed no significant association between years of education and conversion from MCI to dementia (standardised effect size -0.11, 95%CI -0.26, 0.03). Taking account of additional studies and meta-analyses, the authors concluded that there is consistent evidence from higher-grade studies that there is no association between years of education and conversion from MCI to all-cause dementia, or conversion from amnesic MCI to AD.
- A1.6 In relation to risk factors modifiable by dietary means, Cooper et al. (2015) reviewed 3 cardio-metabolic risk-factors (diabetes, hypertension and hypercholesterolemia) and carried out pooled analyses for conversion from MCI to dementia. For diabetes, a pooled analysis of 7 studies showed a significant association (unadjusted OR 1.65, 95%CI 1.12, 2.43). For hypertension, a pooled analysis of 7 studies showed no significant association (unadjusted OR 1.19, 95%CI 0.81, 1.73). For hypercholesterolemia, a pooled analysis of 3 studies showed no significant association (unadjusted OR 0.92, 95%CI 0.50, 1.68).
- A1.7 In comparison to the number of studies on non-dietary factors affecting the risk of cognitive impairment, the systematic review by Cooper et al. (2015) identified only few studies related to dietary factors. A single study was identified which considered Mediterranean dietary patterns. Evidence from this is discussed in chapter 4 (p.17). Cooper et al. (2015) also identified 2 studies in relation to serum folate levels and 2 studies in relation to homocysteine levels. Evidence in relation to these 2 factors is considered in chapter 5 (p.27).
- A1.8 **Barnes & Yaffe (2011)** estimated the percentage of AD cases attributable to a given modifiable risk factor (population attributable risk [PAR]). The study authors selected 7 risk factors for which the evidence appeared to be most consistent. Diet was not considered 'due to heterogeneity in the types of dietary factors studied and lack of data on prevalence'.
- A1.9 For the 7 considered risk factors, the PARs for the United States were estimated as: physical inactivity (PAR 21.0%, 95%CI 5.8%, 36.6%); depression (PAR 14.7%, 95%CI 9.6%, 20.3%); smoking (PAR 10.8%, 95%CI 3.0%, 19.8%); mid-life hypertension (PAR 8.0%, 95%CI 2.2%, 15.1%); mid-life obesity (PAR 7.3%, 95%CI 4.3%, 10.8%); low education (PAR 7.3%, 95%CI 4.4%, 10.3%); diabetes (PAR 3.3%, 95%CI 1.5%, 5.4%). The PAR for all 7 risk factors combined was estimated as 54.1% (maximum).

- A1.10 **Deckers et al. (2015)** undertook a systematic literature review of modifiable factors that may increase or reduce dementia risk. The systematic review was combined with an online Delphi consensus study among 8 international experts in dementia epidemiology and prevention. Diet was only one of many modifiable factors of dementia risk that were identified in the systematic literature review and in the Delphi consensus.
- A1.11 In the Delphi consensus, each expert assigned points to modifiable factors of dementia risk, based on each factors' considered importance in influencing dementia risk (in either a detrimental or beneficial direction). Based on the total number of points assigned by the 8 experts (expert score), 11 modifiable factors of dementia risk were ranked in the following order: 1) depression (120 points) 2) diabetes (115 points); 3) high cognitive activity (113 points); 4) high physical activity (111 points); 5) hypertension (108 points); 6) Mediterranean diet (64 points); 7) obesity (midlife) (50 points); 8) smoking (46 points); 9) low/moderate alcohol (37 points); 10) high cholesterol (31 points); 11) coronary heart disease (5 points).
- A1.12 Mediterranean diet was ranked as the 6th most important modifiable factor of dementia risk with a considerable lower Delphi expert score (64 points) than the preceding factor hypertension (108 points). The other factors modifiable through diet were diabetes (rank 2; expert score 115), hypertension (5; 108), midlife obesity (7; 50); alcohol (9; 37), high cholesterol (10; 31) and coronary heart disease (11; 5). Based on the systematic literature review Deckers et al. (2015) concluded that diet (as well as coronary heart disease and cognitive ability) were modifiable factors of dementia risk that required further validation because of a paucity of available studies or inconsistent results. Deckers et al. (2015) note that there was a lack of consensus among the experts on possible interactions among the identified modifiable factors of dementia risk.
- A1.13 **Di Marco et al. (2014)** carried out a systematic review of a broad range of lifestyle factors that may affect dementia. The review did not include pooled analyses for any of the considered risk factors. While Di Marco and colleagues conclude that 'conflicting results are reported on the putative role of healthy dietary habits (MeDi, dietary antioxidants, omega-3 fatty acids, regular fish consumption)' they draw firmer conclusions for some of the non-dietary lifestyle factors considered in their review. They note a broad consensus on the beneficial role of leisure activities (including physical, social and cognitively stimulating activities) in lowering dementia risk.
- A1.14 The authors conclude further that 'some studies also suggest a protective role of living with others', a factor that may co-vary with dietary intakes. Four studies considered the influence of living arrangements or marital status on dementia risk. One study reported a reduced dementia risk for those living with family (OR 0.36, 95% CI 0.16, 0.80). Another study reported a higher AD risk for those who had never been married (RR 2.31, 95% CI 1.14, 4.68). A third study found similar dementia risks for those who were married or single, but a

borderline higher risk for those living alone (RR 1.5, 95% CI 1.0, 2.1). A fourth study found a non-significant association in the opposite direction (lower risk) between living alone and dementia risk (HR 0.77, 95% CI 0.56, 1.07).

A1.15 The findings by Di Marco et al. (2014) on dietary patterns are presented in chapter 4 (p.21).

Alcohol intake

A1.16 **Anstey et al (2009)** report on a meta-analysis of 15 PCS that showed that light to moderate alcohol consumption in older adults was associated with a 25-28% reduction in risk of Alzheimer's disease; (RR 0.72, 95% CI 0.61, 0.86), vascular dementia (RR 0.75, 95% CI 0.57, 0.98) and any dementia (RR 0.74, 95% CI 0.65, 0.99), compared with non-drinkers (Anstey et al., 2009). In this study, heavy drinking was not associated with increased risk in any of the outcomes although heavy drinkers may have been excluded, lost at follow-up or have died, which would bias the results.

A1.17 **Di Marco et al (2014)** reported in a systematic review of 15 longitudinal studies (Di Marco et al., 2014) that light to moderate alcohol consumption¹⁵ is associated with a reduced risk of dementia compared with non-drinking. However 3 studies showed no association between alcohol consumption and the risk of dementia. One of these studies, and one further study, showed an increased risk for APOE-ε4 carriers who drank once or several times per month, when compared with less-frequent drinkers (HR 7.42, 95% CI 1.51, 36.38) (OR 7.07, 95% CI 1.37, 36.60).

A1.18 **Cao et al (2016)** reported in a meta-analysis of 8 cohort studies a statistically non-significant association between alcohol consumption and the risk of any dementia (risk ratio = 0.74, 95% CI = 0.55, 1.01) (Cao et al., 2016). The study does not state what alcohol intake levels were compared. There was significant heterogeneity between studies ($I^2 = 69\%$, $p = 0.002$).

A1.19 **Ilomaki et al. (2015)** provided an overview of 3 systematic reviews of longitudinal observational studies. One systematic review found that light to moderate drinking vs no drinking¹⁶ was associated with a reduced risk of Alzheimer's disease (pooled risk ratio [RR] 0.72, 95% CI 0.61, 0.86), vascular dementia (RR 0.75, 95% CI 0.57, 0.98) and any dementia (RR 0.74, 95% CI 0.61, 0.91). Heavy to excessive drinking vs no drinking¹⁶ was not associated with either AD (RR 0.92, 95% CI 0.59, 1.45), vascular dementia (RR 1.36, 95% CI 0.68,

¹⁵ Studies used various alcohol levels and measures to define light to moderate consumption. Example lower limits for light consumption include: any drinking; >8g alcohol / week; > 1 alcohol unit per day; >1 drink per week; >1 serving per month. Example upper limits for moderate consumption include: for men (women) <168g (112g) alcohol/week; <=1 drink/day; <21 alcohol units/week; <3 servings/day; <5 standard glasses.

¹⁶ alcohol consumption categories as defined in primary articles that were included in systematic review.

2.71) or any dementia (RR 1.04, 95% CI 0.69, 1.56). Another systematic review considered the link between alcohol consumption and AD and identified 7 studies which reported a protective association, 2 studies which reported a detrimental association and 7 studies which reported no association. None of the systematic reviews considered drinking patterns or former drinkers who were now alcohol abstainers.

Physical activity

- A1.20 **Barnes & Yaffe (2011)** estimated that 21% (95% CI 5.8%, 36.6%) of AD cases were attributable to physical inactivity. In a Delphi consensus study, experts ranked high physical activity as the 4th most important factor of dementia risk, behind depression, diabetes and high cognitive activity (Deckers et al., 2015).
- A1.21 In the Lothian Birth Cohort (**Gow et al 2012**), after controlling for age-11 IQ and social class, physical activity (at age 70) was significantly associated with general cognitive performance and processing speed (both at age 70), explaining around 1% of the observed variance in each (Gow et al., 2012).
- A1.22 A 2014 report by **Alzheimer's Disease International** concluded that the evidence on physical activity and dementia from observational studies is inconsistent, while there is a lack of evidence from RCTs (ADI, 2014).

Annex 2: Assessing the effects of confounding through longitudinal studies

A2.1 Many large UK longitudinal studies hold information that allows the effects of a number of potential confounders to be assessed and provide insights into early life factors thought to influence the cognitive trajectory across the life-course. Important UK longitudinal studies include: the Medical Research Council (MRC) National Survey of Health and Development; National Child Development Study; English Longitudinal Study of Ageing; Avon Longitudinal Study of Parents and Children (ALSPAC); Lothian Birth Cohort (Deary et al., 2007); Aberdeen Birth Cohort (Whalley et al., 2011); and the Boyd Orr Cohort (Martin et al., 2005).

Early life exposures and cognition in childhood

A2.2 Few of the cohorts in which the participants are old enough to experience significant cognitive decline also hold detailed information on diet in early life; the Boyd Orr cohort may be an exception although it was not set up to study cognition in later life. Studies in cohorts where the participants were still relatively young (e.g. ALSPAC) report associations between early nutrition and early cognitive outcomes (intelligence) that are themselves associated with later cognitive decline. However, the potential for residual confounding remains in these studies.

A2.3 Assessment of the long-term effects on cognition of nutrition in early life is complicated by the fact that children whose parents have lower cognitive ability scores also have poorer health and selected health behaviours independent of socioeconomic status and the child's own cognitive ability (Whitley et al., 2013). Interpretation of the independent effects of nutrition in childhood or later life may also be complicated by the persistence of some dietary patterns across the life-course. For example, data from the surviving members of the Boyd Orr cohort aged 61-80 years indicate that vegetable consumption in childhood is related to diet quality in early old age (Maynard et al., 2006).

A2.4 Longitudinal studies have shown that higher childhood socioeconomic status predicts larger hippocampal volumes more than 50 years later (Staff et al., 2012), while larger hippocampal volumes have been associated 'with preserved cognitive function during life despite a high burden of AD pathologic lesions at death' (Erten-Lyons et al., 2009). Hyperintensities on brain magnetic resonance imaging (MRI)¹⁷ are associated with vascular risk factors, cognitive decline, dementia and death. Childhood socioeconomic circumstance predicts

¹⁷ Physiological changes that have been associated with areas of brain hyperintensities in magnetic resonance imaging include demyelination and dilated perivascular spaces (Thomas et al., 2002).

the burden of brain white matter hyperintensities at age 68 years (Murray et al., 2014). The mechanism underlying this effect is unknown, but it has been proposed that it may act through early life programming of cerebrovascular disease (Murray et al., 2014).

- A2.5 While all nutrients are important for development, evidence mainly from animal studies suggests that some nutrients (such as protein, iron, zinc, copper, iodine, selenium and folate) and other dietary components (such as omega-3 long-chain polyunsaturated fatty acids, glucose and choline) which have important functions in the developing brain may influence processes such as neurogenesis, neuronal differentiation, myelination and synaptogenesis (Ramel & Georgieff, 2014).

Specific dietary exposures for which there is limited evidence

- A2.6 This section briefly summarises role of early life exposure to dietary factors for which there was limited evidence: iodine, copper, selenium, long-chain fatty acids and differing dietary patterns during pregnancy.

Iron

- A2.7 Studies in mice have demonstrated that changes which occur in brain function as a consequence of altered iron are related to the actual iron status rather than anaemia (Carlson et al., 2009). In humans there is some evidence that the consequences of iron deficiency in the pre- and perinatal period may be important. The effects are diverse, and can have long-term consequences, such as general reduction in intelligence, reduced learning and memory capacity and altered abilities to undertake social interactions (Fretham et al., 2011; Lukowski et al., 2010; Georgieff, 2011).

Iodine

- A2.8 Iodine deficiency can also have long-term consequences for the developing foetus and neonate (Hetzl, 1983; SACN, 2014). However, the evidence on iodine was not sufficient to be assessed further in this statement. SACN's report on *Early Life Nutrition* noted that a high proportion of women of child-bearing age have iodine intakes below the lower nutrient reference nutrient intake (SACN, 2011). SACN reviewed the evidence on iodine in 2014 (SACN, 2014). A three-year research project on iodine in pregnancy has been commissioned on behalf of SACN and, at the time of writing, is in progress.

Copper

- A2.9 There are many studies in experimental systems that show a critical role for copper in the development of the central nervous system. Early studies in sheep demonstrated that copper deficiency during pregnancy results in severe brain damage, mostly related to myelin formation. From the phenotype in sheep, it was demonstrated that Menkes disease, a neurological inherited condition, was also caused by copper deficiency, as a result of mutations in one of the copper transport ATPases (Kaler, 2011). Less severe forms of this disease

have also been identified, which show continuing neurological effects (Tchan et al., 2013), but there are very limited data showing that dietary copper deficiency in humans can occur to the extent that cognitive function is disturbed. There was a paucity of relevant evidence in humans on copper and the prevention of cognitive impairment and dementias. Copper was therefore not considered further in this position statement.

Selenium

- A2.10 A study in Poland suggests that selenium status can be positively associated with motor development and cognitive score in the offspring at 2 years of age (Polanska et al., 2016), which agrees with data published from a Bangladeshi cohort (Skröder et al., 2015). However, a Chinese study suggests that there may be a U-shaped relationship between selenium status and Neonatal Behavioural Neurological assessment (Yang et al., 2013).

Long-chain polyunsaturated fatty acids

- A2.11 A number of large randomised control trials (RCTs) have been carried out to investigate the effect of long-chain polyunsaturated fatty acids (LCPUFA) supplementation in pregnancy on neuro-behavioural outcomes in the offspring. When the mother is provided with supplemental LCPUFA during pregnancy there is little evidence of a beneficial effect on neuro-behavioural outcomes in children born at term (Makrides, 2013; Makrides et al., 2011; Makrides et al., 2009; Smithers et al., 2011; Gould et al., 2013).

Dietary patterns during pregnancy

- A2.12 Data prospectively collected from women during pregnancy and children up to age 8 years participating in the Avon Longitudinal Study of Parents and Children (ALSPAC) report an association¹⁸ between low maternal seafood intake and suboptimum outcomes related to cognition (prosocial behaviour, fine motor, communication, and social development scores) (Hibbeln et al., 2007). The same ALSPAC study was used to identify dietary patterns that were related to IQ (measured using the Wechsler Intelligence Scale for Children at 8 years) (Smithers et al., 2012)¹⁹. At all ages (6, 15 and 24 months), diets characterised by a higher intake of biscuits, chocolate, sweets, soda, crisps were associated with 1-2 point lower IQ whilst those characterised by home-prepared foods higher in herbs, legumes, cheese, raw fruit and vegetables were associated with 1-2 point higher IQ. At 6 months, a dietary pattern

¹⁸ Analysis was adjusted for: sex of child, age of the mother, parity, maternal educational attainment, housing status, crowding, stressful life events at 18 weeks of gestation, partner at time of birth, smoking status, alcohol use, breastfeeding, ethnicity, family adversity index during pregnancy, measure of parenting, birthweight, gestation at delivery and 12 food groups (sausages/burgers, pies/ pasties, red meat, poultry, green leafy vegetables, other vegetables, salad, chips, fresh fruit, fruit juice, crisps, and biscuits).

¹⁹ The study adjusted all models for sex of child, gestational age, birth weight, ethnicity, singleton/twin, maternal age, parity, maternal education, social class, smoking, marital status, family income, home score and other children.

referred to in the study as “Home-made traditional pattern” (meat, cooked vegetables, desserts) was positively associated with higher IQ scores (at age 8y), but there was non-significant inverse association at 15 or 24 months. Negative associations were found with patterns characterized as “ready-prepared” baby foods at 6 and 15 months and positive associations with a “ready-to-eat” foods pattern at 24 months. The investigators suggest that dietary patterns from 6 to 24 months may have a small but persistent effect on IQ at 8 years (Smithers et al., 2012). The study does not state if findings were adjusted for multiple testing.

Early life exposure and cognition in adulthood

- A2.13 Links between nutrition and age-related neurodegeneration have been reported in brain MRI studies in the Aberdeen Birth Cohort: lower grey matter volume has been associated with lower plasma vitamin C and blood cell folate and higher homocysteine, total cholesterol and low-density lipoprotein (LDL) cholesterol (Whalley et al., 2003), however, these associations were not adjusted for childhood intelligence.
- A2.14 Total omega-3 polyunsaturated fatty acid (PUFA) and docosahexaenoic acid (DHA) concentrations in erythrocyte membranes were associated with improved cognition at approximately 64 years and between 64 and 68 years. After adjustment for sex, APOE genotype, and IQ at 11 years, the association with total omega-3 PUFA remained significant (Whalley et al., 2008). Further studies in the cohort – born in 1921 and without dementia at age 77 years and followed up to age 88 years – found high homocysteine concentrations associated with greater risk of dementia and the association was independent of plasma folate, B12 and antioxidant micronutrient status after adjustment for age, sex, childhood IQ, education, socioeconomic deprivation, presence of heart disease and hypertension (Whalley et al., 2013).
- A2.15 Reported links between nutrition and cognitive decline may also be partly modulated by APOE genetics. It has been reported that higher erythrocyte omega-3 PUFA and DHA concentrations are associated with a reduced rate of cognitive decline in later life after adjustment for sex and childhood IQ but only in the absence of the APOE-ε4 allele (Whalley et al., 2008).
- A2.16 A number of studies in the Lothian Birth Cohort have addressed the link between diet and related factors and cognition in later life. In this cohort, IQ at age 11 years predicted the dietary intake of vitamin C, riboflavin, and the likelihood of taking folate supplements, at age 70 years (McNeill et al., 2011), highlighting the potential for childhood IQ to account for many of the reported associations between adult diet and cognition in later life.
- A2.17 Studies of dietary patterns (described as "Mediterranean-style," "health aware," "traditional" and "sweet foods") in relation to cognitive performance

in old age have been carried out in the Lothian Birth Cohort. A "Mediterranean-style"²⁰ dietary pattern was associated with significantly better cognitive performance whilst the "traditional" dietary pattern was associated with poorer performance on all cognitive domains measured in old age. After adjustment for childhood IQ and socioeconomic status, statistical significance was lost for most associations, with the exception of verbal ability/crystallised intelligence (National Adult Reading Test and the Wechsler Test of Adult Reading) (Corley et al., 2013). Further studies in the Lothian Birth Cohort suggest that intake of total fruit, citrus fruits, apple and tea intakes and flavanone intakes were associated with better cognitive test performance in later life but these associations were no longer significant after adjusting for IQ and other confounding variables (Butchart et al., 2011).

- A2.18 Associations have been reported between intake of vitamins B12, C and folate and cognitive performance at age 70 years in models adjusted for a range of variables, including IQ at age 11 years. In the fully adjusted models, the proportion of total variance in cognitive function at age 70 years accounted for by intake of these nutrients was less than 1% (McNeill et al., 2011).
- A2.19 There was a paucity of relevant evidence in humans on iron, zinc, iodine, copper, selenium or protein and the role of these nutrients in the prevention of cognitive impairment and dementia was therefore not considered in detail this position statement.
- A2.20 Moderate alcohol consumption was associated with better memory performance and verbal ability in late adulthood. Prior intelligence and socioeconomic status are both related to amount and type of alcohol intake and can explain some of the link between alcohol intake and improved cognitive performance at age 70y (Corley et al., 2011). After adjustment for both, prior intelligence and socioeconomic status, alcohol consumption was found to make a small, independent contribution to memory performance and verbal ability (Corley et al., 2011).
- A2.21 People classified as overweight or obese in later adulthood (aged about 70) had significantly lower scores on tests of childhood IQ, IQ at age 70y, g factor (general intelligence factor) and verbal ability (Corley et al., 2010a). After adjusting for childhood IQ and social class the associations with later cognition were mostly non-significant or attenuated though BMI predicted verbal ability (crystallized intelligence) regardless of IQ at age 11y, social class, health behaviours and health measures (Corley et al., 2010a).

20 The "Mediterranean-style" dietary pattern was one of four patterns established through principal component analysis. The dietary pattern "was defined by greater consumption of vegetables (such as leeks or courgettes, broccoli, salad vegetables) and also had positive loadings from fish, poultry, pasta, rice, water, tomato-based sauces, oil and vinegar dressing, and beans" (Corley et al., 2013).

A2.22 The association between physical activity and cognitive abilities has been studied in the Lothian Birth Cohort. When IQ at age 11y and adult social class were controlled, physical activity at age 70 remained significantly and positively associated with general cognitive ability and processing speed at age 70y (Gow et al., 2012). The study did not adjust for markers of ill health, alcohol consumption or smoking.

Conclusions on potential confounders

A2.23 The nature of the links between cognition and nutritional exposures makes it particularly difficult to interpret the findings of the observational studies that make up the bulk of the available evidence in this field. While many large UK longitudinal studies hold information that allows the effects of confounders to be assessed and in some cases adjusted for the potential for residual confounding remains. Evidence based on these longitudinal studies can be considered indicative, but not conclusive.

A2.24 After adjustment for confounding factors, particularly prior intelligence, there remain a small number of significant associations between nutrition and cognition and cognitive decline²¹. The statistical power to detect associations in these studies is not stated and the significant associations are generally small in magnitude and their biological and functional significance is not clear.

²¹ See: paragraph A2.1A2.14 (Whalley et al., 2013) - significant association between total omega-3 PUFA and cognition; significant association between high homocysteine and increased dementia risk; paragraph A2.1A2.15 (Whalley et al., 2013) - higher erythrocyte omega-3 PUFA and DHA are associated with reduced rate of cognitive decline (in the absence of the APOE-ε4 allele); paragraph A2.1A2.17 (Corley et al., 2013) – ‘Mediterranean’/‘Traditional’ style dietary patterns were associated with better/worse verbal ability (crystallised intelligence); paragraph A2.1A2.18 (McNeill et al., 2011) weak but significant associations between intake of vitamins B12, vitamin C and folate and cognitive performance; paragraph A2.1A2.19 (Corley et al., 2011) – alcohol consumption was associated with memory performance and verbal ability; paragraph A2.1A2.21 (Corley et al., 2010a) – BMI was associated with worse verbal ability/crystallised intelligence.

Annex 3: Search strategy

Chapter 4 on 'Dietary patterns, cognitive impairment and dementias'

((("diet"[MeSH Terms] OR "diet"[All Fields] OR "dietary"[All Fields]) AND pattern[All Fields]) OR ("diet, mediterranean"[MeSH Terms] OR ("diet"[All Fields] AND "mediterranean"[All Fields]) OR "mediterranean diet"[All Fields] OR ("mediterranean"[All Fields] AND "diet"[All Fields])) OR (healthy[All Fields] AND ("diet"[MeSH Terms] OR "diet"[All Fields]))) AND (("mild cognitive impairment"[MeSH Terms] OR ("mild"[All Fields] AND "cognitive"[All Fields] AND "impairment"[All Fields]) OR "mild cognitive impairment"[All Fields]) OR ("Cogn Int Conf Adv Cogn Technol Appl"[Journal] OR "cognitive"[All Fields]) AND decline[All Fields]) OR ("dementia"[MeSH Terms] OR "dementia"[All Fields]) OR ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields] OR ("alzheimer's"[All Fields] AND "disease"[All Fields]) OR "alzheimer's disease"[All Fields])) AND (systematic[sb] OR Meta-Analysis[ptyp])

Chapter 5 on 'Nutrients, cognitive impairment and dementias' and chapter 6 on 'Other dietary components: polyphenols, flavonoids and caffeine'

((("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields]) OR ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields]) OR ("vitamin b complex"[Pharmacological Action] OR "vitamin b complex"[MeSH Terms] OR "vitamin b complex"[All Fields] OR "b vitamins"[All Fields]) OR ("vitamin b 6"[MeSH Terms] OR "vitamin b 6"[All Fields] OR ("vitamin"[All Fields] AND "b6"[All Fields]) OR "vitamin b6"[All Fields]) OR ("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields]) OR ("thiamine"[MeSH Terms] OR "thiamine"[All Fields] OR "thiamin"[All Fields]) OR ("thiamine"[MeSH Terms] OR "thiamine"[All Fields]) OR ("ascorbic acid"[MeSH Terms] OR ("ascorbic"[All Fields] AND "acid"[All Fields]) OR "ascorbic acid"[All Fields] OR "vitamin c"[All Fields]) OR ("vitamin e"[MeSH Terms] OR "vitamin e"[All Fields]) OR ("fatty acids, omega-3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega-3"[All Fields]) OR "omega-3 fatty acids"[All Fields] OR "omega 3"[All Fields]) OR ("fatty acids, omega-3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega-3"[All Fields]) OR "omega-3 fatty acids"[All Fields] OR "omega 3 fatty acids"[All Fields]) OR ("tryptophan"[MeSH Terms] OR "tryptophan"[All Fields]) OR ("phytochemicals"[MeSH Terms] OR "phytochemicals"[All Fields]) OR ("flavonoids"[MeSH Terms] OR "flavonoids"[All Fields]) OR ("polyphenols"[MeSH Terms] OR "polyphenols"[All Fields])) AND (("mild cognitive impairment"[MeSH Terms] OR ("mild"[All Fields] AND "cognitive"[All Fields] AND "impairment"[All Fields]) OR "mild cognitive impairment"[All Fields]) OR ("Cogn Int Conf Adv Cogn Technol Appl"[Journal] OR "cognitive"[All Fields]) AND decline[All Fields]) OR ("dementia"[MeSH Terms] OR "dementia"[All Fields]) OR ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields] OR ("alzheimer's"[All Fields] AND "disease"[All Fields]) OR "alzheimer's disease"[All Fields])) AND (Meta-Analysis[ptyp] OR systematic[sb])

Annex 4: Dietary Patterns – Summary of meta-analyses and systematic reviews

PTO

Table 2: Mediterranean dietary patterns and cognition: PCS and RCTs included in considered reviews

Citation	Assessed outcome	Systematic review or Meta-analysis	Statistical comparison	p<0.05	Wengreen et al. (2013)	Tsivgoulis et al. (2013)	Samieri et al. (2013b)	Samieri et al. (2013a)	Martinez-Lapiscina et al. (2013a)	Kesse-Guyot et al. (2013)	Vercambre et al. (2012)	Cherbuin & Anstey (2012)	Tangney et al. (2011)	Cherbuin et al. (2011)	Roberts et al. (2010)	Gu et al. (2010a)	Feart et al. (2009)	Scarmeas et al. (2009a)	Scarmeas et al. (2009b)	Psaltopoulou et al. (2008)	Scarmeas et al. (2007)	Gao et al. (2007)	Scarmeas et al. (2006a)	Scarmeas et al. (2006b)
Yusufov et al. (2016)	AD	SR	N/A	N/A												✓	✓	✓			✓			✓
Cao et al. (2016)	MCI & AD	MA	NS	Yes											✓		✓	✓	✓					✓
Cooper et al. (2015)	MCI & dementia	SR	N/A	N/A																				✓
Deckers et al. (2015)	Dementia	SR	N/A	N/A								✓					✓							
van de Rest et al. (2015)	MCI, dementia, cognitive function, cognitive decline.	SR	N/A	N/A	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓				
Xu et al. (2015)	AD	MA	NS	Yes													✓						✓	
Di Marco et al. (2014)	Dementia, AD	SR	N/A	N/A												✓	✓							✓
Singh et al. (2014)	Normal progressing to MCI	MA	a) T1 vs T3 b) T1 vs T2	a) Yes b) No											✓				✓					
	Normal progressing to MCI	MA	MeDi score (continuous var.)	No									✓						✓					
	Normal progressing to AD	MA	a) T1 vs T3 b) T1 vs T2 c) cont. MeDi	a) Yes b) No c) Yes													✓							✓
	MCI progressing to AD	MA	a) T1 vs T3 b) T1 vs T2 c) cont. MeDi	a) Yes b) Yes c) No														✓						
	Normal progressing to MCI; Normal progressing to AD; MCI progressing to AD;	MA	MeDi score (continuous variable)	Yes										✓				✓	✓	✓				✓
Lourida et al. (2013)	MCI, AD, dementia.	SR	N/A	N/A								✓		✓	✓	✓	✓	✓	✓					✓
Psaltopoulou et al. (2013)	Cognitive impairment (MCI & AD).	MA	MeDi adherence: a) high vs low b) med. vs low	a) Yes b) No											✓		✓	✓	✓					
Sofi et al. (2010)	Neurodegenerative disease (MCI, AD & Parkinson's).	MA	MeDi score (continuous var.)	Yes													✓		✓			✓		✓

AD=Alzheimer's disease; MCI=mild cognitive impairment; Normal=cognitively normal; T1, T2, T3=tertiles of MeDi score; MeDi=Mediterranean Diet Score; NS=not stated

Table 3: Results of meta-analyses on Mediterranean dietary patterns (or other ‘heathy’ dietary patterns) and cognitive impairment

Study	Selection criteria and adjustment for confounders	Health at baseline and outcome	Statistical comparison	Results	p<0.05	Comments / Conclusion
Cao et al. (2016)	<p><u>Selection criteria:</u> <i>Inclusion:</i> cohort studies on dietary patterns and incidence dementia (all-cause or AD) or MCI; white subjects; follow-up >=1 year; risk ratio and 95% CI available, or data from which these can be calculated; exposure: dietary pattern; outcome</p> <p><i>Exclusion:</i> cross-sectional studies; non-original research (e.g. reviews); duplicated studies</p> <p><i>Adjustment for confounders:</i> Adjusted effect estimates were used.</p>	<p>Normal progressing to MCI;</p> <p>Normal progressing to AD;</p> <p>MCI progressing to AD</p>	not stated	<p>5 PCS; No significant heterogeneity ($I^2=1\%$);</p> <p>RR 0.69 (95% CI 0.57-0.84);</p>	yes	This meta-analysis of 5 PCS showed a beneficial association for MD and cognitive impairment.
Xu et al. (2015)	<p><u>Selection criteria:</u> <i>Inclusion:</i> original study reporting OR or RR of AD; prospective cohort studies (case-control studies were also included by analysed separately); study population representative of general population;</p>	<p>Health at baseline: inclusion criteria required study population to be representative of general population</p> <p>Health outcome: AD (based on NINCDS-ADRDA criteria (National Institute of</p>	OR or RR of AD risk as given in component studies	<p>‘Healthy’ dietary pattern (incl. Mediterranean dietary patterns): 5 PCS (n=9,774; follow-up 4 to 14 years) (RR 0.46, 95% CI 0.23, 0.68) ($I^2=60\%$)</p> <p>Mediterranean dietary pattern: 2 PCS (n=3,668; follow-up 4 to 4.1 years) (RR 0.62, 95% CI 0.41, 0.84) ($I^2=0\%$)</p>	yes yes	The meta-analyses for both ‘healthy’ dietary patterns and Mediterranean dietary patterns both showed a beneficial association for AD incidence.

Study	Selection criteria and adjustment for confounders	Health at baseline and outcome	Statistical comparison	Results	p<0.05	Comments / Conclusion
	<p><i>Exclusion:</i> Non-English publications; without dementia specification; cross-sectional studies;</p> <p><i>Adjustment for confounders:</i> Adjusted effect estimates were used.</p>	Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association))				
Singh et al. (2014)	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs or Cohort Follow up > 1 year Adequate information to quantify MeDi Risk estimate available as HR, RR, OR or data from which it can be calculated.</p> <p><i>Exclusion:</i> Case series, case-control, and cross-sectional studies;</p> <p><i>Adjustment for confounders:</i> "The included studies varied according to the adjusting covariates; however, all the studies were adjusted for age, sex, education and Apolipoprotein E (APOE)".</p>	Normal progressing to MCI	a) T1 vs T3; b) T1 vs T2;	2 PCS (2340 subjects); no significant heterogeneity; a) HR 0.73 (95%CI 0.56 – 0.96, p=0.02) b) HR 0.82 (95%CI 0.64 – 1.05, p=0.11)	a) yes b) no	This meta-analysis included 2 PCS
		Normal progressing to MCI	cont. MeDi	2 PCS (2566 subjects); no significant heterogeneity; HR 0.95 (95%CI 0.84 – 1.08, p=0.45) per 1 point increase in MeDi Score	no	This meta-analysis included 2 PCS
		Normal progressing to AD	a) T1 vs T3; b) T1 vs T2; c) cont. MeDi	2 cohort studies (3169 subjects); no significant heterogeneity; a) HR 0.64 (95%CI 0.46– 0.89, p=0.007) b) HR 0.87 (95%CI 0.66 – 1.14, p=0.31) c) HR 0.92 (95%CI 0.85 – 0.99, p=0.03) per 1 point increase in MeDi Score	a) yes b) no c) yes	This meta-analysis included 2 cohort studies
		MCI progressing to AD	a) T1 vs T3; b) T1 vs T2; c) cont. MeDi	1 PCS (409 subjects) a) HR 0.52 (95%CI 0.30 – 0.91; p=0.02) b) HR 0.55 (95%CI 0.34 – 0.90; p=0.02) c) HR 0.89 (95%CI 0.78 – 1.02, p=0.09)	a) yes b) yes c) no	Result based on one single PCS

Study	Selection criteria and adjustment for confounders	Health at baseline and outcome	Statistical comparison	Results	p<0.05	Comments / Conclusion
		Normal progressing to MCI; or Normal progressing to AD; or MCI progressing to AD;	a) T1 vs T3; b) T1 vs T2; c) cont. MeDi;	5 PCS (6144 subjects); no significant heterogeneity ($I^2=0\%$) HR 0.67 (95% CI 0.55– 0.81; p <0.0001) (adjusted HR 0.80, 95% CI 0.67– 0.95; p=0.01) HR 0.92 (95% CI 0.88 – 0.97, p=0.001) HR 0.92 (95% CI 0.88 – 0.96)	a) yes b) yes c) yes	Scarmeas (2009b) and Scarmeas (2006) presented different outcomes from same PCS, possibly over-representing this cohort. For sensitivity analysis without Scarmeas (2009b) see row below.
		Normal progressing to MCI; or Normal progressing to AD; or MCI progressing to AD; Sensitivity analysis: Same studies as row above, but excluding Scarmeas (2009b)	a) T1 vs T3; b) T1 vs T2; c) cont. MeDi;	4 PCS (4945 subjects); no significant heterogeneity; HR 0.67 (95% CI 0.51 – 0.88, p=0.004) HR 0.85 (95% CI 0.67– 1.07, p=0.17) HR 0.94 (95% CI 0.87 – 1.02, p=0.12)	a) yes b) no c) no	This is a sensitivity analysis of preceding row and excludes Scarmeas (2009b). See comment above.
Psaltopoulou et al. (2013)	<u>Selection criteria:</u> <i>Inclusion:</i> > Cohort, cross-sectional or case-control studies. > Direct or indirect effect estimates for relative risk regarding the association between adherence to a Mediterranean dietary pattern	All countries: Normal progressing to MCI; or Normal progressing to AD; or MCI progressing to AD	MeDi score: a) high vs low b) moderate vs low (MeDi score: low / medium / high = MeDi score of	4 PCS (4159 subjects); no significant heterogeneity; a) RR 0.72 (95% CI 0.58 – 0.88) b) RR 0.90 (95% CI 0.75–1.08)	a) yes b) no	This meta-analysis included only cohort studies

Study	Selection criteria and adjustment for confounders	Health at baseline and outcome	Statistical comparison	Results	p<0.05	Comments / Conclusion
	<p>(expressed by means of a variety of scores) and incidence of [...] cognitive impairment (mild or advanced)</p> <p><i>Exclusion:</i> >Case-only studies examining mortality > Studies on childhood populations > In case of overlapping study populations, only the larger study was included.'</p> <p><i>Adjustment for confounders:</i> Maximally adjusted effect estimates were used.</p>		0-3 / 4-5 / 6-9 respectively)			
				<p>4 PCS, 4 cross-sectional studies, 1 case-control study</p> <p>a) RR 0.60 (95%CI 0.43 – 0.83); significant heterogeneity</p> <p>b) RR 0.79 (95%CI 0.67–0.94); no significant heterogeneity</p>	<p>a) yes</p> <p>b) yes</p>	<p>This meta-analysis included PCS, cross-sectional and case-control studies</p>
		<p>Non-Mediterranean countries only:</p> <p>Normal progressing to MCI; or Normal progressing to AD; or MCI progressing to AD</p>		<p>3 PCS, 2 cross-sectional studies, 1 case-control study;</p> <p>a) RR 0.49 (95%CI 0.34 - 0.70); significant heterogeneity (I²=71%)</p> <p>b) RR 0.74 (95%CI 0.60 - 0.91); no significant heterogeneity</p>	<p>a) yes</p> <p>b) yes</p>	<p>This meta-analysis included PCS, cross-sectional and case-control studies</p>
		<p>Mediterranean countries only:</p> <p>Normal progressing to MCI; or Normal progressing to AD; or MCI progressing to AD</p>		<p>1 PCS, 2 cross-sectional studies;</p> <p>a) RR 1.01 (95%CI 0.80 - 1.28); no significant heterogeneity</p> <p>b) RR 1.02 (95%CI 0.73 - 1.43); no significant heterogeneity</p>	<p>a) no</p> <p>b) no</p>	<p>This meta-analysis included PCS and cross-sectional studies.</p>

Study	Selection criteria and adjustment for confounders	Health at baseline and outcome	Statistical comparison	Results	p<0.05	Comments / Conclusion
Sofi et al. (2010)	<p><i>Selection criteria:</i> <i>Inclusion:</i> > prospective cohort studies</p> <p><i>Exclusion:</i> > Studies with patients with prior clinical event > Studies that did not adjust for confounders</p> <p><i>Adjustment for confounders:</i> Results from most complete adjustment for potential confounders were used.</p>	Neurodegenerative disease: Normal progressing to MCI or AD or Parkinson's	MeDi score (continuous variable)	4 PCS; no significant heterogeneity ($I^2=0\%$); RR 0.87 (95% CI 0.81, 0.94; $p < 0.00001$) per 2 point increase in MeDi Score	yes	

Table 4: Results of systematic reviews on dietary patterns (incl. Mediterranean diet) and cognitive impairment (cohort studies and RCTs only)

Study	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Yusufov et al. (2016)</p> <p>Alzheimer's disease and diet: a systematic review</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> Peer-reviewed articles published between 1/1/1995 and 31/12/2015; Original studies with multiple human subjects; AD incidence as a primary study outcome;</p> <p><i>Exclusion:</i> No reviews or meta-analyses; No animal studies</p>	<p>MMSE, NPE, DSM-III,</p>	<p><u>Mediterranean diet studies (on AD):</u> 5 PCS: 4 PCS showed a beneficial association:</p> <ul style="list-style-type: none"> • Gu et al. (2010a) HR_{T3 v T1}=0.66, 95% CI 0.41, 1.04; (USA; n=1219; follow-up 4y; mean age 76.7y) p_{trend}=0.04; • Scarmeas et al. (2007) HR_{T3 v T1}=0.27, 95% CI 0.10, 0.69; (USA; n=192; follow-up 4y.4; mean age 82.9y) • Scarmeas et al. (2009a) HR_{T3 v T1}=0.60, 95% CI 0.42, 0.87; (USA, n=282; follow-up 5.4y; mean age 77.2y) • Scarmeas et al. (2006b) HR_{T3 v T1}=0.60, 95% CI 0.42, 0.87; (USA, n=2258; follow-up 4y; mean age 77.2y) <p>1 cohorts showed no association:</p> <ul style="list-style-type: none"> • Feart et al. (2009) HR 1.12, 95% CI 0.60, 2.10 (France, n=1410; follow-up 5y; mean age 75.9y) <p><u>Healthy diet study (on AD):</u> 1 PCS showed beneficial association:</p> <ul style="list-style-type: none"> • Morris et al. (2015) (MIND diet) HR_{T3 v T1}=0.47, 95% CI 0.26, 0.76 (USA, n=923; follow-up 4.5y; mean age 81.2y) 	<p>For MD, out of 5 PCS, 4 cohorts showed a beneficial association with AD while 1 cohort showed a non-significant detrimental association.</p> <p>For 'healthy' diets 1 PCS showed a beneficial association of the 'MIND' diet with AD</p>

Study	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Cooper et al. (2015)</p> <p>Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis</p>	<p><u>Selection criteria:</u> <u>Inclusion:</u> longitudinal studies reporting incident dementia in people with MCI; subjects representative of study population; response rate >60%; follow-up >1year with >70% of participants; Objective criteria for diagnosing MCI or dementia;</p> <p><u>Exclusion:</u> NS</p>	<p>Objective criteria for diagnosing MCI or dementia;</p>	<p><u>Mediterranean diet studies:</u></p> <p>1 PCS:</p> <ul style="list-style-type: none"> Study showed beneficial association of adherence to a Mediterranean dietary patterns and conversion from amnesic MCI to AD (Scarmeas et al., 2009b) 	<p>The one considered PCS showed a beneficial association of adherence to Mediterranean dietary pattern and conversion from amnesic MCI to AD.</p>
<p>Deckers et al. (2015)</p> <p>Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies.</p>	<p><u>Selection criteria :</u> <u>Inclusion:</u> prospective observational studies; published between 28/10/2009 to 5/12/2012; population-based sample; >200 participants; > 45 years of age; > 1 year of follow up.</p> <p><u>Exclusion:</u> Cross-sectional studies; Retrospective case-control studies.</p> <p><u>Exposures:</u> MD; Healthy diets;</p> <p><u>Outcome:</u> dementia</p> <p><u>Confounding:</u> NS;</p>	<p>NS</p>	<p><u>Mediterranean diet studies</u></p> <p>2 PCS :</p> <ul style="list-style-type: none"> 1 study showed beneficial association (Cherbuin & Anstey, 2012) 1 study showed no association (Gu et al., 2010a) <p><u>Healthy diet studies</u></p> <p>3 PCS:</p> <ul style="list-style-type: none"> 2 studies showed beneficial association (Gu et al., 2010b; Shatenstein et al., 2012) 1 study showed no association (Gelber et al., 2012) <p>Note: No effect sizes or study durations were reported by Deckers et al. (2015).</p>	<p>Deckers et al. (2015) concluded that further studies were needed (esp. RCTs) to clarify the relationship between diet and dementia prevention.</p>
<p>van de Rest et al. (2015)</p> <p>Dietary patterns, cognitive decline, and</p>	<p><u>Selection criteria:</u> <u>Inclusion:</u> Studies in older or elderly persons</p> <p><u>Exclusion:</u> NS</p> <p><u>Exposures:</u> Mediterranean dietary patterns; Non-Mediterranean healthy dietary patterns;</p>	<p>MMSE, DSM-III-R , CDR, NINCDS-ADIRDA, HDS, HDSR,</p>	<p><u>Mediterranean diet studies :</u></p> <p><u>MCI (1RCT; 2 PCS)</u> 1 RCT (Martinez-Lapiscina et al., 2013b)</p> <ul style="list-style-type: none"> MD with olive oil: (OR 0.34, 95%CI 0.12, 0.97); MD with nuts: (OR 0.56, 95%CI 0.22, 1.43) (Spain; n=268; duration 6.5y; mean 	<p>For MDs and MCI, one RCT showed a beneficial effect for a MD with olive oil, but no so for a MD with nuts. Three PCS showed inconsistent results.</p> <p>For MD and AD 4 PCS in the US showed a beneficial association,</p>

Study	Methods	Measures of cognitive function	Results	Comments / Conclusion
dementia: a systematic review	<p><u>Outcomes:</u> MCI; dementia (incl. Alzheimer's); (cognitive function, cognitive decline)</p> <p><u>Confounding:</u> For some included studies it is stated that results have been adjusted.</p>		<p>age 74.1y)</p> <p>2 PCS:</p> <p>1 PCS showed beneficial association:</p> <ul style="list-style-type: none"> Scarmeas et al. (2009b) HR 0.85, 95% CI 0.72, 1.00; (USA; n=1393, follow-up 4.5y; mean age 76.9); <p>1 PCS showed detrimental association</p> <ul style="list-style-type: none"> Cherbuin & Anstey (2012) OR 1.41, 95% CI 0.95, 2.10; (Australia; n=1528, follow-up 4y; mean age 62.5); <p><u>MCI or dementia (1 PCS)</u></p> <ul style="list-style-type: none"> Roberts et al. (2010) HR_{T3 v T1} = 0.75, 95% CI 0.46, 1.21; (USA, n=1233; follow-up 2.2y; mean age 79.6y) <p><u>AD (5 PCS):</u></p> <p>4 PCS showed beneficial association:</p> <ul style="list-style-type: none"> Scarmeas et al. (2009b) HR 0.71, 95% CI 0.53, 0.95; (USA; n=1393, follow-up 4.5y; mean age 76.9; MCI at baseline) Gu et al. (2010a) HR 0.87, 95% CI 0.78, 0.97; (USA, n=1219; follow-up 3.8y; mean age 76.7y) Scarmeas et al. (2006b) HR 0.91, 95% CI 0.83, 0.98; (USA, n=2258; follow-up 4y; mean age 77.2y) Scarmeas et al. (2009a) HR_{T3 v T1} = 0.60, 95% CI 0.42, 0.97; (USA, n=1880; follow-up 5.4y; mean age 77.2y) <p>1 PCS showed no association:</p> <ul style="list-style-type: none"> Feart et al. (2009) HR 1.00, 95% CI 0.85, 1.19 (France, n=1410; follow-up 5.4y; mean age 75.9y) 	<p>while 1 cohort study in France showed no association.</p> <p>One PCS investigating a 'Japanese' dietary pattern showed a beneficial association with the all-cause dementia, Alzheimer's disease and vascular dementia.</p> <p>One PCS investigating a 'Healthy' dietary pattern showed a beneficial association with Alzheimer's disease.</p>

Study	Methods	Measures of cognitive function	Results	Comments / Conclusion
			<p>Healthy diet studies:</p> <ul style="list-style-type: none"> 1 PCS investigated 'Japanese' dietary pattern (defined via reduced rank regression) (Ozawa et al., 2013) <u>All-cause dementia:</u> HR 0.66, 95% CI 0.46, 0.95; <u>Alzheimer's disease:</u> HR 0.65, 95% CI 0.40, 1.06; <u>Vascular dementia:</u> HR 0.45, 95% CI 0.22, 0.91; (Japan, n=1006; follow-up 15y; mean age 68.5): 1 PCS investigated 'Healthy' dietary pattern (defined via reduced rank regression) (Gu et al., 2010b) <u>Alzheimer's disease:</u> HR_{T3 v T1}=0.62, 95% CI 0.43, 0.89; (USA, n=2148; mean age 77.2y; follow-up 3.9y): 	
<p>Di Marco et al. (2014)</p> <p>Modifiable lifestyle factors in dementia: a systematic review of longitudinal observational cohort studies</p>	<p><u>Selection criteria:</u> <u>Inclusion:</u> Cohort studies; Population-based; non-demented adults age > 35y; Adjusted at least of demographic factors; Published before 10/12/13; Published in English;</p> <p><u>Exclusion:</u> Studies with potential sampling bias (e.g. studies on twins, religious groups, war veterans etc.)</p> <p><u>Exposure:</u> MD</p> <p><u>Outcome:</u> Dementia or any sub-type thereof</p> <p><u>Confounding:</u> Studies were excluded if not adjusted at least for demographic factors</p>	NS	<p>Mediterranean diet studies :</p> <p><u>Dementia (2 PCS)</u></p> <ul style="list-style-type: none"> Scarmeas et al. (2006b) HR_{T3 v T1}=0.60, 95% CI 0.42, 0.87; Feart et al. (2009) HR 1.12, 95% CI 0.60, 2.10; <p><u>AD (1 PCS)</u></p> <ul style="list-style-type: none"> Gu et al. (2010a) HR_{T3 v T1}=0.66, 95% CI 0.41, 1.04; (p_{trend}=0.04 for continuous variable); Feart et al. (2009) HR 0.86, 95% CI 0.39, 1.88; 	<p>For Dementia, 1 PCS showed a beneficial association while a 2nd cohort did not show a significant association.</p> <p>For AD, 1 PCS showed a borderline significant association in a beneficial direction (T3 vs T1) with a statistically significant p for trend for the MeDi score as a continuous variable..</p> <p>Di Marco et al. (2014) conclude that conflicting results are reported.</p>

Study	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Lourida et al. (2013)</p> <p>Mediterranean diet, cognitive function, and dementia: a systematic review</p>	<p><u>Selection criteria:</u> <u>Inclusion:</u> A defined score to measure MD adherence; Published before January 2012; No restriction on study design or language.</p> <p><u>Exclusion:</u> Dietary patterns other than MD; Individual components of MD.</p> <p><u>Exposure:</u> MD</p> <p><u>Outcome:</u> MCI; AD; all-cause dementia;</p> <p><u>Confounding:</u> except for the RCT, all studies controlled for age, sex, education and various other potential confounders</p>	<p>International Consensus Criteria; CDR; DSM-IV, DSM-III-R NINCDS-ADRDA; Blessed Functional Activities Scale; Disability and Functional Limitation Scale</p>	<p><u>Studies (TOTAL=8 PCS):</u> Overall the quality of studies was judged to be moderate;</p> <p>(HR*=HR per unit increase in MeDi score)</p> <p><u>MCI: (4 PCS)</u></p> <ul style="list-style-type: none"> • Cherbuin & Anstey (2012) OR 1.41, 95% CI 0.95, 2.10; (Australia; n=1528; follow-up 4y; mean age 62.5y, 51% women) • Cherbuin et al. (2011) HR*=1.06, 95% CI 0.85, 1.34; (Australia; n=1474; follow-up 8y; mean age 62.5y, 51% women) • Roberts et al. (2010) HR_{T3 v T1}=0.75, 95% CI 0.46, 1.21; (USA; n=1233 ; follow-up 2.2; mean age 79.6y; 49% women) • Scarmeas et al. (2009b) HR_{T3 v T1}=0.72, 95% CI 0.52, 1.00; HR*=0.92, 95% CI 0.85, 0.99; (USA; n=1393; follow-up 4.5y; mean age 76.9y, 68% women) <p><u>Alzheimer's Disease: (4 PCS)</u></p> <ul style="list-style-type: none"> • Gu et al. (2010a) HR_{T3 v T1}=0.66, 95% CI 0.41, 1.04; HR*=0.87, 95% CI 0.78, 0.97; (USA; n=1219; follow-up 3.8y; mean age 76.7y, 67% women) • Scarmeas et al. (2006b) HR_{T3 v T1}=0.60, 95% CI 0.42, 0.87; HR*=0.91, 95% CI 0.83, 0.98; (USA; n=2258; follow-up 4y; mean age 77.2y, 68% women) • Scarmeas et al. (2009a) 	<p>In relation to MCI only 1 of 4 PCS showed a beneficial association and overall the evidence was inconsistent.</p> <p>For AD, in all 4 PCS higher adherence to a Mediterranean dietary pattern was consistently associated with a lower risk of AD.</p> <p>For all-cause dementia, one PCS showed a significantly reduced risk, while results of the second PCS were non-significant.</p>

Study	Methods	Measures of cognitive function	Results	Comments / Conclusion
			<p>HR_{T3 v T1}=0.60, 95% CI 0.42, 0.87; (USA; n=1880; follow-up 5.4y; mean age 77.2y, 69% women)</p> <ul style="list-style-type: none"> Scarmeas et al. (2009b) HR_{T3 v T1}=0.52, 95% CI 0.30, 0.91; HR*=0.89, 95% CI 0.78, 1.02; (USA; n=1393; follow-up 4.5y; mean age 76.9y, 68% women, MCI at baseline) <p><u>All-cause dementia (2 PCS)</u></p> <ul style="list-style-type: none"> Feart et al. (2009) HR_{T3 v T1}=1.12, 95% CI 0.60, 2.10; (France; n=1410; follow-up 5y; mean age 75.9y, 63% women) (Roberts et al., 2010) HR_{T3 v T1}=0.75, 95% CI 0.46, 1.21; (USA; n=1233 ; follow-up 2.2; mean age 79.6y; 49% women) 	

Annex 5: Nutrients – Summary of meta-analyses and systematic reviews

Table 5: Meta-analyses and systematic reviews of studies on supplementation with B vitamins in combination and cognitive function

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
Forbes et al. (2015)	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs with participants randomised to either dietary intervention or control arm; cognition as outcome measure and intervention period ≥ 3 months; participants aged ≥ 40y and cognitively normal or with MCI, but not dementia;</p> <p><i>Exclusion:</i> Trials which did not explicitly excluded participant with confirmed or suspected dementia.</p> <p><u>Outcome:</u> Cognitive function</p> <p><u>Analysis:</u> Meta-analysis was performed if ≥ 3 studies were available; meta-analysis calculated summary mean difference using fixed effect model. Heterogeneity was assessed using chi-square and I^2 statistic.</p>	For meta-analysis: MMSE	<p><u>Studies:</u> 7 RCTs; n=152 to 2009; age=≥ 60y; duration=12 weeks to 6.6 years; interventions were combinations of folate (0.4 to 5 mg/d) and vitamins B6 (10 to 50mg/d) and/or B12 (0.1 to 1 mg/d); PPs were cognitively normal or had MCI, but not dementia</p> <p>Results of 7 RCTs were inconsistent. While some showed benefits in at least one of the assessed cognitive domains (4 RCTs), others did not (3 RCTs).</p> <p><u>MMSE and B vitamins meta-analysis:</u> 3 RCTs; n=798; age=≥ 70y; duration=2 years; interventions were combinations of folate (0.8 to 2 mg/d), vitamin B6 (10 to 25 mg/g) and B12 (0.4 to 0.5 mg/d)</p> <p>No significant difference in MMSE score between intervention and control groups: MD=0.02 (95% CI -0.22, 0.25)</p>	
Cao et al., 2015	<p><u>Research question:</u> Consider the association between diet and the risk of dementia</p> <p><u>Selection criteria:</u> <i>Inclusion:</i> cohort studies of white subjects with ≥ 1 y follow-up; include RR & corresponding 95 % CI or enough data to calculate these numbers; consider dietary patterns or food consumption and incidence dementia (based on clearly stated diagnostic criteria or identified through diagnostic codes); ≥ 2 samples; English-language publications</p>	MMSE to detect cognitive impairment; dementia diagnosis made in accordance with internationally accepted criteria for dementia (DSMIII-R or DSM-IV), vascular dementia (NINDS-AIREN), & AD (NINCDS-ADRDA).	<p><u>Studies:</u> 4 PCS; n=not reported; age=≥ 65 y; follow-up=1.5 to 9.3 y; cognitively healthy Pps at baseline</p> <p><u>Results:</u> RR=0.72 (95 % CI 0.54, 0.96; p=0.026; $I^2=41.6\%$ $P_{\text{het}}=0.072$) No publication bias observed from the funnel plot or Begg's test (p=0.782).</p>	

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
	<p><u>Exclusion:</u> cross-sectional studies; non-original research (reviews, editorials, or commentaries); duplicated studies</p> <p><u>Search dates:</u> 1st Jan 1997 – 1st Sep 2014</p> <p><u>Analysis:</u> Random effect model used to calculate the summary RR and its 95 % CI. I² statistic used to assess statistical heterogeneity.</p> <p><u>Evaluation of study quality:</u> Not considered</p> <p><u>Dietary assessment method:</u> FFQ</p>			
<p>Li et al., 2014</p>	<p><u>Selection criteria:</u> <i>Inclusion criteria:</i> double blind, placebo controlled trials with random assignment to a marketed multivitamin B supplements (vitamin B12 + vitamin B6 + folic acid) or individual B vitamins supplement (vitamin B12 or vitamin B6 or folic acid); inclusion of patients with diagnosed MCI or diagnosed probable or possible AD; baseline characteristics similar between intervention and control group; duration of >26 weeks; measured one of the following – cognition, function, behaviour, global assessment of change; specification of the numbers of patients randomized and outcome measures.</p> <p><i>Exclusion:</i> trials concerning other cognitive disorders; supplementation with other vitamins.</p> <p><u>Outcome measures:</u> Cognitive function, behaviour, global assessment of change.</p>	<p>Telephone Interview for Cognitive Status (TICS), MMSE, 10 word learning test (WLT) delayed recall, National Institute of Neurological and Communicative Diseases and Stroke and the AD Related Disorders Association criteria, ADAS-Cog</p>	<p><u>Studies:</u> 5 RCTs (2 in patients with MCI; 3 in patients with AD)</p> <p><u>Sample size:</u> <i>MCI RCTs:</i> n=71 – 110 Pps <i>AD RCTs:</i> n=41 – 409 Pps (total=539 Pps)</p> <p><u>Duration:</u> <i>MCI RCTs</i>=12 – 24 months <i>AD RCTs</i>=26 weeks – 18 months</p> <p><u>Supplementation</u> <i>MCI RCTs:</i> Multivitamin B supplements (B12 [0.4 – 0.5mg/d] + B6 [20 – 50mg/d] + folic acid [0.8 – 5 mg/d]) <i>AD RCTs:</i> Multivitamin B supplements (B12 [1 – 500mg/d], B6 [5 – 25mg/d], folic acid [1 – 5mg/d]; folic acid alone (1mg/d).</p> <p><u>Health at baseline:</u> Diagnosed MCI or diagnosed probable or possible AD</p> <p><u>MCI RCTs</u></p>	<p>Although B vitamins were found to improve memory the data considered in this review does not support an effect of B vitamins on cognition in people with MCI or stabilize or slow cognitive decline in patients with AD.</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
	<p><u>Statistical analysis:</u> Analysis using the same measurement scale=weighted mean difference (WMD) and 95% confidence intervals (CI) for changes from baseline in a fixed or random effects model. Analysis of disparate tests=standard mean difference (SMD) with 95%CI. Heterogeneity= $I^2 > 50\%$</p>		<p><i>Global cognitive function</i>=no significant difference between intervention and placebo groups (WMD -0.10; 95%CI -0.80, 0.59; p=0.77; 2 RCTs; 361 Pps) <i>Memory</i>=B vitamins improved memory (MD=0.60; 95%CI 0.20, 1.00; 2 RCTs; 361 Pps); no significant difference when high tHcy group data was excluded (SMD=0.19; 95%CI -0.30, 0.68; p=0.86) <i>Executive function</i>=no significant difference between intervention and placebo groups (SMD=0.05; 95%CI -0.11, 0.21, p=0.54; 2 RCTs; 361 Pps) <i>Attention</i>=no significant difference between intervention and placebo groups (WMD=-0.03; 95%CI -1.20, 1.14; p=0.96; 1 RCT; 138 participants)</p> <p><u>AD RCTs</u> <i>Cognitive function</i>=no significant difference between intervention and placebo groups MMSE score (WMD -0.22; 95%CI -1.00, 0.57; p=0.59; 539 Pps); or ADAS-cog (WMD=1.01; 95%CI -0.68, 2.70; p=0.24; 2 RCTs; 498 Pps) <i>Global assessment</i>=no significant difference between intervention and placebo groups (WMD 0.07, 95%CI -0.48, 0.62)</p>	
<p>Clarke et al. 2014</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCT, duration of >3 months; >100 participants unselected for cognition-related diseases other than heart attack or stroke/transient ischemic attack; homocysteine-lowering treatment only, availability of sufficient data by September 2010.</p> <p><i>Exclusion:</i> none stated.</p> <p><u>Outcome:</u> Cognitive function</p> <p><u>Confounding:</u> MMSE-type global scores were adjusted for age</p>	<p>4 trials assessed effects of B vitamin treatment on specific cognitive domains (i.e., memory, speed and executive function and their sum i.e., domain-composite score). 7 trials assessed effects on MMSE-type global cognitive function scores (i.e., MMSE, the Telephone Interview for Cognitive status (TCIS), or the Telephone Interview for Cognitive status-modified (TCIS-M)).</p>	<p><u>Studies:</u> 11 RCTs (4 domain specific RCTs; n=1423, 7 global cognition RCTs; n=20431; age: 60 – 82 y)</p> <p><u>Duration:</u> (mean range) <i>Domain specific</i> RCTs =0.3 - 3.0 y (overall mean 2.3 y) <i>Global cognition</i> RCTs = 1.0 - 7.1 y (overall mean 5.0 y)</p> <p><u>Supplementation:</u> 0.4 – 2.5 mg/d folic acid compared with placebo (one RCT used 5-methyltetrahydrofolate). All but one RCT also added 0.02 – 1.00 mg/d vitamin B12.</p> <p><u>Health at baseline:</u> cognitively healthy</p> <p><u>Domain specific</u> RCTs Allocation to B vitamins had no significant effect on changes in</p>	<p>Supplementation with B vitamins for ~5 years does not have a significant effect on cognitive aging in older people with or without vascular disease.</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
			<p>domain specific scores: Memory (Z score difference 0.02; 95%CI -0.06, 0.10; $\chi^2_3=11.3$; $P_{het}=0.01$) Speed (0.03; 95%CI -0.02, 0.08; $\chi^2_3=12.3$; $P_{het}=0.006$) Executive function (-0.05; 95%CI -0.14, 0.03; $\chi^2_3=1.4$; $P_{het}=0.71$) Domain-composite score (0.00; 95%CI -0.05, 0.06; $\chi^2_3=13.6$; $P_{het}=0.004$)</p> <p>Global cognition RCTs Allocation to B vitamins had no significant effect on MMSE-type scores (Z score difference -0.01, 95%CI -0.03, 0.02) (no significant effect of B vitamins on MMSE-type score in any subgroups considered – age at randomization, sex, smoking status, history of stroke, folic acid fortification, duration of treatment, presence of cognitive impairment at baseline, pre-treatment concentrations of folate, vitamin B12, and homocysteine)</p>	

Table 6: Systematic review of studies on vitamin B6 supplementation and cognitive function

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Malouf and Grimley Evans, 2003</p>	<p><u>Selection criteria</u> <i>Inclusion:</i> un-confounded, randomized, double blind trials, comparing effects of vitamin B6 supplementation (any dose and duration) and placebo on cognitive function, involving healthy older people and those with cognitive impairment or any type of dementia and those with or without evidence of vitamin B6 deficiency. <i>Exclusion:</i> trials in which allocation was not randomized, trials of combinations of different vitamins.</p> <p><u>Outcome:</u> <i>Primary:</i> cognitive function, functional performance, behavioural disorders. <i>Secondary:</i> blood homocysteine levels, vitamin B6 status, safety and adverse effects.</p> <p><u>Subgroup analysis:</u> Age, sex, vitamin B6 status, treatment duration, cognitive impairment at baseline.</p>	<p>The boxes Test, Digit Symbol Coding, Symbol Search Task, Digit Span Backwards Test, Letter Number Sequencing Test, The Ray Auditory Verbal Learning Test (RAVLT), Symbol Recall, Activity Recall, Stroop Test, Self-Ordered Pointing Task, The Common Objects Uses Test, The Trail Making Test, The Verbal Fluency Task, WAIS-III Vocabulary, Spot the Word Test, Sperling whole report task, Associated Learning Task, Associated Recognition Task, Associated Learning Task + tests of long term visual memory, attention and performance and perceptual motor skills.</p>	<p><u>Studies:</u> 2 RCTs (one RCT was restricted to women and the other to men); n=109; age: 65-92 y; duration=5 – 12 weeks; supplementation=20 – 75 mg/d vitamin B6 vs placebo; cognitively healthy at baseline.</p> <p>No beneficial effects from short-term vitamin B6 supplementation were found for any measure of cognitive function in either men or women.</p>	<p>This review found no evidence for short-term benefit of vitamin B6 on cognitive function.</p> <p>RCTs were of short duration and involved a small number of participants.</p>

Table 7: Systematic review of studies on vitamin B12 supplementation and cognitive function

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Doets et al., 2013</p>	<p><u>Research question</u> Evaluate the relationship between vitamin B12 and cognitive function in adults and elderly people</p> <p><u>Selection criteria:</u> <u>Inclusion:</u> human subjects ≥ 18 y; considered cognitive function; COHORTS – prospective cohort or nested case-control design, exposure measured using validated dietary assessment methods or serum/plasma concentrations; RCTs – randomised placebo controlled design, studied the effect of supplements, fortified foods or dietary intake, minimum intervention duration > 2 weeks</p> <p><u>Exclusion:</u> included patients with pre-existing conditions</p> <p><u>Search dates:</u> up to Feb 2009 (update search up to Feb 2010, checked database updates from Feb 2010 to Jan 2012)</p> <p><u>Analysis:</u> < 3 studies, studies described narratively ≥ 3 studies considering the cognitive outcome dose-response M-A conducted</p> <p><u>Evaluation of study quality:</u> Not assessed</p> <p><u>Dietary assessment method:</u> Not reported</p>	<p>Executive function: Rey Osterrieth copy; Shipley-Hartford Abstraction; Spatial copying</p> <p>Memory: Rey-Osterrieth recall; WMS logical memory; WMS visual reproduction; Working memory; Recall memory</p> <p>Global cognition: MMSE</p> <p>Incidence of AD: commonly used criteria</p>	<p><u>Studies:</u> 6 PCS; n=9415; age (mean)=67 – 75 y; follow-up=3y to 9.3y; cognitively healthy at baseline</p> <p>2 RCT's; n=142; age (mean)=77=85 y; duration=4 to 24 weeks; supplementation=10 – 1000 µg/d; cognitively healthy at baseline</p> <p><u>Incidence of AD</u> No association between vitamin B12 intake and incidence of AD per 1 µg increase in vitamin B12 intake at baseline after 3.9–9.3 y follow-up RR=0.99; 95% CI 0.99, 1.00; 3 PCS; 5254 Pps; 431 cases</p> <p><u>Incidence of dementia</u> No association between vitamin B12 intake and incidence of dementia after 9 y HR=0.87; 95% CI 0.52, 1.46; 1 PCS; 3634 Pps; 352 cases</p> <p><u>Executive function</u> 2 PCS reported that higher vitamin B12 intakes at baseline were associated with significantly better cognitive performance after 3 or 6 years of follow-up 1 RCT reported no significant difference between intervention and control groups</p> <p><u>Memory</u> 1 PCS reported that higher vitamin B12 intake at baseline was associated with significantly better memory after 6 years and 2 PCS reported no significant association 1 RCT reported a significant effect of vitamin B 12 on memory; with memory improving significantly more in the placebo group than the intervention group</p> <p><u>Speed</u> No associations with vitamin B12 observed (1 PCS)</p> <p><u>Language</u> No associations with vitamin B12 observed (1 PCS)</p>	

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Malouf and Areosa Sastre, 2003</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> randomized placebo-controlled double blind-trials, comparing effect of vitamin B12 supplementation (any dose, duration, route of administration) and placebo on cognitive function, involving healthy older people and those at any stage of cognitive impairment with or without vitamin B12 deficiency. <i>Exclusion:</i> trials in which combinations of folic acid and vitamin B12 were administered.</p> <p><u>Outcome:</u> Cognitive function</p>	<p>MMSE, ADAS-Cog, Cambridge Cognitive Examination (CAMCOG), 12-words learning test, MDI.</p>	<p><u>Studies:</u> 3 RCTs; n=182 Pps; age (mean at baseline)=74 – 81 y; cognitively healthy, dementia (moderate to severe), AD (moderate) all with low blood levels of vitamin B12/vitamin B12 deficiency.</p> <p><u>Supplementation and duration:</u> oral dose of 0.01 – 0.05mg/d vitamin B12 for 1 month; injection of 1mg/d vitamin B12 for 5 days and the 1 injection/month for 5 months; injection of 1mg/week vitamin B12 for 4 weeks.</p> <p>Meta-analysis including 2 RCTs found no benefit from vitamin B12 supplementation on cognitive function of people with low serum vitamin B12</p> <p>No significant effect of vitamin B12 supplementation on cognitive function measured using: <u>MMSE</u> 0.05 mg/d treatment (MD -0.06, 95% CI -3.06, 1.86; p=0.63) 0.01 mg/d treatment (MD -1.60, 95% CI -3.99, 0.79; p=0.19) 1mg/d treatment followed by 1 a month(MD 0.1, 95% CI -0.6, 0.8; p=0.70) <u>ADAS-Cog</u> 1mg/d treatment followed by 1 a month (MD 0.04, 95% CI -5.95, 6.03; p=0.99) <u>CAMCOG</u> 1 mg/week (MD -0.6, 95% CI -2.2, 0.9; p=0.43) <u>12-words learning test immediate recall</u> 1 mg/week (MD -0.2, 95% CI -0.7, 0.3; p=0.42) <u>12-word learning delayed recall</u> 1 mg/week (MD -0.50, 95% CI -1.0, 0.0; p=0.05)</p>	<p>Insufficient evidence of any effect of vitamin B12 supplementation on cognitive function of older people with low serum vitamin B12 levels and dementia.</p> <p>RCTs were of short duration and involved a small number of participants.</p>

Table 8: Meta-analyses and systematic reviews of studies on folic acid supplementation and cognitive function

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Xu et al. (2015)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> original study reporting OR or RR of AD; prospective cohort studies (case-control studies were also included by analysed separately); study population representative of general population;</p> <p><i>Exclusion:</i> Non-English publications; without dementia specification; cross-sectional studies;</p> <p><u>Outcome:</u> OR or RR of AD risk</p>	<p>National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria</p>	<p><u>Studies:</u> 4 prospective cohort studies; n=6219; age (mean)=69 – 78 y; follow-up=3.9 to 9.3 y; health at baseline not reported</p> <p>Meta-analysis showed a beneficial association of folate intake and AD incidence: RR 0.51; 95% CI 0.29, 0.73; I²= 16%; P_{het}=0.312</p>	
<p>Dangour et al., 2010</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> randomized or non-randomized clinical trials or prospective cohort studies, cognitive function measured at baseline and follow up, studies examining the effects of both single and multi-nutrient status or supplementation.</p> <p><i>Exclusion:</i> case-control studies, cross-sectional studies or studies that provided only cross-sectional correlation data.</p> <p><u>Outcomes:</u> Cohort studies: AD or dementia risk RCTs: change in cognitive performance</p> <p><u>Dietary assessment methods:</u> FFQ and 7 day record</p>	<p>Dementia or AD generally diagnosed using International Classification of Diseases (ICD-10), Diagnostic and Statistical Manual of Mental Disorders (DSM), and NINCDS-ADRDA.</p> <p>Cognitive function assessed using a large number of psychometric tests.</p>	<p><u>PCS Studies:</u> 3 PCS; n=579 – 1041; 57 – 192 cases of AD; age=>60 y; follow-up=3.9 – 9.3 years; Pps were community dwelling and free of AD at baseline</p> <p><u>Folate</u> 2 PCS reported higher folate consumption of folate to be significantly associated with decreased risk of AD (HR=0.5; 95% CI 0.3, 0.9 and RR=0.41; 95% CI 0.22, 0.76 1 cohort reported no association</p> <p><u>Vitamin B6</u> 1 PCS reported higher folate consumption of vitamin B6 to be significantly associated with decreased risk of AD 2 PCS reported no association</p> <p><u>Vitamin B12</u> 3 PCS reported no association between vitamin B12 intake and AD risk</p> <p><u>RCTs</u> 10 RCTs; n=7 – 818; age > 20 y (mean=60 – 82 y); duration=35 days – 3 years; supplementation=0.4 – 15 mg/d folic acid and 0.75 -1.1 mg/d folate; Pps were a mixture of community, institutional and hospital dwelling</p>	<p>The available evidence is insufficient to draw definitive conclusions on the association of folic acid with cognitive decline or dementia</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
			<p>who were cognitively healthy or had mild to moderate severity cognitive decline or diagnosed dementia</p> <p><u>Folate/folic acid supplementation only</u> 4 RCTs 3 RCTs, in cognitively healthy Pps, reported statistically significant improvements in some of cognition tests with folate/folic acid supplementation 1 RCT, in Pps with diagnosed dementia, reported no association between folate/folic acid supplementation and cognition test scores</p> <p><u>Folate/folic acid and B vitamin supplementation</u> 6 RCTs 6 RCTs reported no association between folate/folic acid and B vitamin supplementation and cognition test scores</p>	
<p>Wald et al., 2010</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> Randomised, placebo-controlled trials; folic acid (with or without other vitamins or minerals) supplementation compared with placebo; ≥20 participants; ≥45 years of age; without evidence of dementia at outset; recorded 1 or more measure of cognitive function at baseline and completion for both intervention and control group. <i>Exclusion:</i> none stated.</p> <p><u>Outcome:</u> Cognitive function</p> <p><u>Confounding:</u> None stated</p> <p><u>Analysis:</u> Results of each test expressed as standardized mean difference (SMD) (difference between folic acid and placebo groups in change in cognitive function test score across trial divided by average standard deviation across</p>	<p>45 tests used across all RCTs</p>	<p><u>Studies:</u> 9 RCTs; n=2835; age=60 – 83 y; duration=1.2 months – 3 years; supplementation=0.2 – 15mg/d folic acid (folic acid was used alone in 4 RCTs, combined with other B vitamins (B6, B2 or B12) in 4 RCTs, with multiple vitamins in 1 RCT); PPs were healthy at baseline</p> <p>No effect of folic acid supplementation on cognitive function (SMD=0.01; 95% CI -0.08, 0.10)</p> <p>No effect of folic acid supplementation on 4 cognitive function categories: memory (SMD=0.01; 95% CI -0.08, 0.09) speed (SMD=0.01; 95% CI -0.10, 0.13) language (SMD=-0.05; 95% CI -0.15, 0.04) executive function (SMD=0.03; 95% CI -0.13, 0.19)</p> <p>subgroup analysis: No significant difference in cognitive function with: age (<75 years vs ≥75 years) $p=0.97$ treatment used (folic acid alone vs folic acid + other B vitamins) $p=0.20$ dose (≥0.8mg/d vs <0.8mg/d) $p=0.88$ trial duration (≥24 months vs <24 months) $p=0.94$</p>	<p>No evidence that folic acid supplementation for up to 3 years prevents age-related cognitive decline among individuals without pre-existing dementia.</p> <p>Many of the included RCTs were of short duration (possibly too short to observe neuroprotective effect of folic acid, if there were one to be observed).</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
	<p>the folic acid and placebo groups). Meta-analysis used random-effects model. Heterogeneity assessed using chi-squared test and I².</p>			
<p>Malouf & Grimley Evans, 2008</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> All randomized double-blind, placebo-controlled trials in which folic acid with or without vitamin B12 was compared with placebo. <i>Exclusion:</i> None stated.</p> <p><u>Outcome measures:</u> Cognitive measurements</p> <p><u>Analysis:</u> No meta-analysis was undertaken due to heterogeneity in sample selection, outcomes, trial duration and dosage.</p> <p><u>Dietary assessment method:</u> FFQ</p>	<p><u>Speed of processing:</u> box tests, Digital Symbol Coding Task, Symbol Search Task, CAT, FCRT, DSS; <u>Working memory:</u> Digit Span-Backwards, Letter Number Sequencing; <u>Memory:</u> RAVLT, Symbol Recall, Activity Recall, Word learning test, SMS; <u>Executive function:</u> Stroop Test, Self-Ordered Pointing Task, Uses of Common Objects, The Trail Making Test, Verbal Fluency Task, Verbal Fluency Task, Concept shifting test, letter digit substitution test; <u>Verbal abilities:</u> Vocabulary (WAIS-III), Spot-the-Word Task; <u>Mood:</u> CESD; POMS; <u>Primary global measures:</u> Global Deterioration Scale, DSM-IV, Rosen scale; <u>Cognitive function and memory measures:</u> MMSE, RMT, TICS-M, ADAS-Cog, DSST, Prorated Verbal IQ, Boston Naming Test, Controlled Oral Word Association Test, Logical Memory and Associated Learning subtests from the Wechsler Memory Scale, Benton Visual Retention Test, Trial Making Test A and B, Finger Tapping Test; <u>Activities of daily living and behaviour:</u> Bristol Activities of Daily Living Scale; SB subscale of the NOSGER;</p>	<p><u>Studies:</u> 8 RCTs; n=11-818 ; age=50 – 92 y; duration=35 days – 3 years; supplementation=0.4-15mg/d folic acid (with and without vitamin B12); 4 RCTs enrolled healthy older people; 4 recruited participants with mild to moderate cognitive impairment or dementia</p> <p><u>Healthy Pps</u> There was insufficient evidence to support a beneficial effect of folic acid, with or without vitamin B12, on cognitive function and mood of unselected healthy elderly people. 1 RCT involving healthy elderly people with high homocysteine levels, 800 µg/d folic acid supplementation over 3 years was associated with significant benefits in terms of global cognitive functioning (WMD 0.05, 95%CI 0.004 to 0.096, p=0.033); memory storage (WMD 0.14, 95%CI 0.04 to 0.24, p=0.006) and information-processing speed (WMD 0.09, 95%CI 0.02 to 0.16, p=0.016).</p> <p><u>Cognitively impaired Pps</u> In one pilot trial (Connelly et al., 2008) enrolling people with AD, the overall response to cholinesterase inhibitors significantly improved with folic acid at a dose of 1 mg/d (odds ratio: 4.06, 95%CI 1.22 to 13.53; p=0.02) and there was a significant improvement in scores on the Instrumental Activities of Daily Living and the Social Behaviour subscale of the Nurse's Observation Scale for Geriatric Patients (WMD 4.01, 95%CI 0.50 to 7.52, p=0.02). Other RCTs involving people with cognitive impairment did not show any benefit in measures of cognitive function from folic acid, with or without vitamin B12.</p>	<p>The small number of studies identified provided no consistent evidence for either beneficial or adverse effects of folic acid, with or without B12, on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvements in the response of people with AD to cholinesterase inhibitors. In another study, long term used appeared to improve the cognitive function of healthy older people with high homocysteine levels.</p>

Table 9: Systematic review of studies on thiamin supplementation and cognitive function

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
<p>Rodriguez-Martin et al., 2001</p>	<p><u>Selection criteria:</u></p> <p><i>Inclusion:</i> Un-confounded, double-blind, randomized controlled trials; duration >1 day; supplementation with thiamin or a derivative in any dose and any method of administration; participants of any age or gender</p> <p><i>Exclusion:</i> Trials in which allocation to treatment or placebo was not random; treatment allocation was not concealed</p>	<p>AD: NINCDS-ADRACognitive function: MMSE; ADAS-Cog; the behavioural scale of Haycox; the Consortium to establish a Registry for Alzheimer's Disease (CERAD); the Blessed Dementia Scale (BDS)</p>	<p>AD or possible AD</p>	<p><u>Studies:</u> 3 RCTs; n=<50; age=59 – 87y (mean 71 – 76y); duration=2 – 12 month; supplementation=3 mg/d thiamin hydrochloride; Pps had mild to moderate AD</p> <p><u>MMSE:</u> 1 RCT reported no significant effect on MMSE score at 3, 6, 9 & 12 months for thiamin compared with placebo</p> <p><u>ADAS-Cog</u> 1 RCT reported no significant effect on ADAS-Cog after 3 months (ADAS-Cog declined in 3 of 8 Pps on thiamin compared with 6 of 9 Pps in the control group)</p> <p>The results of 1 RCT were not reported</p>	<p>The authors concluded that it was not possible to draw any conclusions from the identified RCTs.</p> <p>It was not possible to combine data in meta-analysis due to insufficient detail in the results and the small number of participants.</p>

Table 10: Meta-analyses and systematic reviews of studies on vitamins C and E supplementation/intake and cognitive function

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Xu et al. (2015)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> Original study reporting OR or RR of AD; prospective cohort studies (case-control studies were also included by analysed separately); study population representative of general population;</p> <p><i>Exclusion:</i> Non-English publications; without dementia specification; cross-sectional studies.</p> <p><u>Outcomes:</u> OR or RR of AD risk.</p> <p><u>Analysis:</u> Fixed-effect meta-analysis</p>	<p>NINCDS-ADRDA criteria.</p>	<p><u>Studies:</u> 6 PCS; n=633 to 5395; age (mean)=77 y; follow-up=3.9 to 9.3years</p> <p><u>Vitamin E</u> Higher vitamin E intake associated with reduced risk of AD RR=0.73; 95%CI 0.62, 0.84; n=12014</p> <p><u>Vitamin C</u> Higher vitamin C intake associated with reduced risk of AD RR=0.74; 95%CI 0.55, 0.93; n=11788</p> <p><u>Vitamin C and E in combination</u> 4 PCS; n=894-3508; follow-up 3 to 5.5 years No association between intake of vitamins C and E in combination and risk of AD RR=0.82; 95%CI 0.60, 1.04; n=10588</p>	<p>Meta-analysis of PCS showed a beneficial association of vitamin C or vitamin E and AD incidence and a non-significant inverse association for vitamin E and C combined.</p>
<p>Forbes et al. (2015)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs with cognition as outcome measure; intervention period ≥3 months; participants aged ≥40y; cognitively normal or with MCI, but not dementia; published between 2003 and June 2013.</p> <p><i>Exclusion:</i> Trials which did not explicitly exclude participants with confirmed or suspected dementia.</p> <p><u>Analysis:</u> Meta-analysis was performed if 3 or more studies were available; meta-analysis calculated summary mean difference using fixed effect model. Heterogeneity was assessed using chi-square and I² statistic.</p>	<p>Possible or probable AD; TICS-M;</p> <p>TICS; East Boston Memory Test; MMSE; ADAS-Cog; global CDR; CDR sum of boxes; Global Deterioration Scale; New York University paragraph-recall test; the symbol digit modalities test; category-fluency</p>	<p><u>Studies:</u> 3 RCTs; n=769-6377; age ≥65y; duration=3 – 9.6 y; supplementation=200 – 1300 mg/d of vitamin E (1 RCT combined vitamin E with vitamin C and βcarotene); Pps were cognitively healthy or had MCI</p> <p>No statistically significant effect on any of the cognitive outcomes examined was found in any of the 3 RCTs</p>	

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
		test; a number cancellation test; Boston Naming Test; Digits-backward test; clock drawing test; maze-tracing task.		
Cao et al., 2015	<p><u>Research question:</u> Consider the association between diet and the risk of dementia</p> <p><u>Selection criteria:</u> <i>Inclusion:</i> cohort studies of white subjects with ≥ 1 y follow-up; include RR & corresponding 95 % CI or enough data to calculate these numbers; consider dietary patterns or food consumption and incidence dementia (based on clearly stated diagnostic criteria or identified through diagnostic codes); ≥ 2 samples; English-language publications</p> <p><i>Exclusion:</i> cross-sectional studies; non-original research (reviews, editorials, or commentaries); duplicated studies</p> <p><u>Search dates:</u> 1st Jan 1997 – 1st Sep 2014</p> <p><u>Analysis:</u> Random effect model used to calculate the summary RR and its 95 % CI. I^2 statistic used to assess statistical heterogeneity.</p> <p><u>Evaluation of study quality:</u> Not considered</p> <p><u>Dietary assessment method:</u> FFQ</p>	MMSE to detect cognitive impairment; dementia diagnosis made in accordance with internationally accepted criteria for dementia (DSMIII-R or DSM-IV), vascular dementia (NINDS-AIREN), & AD (NINCDS-ADRDA).	<p><u>Studies</u> 10 PCS; n=not reported; age\geq 45 y; follow-up=3 – 30 y; Pps were cognitively healthy at baseline</p> <p><u>Vitamin C</u> No significant association between vitamin C intake and risk of dementia RR=0.89; 95% CI 0.74, 1.06; p=0.192; $I^2=24.0\%$, $P_{het}=0.24$</p> <p><u>Vitamin E</u> Greater intake of vitamin E significantly associated with reduced risk of dementia RR=0.80; 95% CI 0.65, 0.98; p=0.034; $I^2=33.6\%$, $P_{het}=0.14$</p> <p>Vitamins C & E & flavonoids Greater consumption of vitamins C & E & flavonoids significantly associated with a reduced risk of dementia RR=0.87; 95% CI 0.77, 0.98; p=0.026; $I^2=36.2\%$, $P_{het}=0.051$</p>	

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
Beydoun et al., 2014	<p><u>Selection criteria:</u> <i>Inclusion:</i> Original research published between January 1990 & October 2012; study sample size > 300; cross-sectional or prospective cohort studies; outcomes include dementia, AD, cognitive function, cognitive decline or cognitive impairment; general healthy population</p> <p><i>Exclusion:</i> None stated</p> <p><u>Analysis:</u> When data were heterogeneous, based on Q-test ($p < 0.05$), RRs pooled using random-effects model When data were homogenous ($p > 0.05$), RRs pooled using fixed-effect model</p> <p><u>Evaluation of study quality:</u> Not assessed</p> <p><u>Dietary assessment method:</u> Not reported</p>	<p>Cognitive function, cognitive decline, cognitive impairment, incident AD and dementia</p> <p>Specific tests used not reported</p>	<p><u>Studies</u> 21 PCS; $n=526 - 16010$; age ≥ 45 y; follow-up=not reported; Pps healthy at baseline</p> <p><u>Risk of dementia or AD</u> <u>Antioxidant (including vitamin E) supplementation</u> 8 PCS 4 PCS reported a significant association between grated antioxidant supplementation and reduced risk of dementia & AD 4 PCS reported no significant association</p> <p><u>Dietary intakes of antioxidants (including vitamin E)</u> 3 PCS 2 PCS reported a significant association between higher dietary antioxidant intakes & reduced risk of dementia and AD 1 PCS reported no association</p> <p><u>Cognitive function</u> 10 PCS <u>Antioxidant (including vitamin E) supplementation</u> 4 PCS 3 PCS reported a significantly reduced risk of cognitive decline with supplement use 1 PCS reported no significant association</p> <p><u>Dietary intakes of antioxidants (including vitamin E)</u> 6 PCS 6 PCS reported a significantly reduced risk of cognitive decline with higher antioxidant intakes</p>	<p>This review provides no information on supplement doses or dietary intakes, study duration or study quality</p>
Crichton et al. 2013	<p><u>Selection criteria:</u> <i>Inclusion:</i> Cross-sectional, prospective cohort and longitudinal studies; report an association between dietary antioxidant intake (individual or multiple classes of antioxidants) and cognitive function; adults only; English language studies only unless translation available; only studies that included a quantitative</p>	<p>17 studies used a dementia-screening tool, typically the MMSE, as a measure of global cognitive function.</p> <p>Eight studies used a variety of</p>	<p><u>Studies</u> 21 studies (8 cross-sectional, 13 PCS); $n=117 - 12000$; age ≥ 50 y; follow-up=3 to 30 y; community dwelling Pps without dementia</p> <p><u>Vitamin C</u> <u>Cross-sectional</u> <u>Cognitive Performance (7 studies)</u> 4 studies reported positive associations between dietary vitamin C intake and verbal fluency, abstract thinking and problem-solving, MMSE 3 studies reported no association between vitamin C and cognitive</p>	<p>Findings did not consistently show that habitual intakes of dietary antioxidants are associated with better cognitive performance or a reduced risk of dementia.</p> <p><i>Limitations</i> There was large heterogeneity in study design, differential control of confounders,</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
	<p>assessment of dietary antioxidant intake; provide measures for at least one aspect of cognitive function obtained from neuropsychological testing or provide an estimate of probable dementia, including AD.</p> <p><i>Exclusion:</i> Studies on wholefoods or beverages (e.g. fruits, vegetables, chocolate, tea), antioxidant supplements and blood levels of antioxidants in relation to cognition; studies that used self-reported cognitive function.</p> <p><i>Outcome:</i> Cognitive function</p> <p><i>Analysis:</i> A meta-analysis was not conducted because of the heterogeneity of dietary variables, outcome parameters and statistical analyses used to present results.</p> <p><i>Dietary assessment methods:</i> FFQ, 24-hour dietary recall, 3- or 7-day food records, interview method to ascertain usual food consumption during the preceding 2-4 weeks.</p>	<p>neuropsychological tests, with or without a global screening measure.</p> <p>Nine longitudinal studies used clinical evaluations and standardised diagnostic criteria.</p>	<p>performance on a range of cognitive tasks including verbal learning and memory, psychomotor function, MMSE</p> <p>PCS <i>Cognitive Performance (3 PCS)</i> 2 studies reported no association between vitamin C intake (including vitamin C supplements) and cognition measured using MMSE, category or verbal fluency 1 study reported that cognitive function was poorest in subjects with the lowest vitamin C intakes at baseline</p> <p><i>Dementia Risk (7 PCS)</i> 6 studies reported no association between dietary vitamin C and risk of dementia (3 studies) or AD (3 studies) 1 study reported an association between high vitamin C intake and a reduced risk for AD over six years (intake > 133 mg/d; RR=0.66; 95% CI: 0.44, 1.00) but the risk was no longer significant after 10 years</p> <p>Vitamin E <i>Cross-sectional</i> <i>Cognitive Performance (4 studies)</i> 4 studies reported no association between vitamin E intake and MMSE or neuropsychological testing</p> <p>PCS <i>Cognitive Performance (1 PCS)</i> 1 study reported that past intake of vitamin E was positively associated with better visuo-spatial recall and/or abstraction performance six years later</p> <p><i>Dementia Risk (6 PCS)</i> 3 studies reported a reduced risk of AD (2 studies) and dementia (1 study) with highest intakes of vitamin E 3 studies reported no association between vitamin E intake & AD or dementia risk</p>	<p>insufficient measures of cognitive performance and well recognised difficulties associated with different types of dietary assessment.</p>
<p>Rafnsson et al. 2013</p>	<p><i>Selection criteria:</i> <i>Inclusion:</i> Original primary studies; population-based cohort studies; at least a single baseline measurement of one or more major antioxidant nutrients, including carotene, flavonoids, antioxidant vitamin C and E and selenium; assessment of cognitive function with</p>	<p>Tests of overall (global) function, most commonly the MMSE; Four studies also used different tests for assessing domain-specific</p>	<p><i>Studies</i> 10 PCS ; n= 187 – 5092; age=> 60 y; follow-up=8.5 months to 10 y; Pps health at baseline not reported</p> <p>In 5 PCS, levels of individual antioxidant nutrients were estimated from food intake data, four studies directly determined antioxidant levels in the blood and in one study antioxidant information was based on self-reported use of vitamin supplements.</p>	<p>A narrative rather than quantitative approach was used to synthesize the results due to substantial methodological heterogeneity. There were insufficient studies examining the same antioxidant to be confident about the replicability of the reported results.</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
	<p>standardized tests on at least two different occasions; English language reports only;</p> <p><i>Exclusion:</i> Non-human studies; other study designs; hospital inpatients or patient samples; studies without appropriate antioxidant nutrient data; studies without information on cognitive performance assessed on more than one occasion.</p> <p><i>Outcome:</i> Cognitive performance</p> <p><i>Analysis:</i> No statistical analysis was undertaken; studies were assessed for quality and between study heterogeneity.</p>	<p>function, including memory performance, executive function, attention and psychomotor speed.</p>	<p><u>Supplementation</u> The number of different antioxidant nutrients assessed in different studies ranged from one to six; antioxidants C and E and tocopherols were reported in 7 PCS; carotenes were reported in 4 PCS; flavonoids and selenium were reported in two PCS. Other anti-oxidant nutrients were measured less frequently. <i>The dosage was not reported.</i></p> <p>The main supportive evidence came from two PCS, both judged to be of high quality. The first observed an accelerated decline in global cognition, attention, and psychomotor speed over 9 years, concomitant to a decrease in plasma <u>selenium</u> levels over the same period; the second PCS reported a slower rate of global cognitive decline over 3 years in persons in the highest quartile of intake of <u>vitamins C, E and carotenes</u>. However, at the 7 year follow-up, the protective effects were no longer observed in this PCS. All associations persisted after adjustment for confounding factors.</p> <p>Three additional PCS provided further evidence for a protective effect of vitamin E, beta carotene and flavonoids on cognitive decline. One of these limited to APOE 4-positive persons. These studies were of lower quality (rated 'adequate').</p> <p>No beneficial cognitive effects of beta carotene observed in 3 PCS; of flavonoids in 1 PCS; of selenium in 1 PCS; of vitamin C in 3 PCS; or of vitamin E in 6 PCS.</p>	
<p>Li et al. 2012</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> Studies should include RR or OR, or provide sufficient data to calculate these numbers; studies should provide CIs; studies must define outcome of interest as incident AD based on clearly stated diagnostic criteria or identified through diagnostic codes with additional confirmation.</p> <p><i>Exclusion:</i> none stated.</p> <p><u>Outcome:</u> Incident Alzheimer's disease</p>	<p>Not described.</p>	<p><u>Studies</u> 7 PCS (vitamin E: 7 studies, vitamin C: 6 studies); n=343 – 5760; age=not reported; follow-up=not reported; Pps health at baseline not reported</p> <p>Vitamin E and vitamin C intake were associated with a significantly reduced risk of AD. There was no significant heterogeneity between studies.</p> <p><i>Vitamin E (n=15,714)</i> RR 0.76; 95% CI: 0.67, 0.84; I²=43.2%</p> <p><i>Vitamin C (n=14,511)</i> RR 0.83; 95% CI: 0.72, 0.94; I²=0%</p>	<p>Although the meta-analysis suggested a protective effect of vitamin E and vitamin C on the risk of AD, the paper had several limitations.</p> <p><i>Limitations</i> It only provided very limited information on the characteristics of the included studies, e.g. it was not clear what type of studies were included, whether they were undertaken in healthy populations or those with</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
	<p><u>Analysis:</u> A fixed effect model was used to calculate summary RR and 95% CI across homogeneous studies and a random effect model was used to calculate summary RR and 95% CI across heterogeneous studies.</p>			<p>cognitive impairment, the duration of studies, the supplementation dosage and the age of study participants. Additionally, there was no assessment of study quality and dietary assessment methods were not discussed.</p>

Table 11: Meta-analyses and systematic reviews of studies on omega-3 fatty acids supplementation and cognitive function

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
<p>Zhang et al., 2016</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> the targeted association was investigated; fish consumption, total PUFAs (including both n-3 and n-6 PUFAs), total n-3 PUFAs, or at least one n-3 PUFA concentration was evaluated from the diet or measured as a blood biomarker; at least one endpoint from MCI, cognitive decline, dementia, AD, or Parkinson's disease was investigated; follow-up ≥ 2 y. There was no restriction for age ranges and sample sizes of participants in eligible cohort studies.</p> <p><i>Exclusion:</i> cross-sectional studies; only 2 categories were considered; the reference group was not the lowest category showing the amounts of fish consumption, dietary PUFA intake, or blood biomarker measurements</p> <p><u>Analysis:</u> associations were estimated as RRs and 95% CIs</p> <p><u>Quality assessment:</u> Newcastle-Ottawa quality-assessment scale</p>	<p>MCI, cognitive decline, dementia, AD</p>		<p><u>Studies</u> 21 studies (17 cohorts); n=181580 (263 cases of MCI; 320 cases cognitive decline; 1864 cases of dementia; 1332 cases or AD); age ≥ 52 y</p>	
<p>Forbes et al. (2015)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs with cognition as outcome measure and intervention period ≥ 3 months; participants aged ≥ 40y and cognitively normal or with MCI, but not dementia;</p> <p><i>Exclusion:</i> Trials which did not explicitly excluded participant with confirmed or suspected dementia.</p>	<p>For meta-analyses: MMSE, digit forward span;</p>	<p>Age ≥ 50y; cognitively normal or with MCI, but not dementia; largest study in coronary heart disease patients (n=2911);</p>	<p><u>Studies:</u> 6 RCTs (n=36 to 2911; duration 6 to 40 months; intervention dose 400 to 2200 mg)</p> <p>3 RCTs showed beneficial effect on memory and/or executive function while the other 3 did not (no meta-analysis was performed)</p> <p><u>MMSE and n-3 FAs meta-analysis:</u> 4 RCTs (total n=4299; duration 5 to 40 months);</p>	

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
	<p><u>Analysis:</u> Meta-analysis was performed if 3 or more studies were available; meta-analysis calculated summary mean difference using fixed effect model. Heterogeneity was assessed using chi-square and I² statistic.</p>			<p>No significant effect: summary mean difference=0.06 (95% CI -0.08, 0.19)</p> <p><u>Forward digit span and n-3 FAs meta-analysis:</u> 3 RCTs (total n=1205; duration 5 to 24 months);</p> <p>No significant effect: summary mean difference=-0.02 (95% CI -0.30, 0.25)</p>	
<p>Wu et al. (2015)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> prospective cohort studies considering dietary intake of omega-3 fatty acids or fish; reporting of relative risk of dementia or AD for highest vs lowest category of dietary intake; follow-up at least 1 year; general or at risk population (e.g. elderly)</p> <p><i>Exclusion:</i> animal studies, mechanistic studies, reviews</p> <p><u>Outcome:</u> Incidence of dementia or AD</p> <p><u>Analysis:</u></p> <ul style="list-style-type: none"> • Meta-analyses for relative risk of highest vs lowest category of dietary intake • Dose-response meta-analysis per 100g/week fish intake 		<p><u>Dementia:</u></p> <p>a) n=5395; age >55 (mean 68)</p> <p>b) n=488; mean age 76</p> <p><u>AD:</u> n=488 to 5395; mean age=68 to 76</p> <p><u>Dementia & AD:</u> n=488 to 5395; mean age=68 to 76</p> <p><u>Dose-response for dementia & AD:</u> n=2233 (AD 815) to 5395; mean age=68 to 72</p>	<p><u>Studies: 6 PCS</u></p> <p><u>Dementia and n-3 FAs (2 PCS)</u> No significant association in either cohort (a or b): a) (follow-up 9.6y) Total n-3 LCPUFAs (RR 0.97, 95% CI 0.77, 1.21) DHA (RR 0.99, 95% CI 0.79, 1.24) EPA (RR 0.97, 95% CI 0.77, 1.21) b) (follow-up 9.1y) DHA (RR 0.56, 95% CI 0.23, 1.40)</p> <p><u>AD and n-3 FAs (3 PCS; follow-up 3.9 to 9.6y)</u> Meta-analyses showed no significant association for: Total n-3 LCPUFAs (RR 0.85, 95% CI 0.51, 1.13) DHA (RR 0.77, 95% CI 0.49, 1.21) EPA (RR 0.96, 95% CI 0.76, 1.22)</p> <p><u>Dementia and fish intake (5 PCS, follow-up 2.1 to 9.6y)</u> RR 0.84 (95% CI 0.71, 1.01)</p> <p><u>AD and fish (6 PCS, follow-up 2.1 to 9.6y)</u> RR 0.64 (95% CI 0.44, 0.92)</p> <p><u>Dose-response meta-analysis (per 100g/week fish intake):</u> Dementia (4 PCS, follow-up 2.1 to 9.6 y): RR 0.95 (95% CI 0.91, 1.01) AD (5 PCS, , follow-up 2.1 to 9.6 y): RR 0.89 (95% CI 0.79, 0.99)</p>	

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
Xu et al. (2015)	<p><u>Selection criteria:</u> <u>Inclusion:</u> original study reporting OR or RR of AD; prospective cohort studies (case-control studies were also included by analysed separately); study population representative of general population;</p> <p><u>Exclusion:</u> Non-English publications; without dementia specification; cross-sectional studies;</p> <p><u>Outcome:</u> OR or RR of AD risk</p>	NINCDS-ADRDA criteria	<p><u>DHA</u> mean age NS</p> <p><u>EPA</u> mean age NS</p> <p><u>n-3 FAs</u> mean age NS</p> <p><u>Fish intake</u> mean age NS</p> <p><u>Frequency</u> mean age NS</p>	<p><u>Studies:</u> <u>DHA</u> 4 PCS (n=663 to 5395; follow-up 3.9 to 9.6 years)</p> <p>Meta-analysis (n=7,772) showed a non-significant inverse association for DHA intake and AD incidence: (RR 0.70, 95%CI 0.37, 1.03)</p> <p><u>EPA</u> 3 PCS (n=663 to 5395; follow-up 3.9 to 9.6 years)</p> <p>Meta-analysis (n=6,873) did not show a significant association of EPA intake and AD incidence: (RR 0.96, 95%CI 0.75, 1.16)</p> <p><u>n-3 FAs</u> 3 PCS (n=663 to 5395; follow-up 3.9 to 9.6 years)</p> <p>Meta-analysis (n=6,873) did not show a significant association of n-3 FA intake and AD incidence: (RR 0.81, 95%CI 0.39, 1.23)</p> <p><u>Fish intake</u> 6 PCS (n=815 to 8085; follow-up 2.1 to 9.6 years)</p> <p>Meta-analysis (n=23,510) showed a -significant inverse association for fish intake and AD incidence: (RR 0.66, 95%CI 0.43, 0.90)</p> <p><u>Fish consumption frequency</u> 4 PCS (n=815 to 8085; follow-up 3.5 to 7 years)</p> <p>Meta-analysis (n=12,549) showed a -significant inverse association for fish intake and AD incidence: (RR 0.64, 95%CI 0.46, 0.82)</p>	<p>Meta-analysis showed no significant association of DHA, EPA or n-3 FAs and AD incidence.</p> <p>Meta-analysis showed a significant inverse association of fish intake and consumption frequency and AD incidence.</p>

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
<p>Jiao et al., 2014</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs; implemented in primary or secondary outcome settings; only n-3 PUFAS implemented as supplements (formula was also included in the study but is not reported here); no language or publication restrictions; intervention group received at least one dose level of n-3 PUFA treatment and control group received appropriate placebo treatment.</p> <p><i>Exclusion:</i> intervention duration < 3 months; inclusion of multi-nutrient interventions besides n-3 PUFAS; a treatment mixed by n-6 PUFAS; inclusion of an effect of an n-3 PUFA-rich diet.</p> <p><u>Outcome:</u> Cognitive function, including cognitive performance in adults, the elderly and possible cognitive decline in the elderly. <i>The study also included infants and children but this will not be reported.</i></p> <p><u>Analysis:</u> The standardized mean differences were calculated as the mean difference in the change of cognitive function between the n-3 PUFA group and the placebo group, divided by the pooled SD, with an adjustment for small sample size (Hedges g). Several studies provided means and SD at baseline and follow up but did not report the within-subject change in SD, which was required for meta-analysis. In these cases an “imputation” approach was used.</p> <p>The risk of bias of included studies was assessed using the Cochrane Risk of Bias Tool.</p>	<p>Primary outcome measures: Composite memory, executive function, attention and processing speed. Secondary outcome measures: recognition, immediate word recall, delayed word recall, digit span backward, digit span forward, the Stroop effect, rapid visual information processing, verbal fluency, simple reaction time and choice reaction time. The MMSE result was used as a primary outcome to screen for cognitive decline in elderly people. The score of the ADAS-Cog was used as a secondary outcome.</p>	<p><u>Health at baseline :</u> Not described</p> <p><u>Age (mean):</u> studies in children and adults: mean - 22.2 (range: 9.0 – 30.5) years; studies in elderly people - mean: 71.4 (range: 68.9-74.2) years</p> <p><u>Gender:</u> studies in children and adults: 64% female; studies in elderly people: 51.5% female</p> <p><u>Sample sizes:</u> studies in children and adults: 5174 total participants; studies in elderly people: 6794 participants</p>	<p><u>Studies:</u> 27 publications; 15 investigated cognitive function in children and adults; 12 investigated cognitive function, decline and related diseases (e.g. AD) in the elderly. N-3 PUFA supplementation significantly improved the attention domain as a whole (SMD: 0.13, 95% CI 0.01, 0.25) for children, adults and the elderly combined. Subgroup analysis showed that improvements in the attention domain were significant in the elderly (0.29, 95% CI 0.10, 0.47) but not in children or adults. The treatment effect was significantly heterogeneous across studies ($I^2=59%$, $p=0.032$), which may be generated by the differential effects in the subgroup of elderly people. N-3 PUFAs did not significantly improve the domains of composite memory, executive function, and processing speed in either the overall or subgroup meta-analyses.</p> <p><u>Duration:</u> studies in children and adults: 4.5 months (3.7-7.5); studies in elderly people: 6.1 months (5.9-19.5)</p> <p><u>Supplementation:</u> studies in children and adults - mean: 0.9 g/d (range: 0.6-1.5); studies in elderly people - mean: 1.4 g/d (range: 0.9-1.8);</p>	<p>Evidence indicates that n-3 PUFAs do not improve cognitive performance in children, adults or the elderly.</p>

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
Abubakari et al., 2014	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs reporting on healthy or clinical populations of any age; comparing supplementation with any omega-3 fatty acids (ALA, EPA, DHA, DPA) (or combination of omega-3 fatty acids) or fish (or fish oil) of any dose to control or placebo; recorded measure of cognitive endpoints using an appropriate measure or scale; any length of follow up.</p> <p><i>Exclusion:</i> insufficient data reported to permit the calculation of effect sizes; considered another active compound where data for omega-3 fatty acids or fish could not be isolated</p> <p><u>Confounding:</u> No adjustments for confounders reported</p> <p><u>Analysis:</u> Standardized mean difference (SMD) was used to calculate the pooled treatment effect comparing intervention and control groups. The SMD is expressed as the absolute difference in means of the intervention and control groups divided by the pooled standard deviation.</p> <p>Meta-analysis used the fixed effects model</p>	<p>Stroop test; DDT; RBANS; WLTtot; MMSE; ADAS-cog; CDR; verbal fluency; CIBIC-plus; WLT (immediate recall-75 words); 15-word list memory test; 24 week Cantab PAL; CVLT; immediate story recall; delayed story recall; verbal fluency</p>	<p><u>Health at baseline:</u> general or healthy populations + adults with specific clinical or special populations (schizophrenia, memory problems, depression, pregnant women)</p> <p><u>Participants:</u> n=2510</p>	<p><u>Studies:</u> 12 RCTs - 5 involved young/middle aged adults (mean age ≤ 40 years), 7 involved older adults (mean age ≥ 68 years),</p> <p><u>Duration:</u> 4 weeks to 24 months (median 23 weeks)</p> <p><u>Supplementation:</u> combinations of DHA and EPA (dose 0.58 - 1.8g/d), DHA only (dose 0.8 - 2g/d), EPA only (3g/d), ALA (dose 2.82g/d), or fish oil (dose 3g/d).</p> <p>Loss to follow up was reported in 10 studies (range 3% to 27%)</p> <p>No significant change in cognitive function following supplementation with omega-3 fatty acids (pooled SMD -0.04, 95% CI -0.09, 0.01). Heterogeneity not statistically significant ($X^2=11.99$, $df=23$, $p=0.97$).</p> <p>No significant difference in cognitive function between intervention and control groups when stratified for: duration ([short-term <6 months SMD -0.08, 95% CI -0.16, 0.01]; [long term ≥6 months SMD -0.03, 95% CI -0.09, 0.03]); types of participants ([general/healthy population SMD -0.04, 95% CI -0.10, 0.01]; [diseased/clinical populations SMD 0.00, 95% CI -0.10, 0.09]).</p> <p>Significant difference in cognitive function between intervention and control groups when stratified for supplement dose ([low dose ≤1.73g/d SMD -0.07, 95% CI -0.13, -0.02]; [high dose >1.73g/d SMD 0.04, 95% CI -0.06, 0.14]).</p>	<p>Only 1 of the 12 RCTs showed significant improvements in cognitive function following omega-3 fatty acids supplementation</p>
Loef & Walach (2013)	<p><u>Selection criteria:</u> <i>Inclusion:</i> studies considering association of n-6/n-3 ratio and incidence of dementia, AD or cognitive performance in the elderly.</p> <p><i>Exclusion:</i> studies that considered n-3 fatty</p>	<p>Trial: NS</p>	<p>Elderly (see results column for further details)</p>	<p>1 trial, 6 prospective studies, (also: 3 cross-sectional and 3 case-control studies)</p> <p>1 trial: n=21; duration 90 days, interventions were 240mg of either DHA/AA (1:1 ratio) or olive oil. Compared</p>	

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
	acids only, without also considering n-3/n-6 ratio	<p>Consumption ratio cohorts: a) DSM-IV, NINCSDADRDA</p> <p>b) DECO score</p> <p>Blood ratio cohorts: a) tests in delayed word recall, psychomotor speed, and verbal fluency</p> <p>b) MMSE</p> <p>c) DSM IV</p> <p>N-3 & DHA level cohort: NS</p>		<p>with baseline, significant improvements in DHA/AA group in immediate memory and attention score, but not in olive oil group. . No baseline data for dietary or plasma FA levels were reported.</p> <p>2 PCS reported on ratio of consumption of n-3/n-6 FAs: a) n=8085; follow-up 3.5y; age 65+: For APOE-ε4 non-carriers, increased n-6 consumption was significantly associated with increase AD incidence (HR 2.12, 95% CI 1.30, 3.46), unless accompanied by consumption of n-3 rich foods. No association was for APOE-ε4 carriers. b) n=4809; follow-up 13y; age 76+: n-3/n-6 consumption significantly associated with increased cognitive decline (OR_{T3 v T1}=1.25, 95% CI 1.01 – 1.55).</p> <p>3 cohort studies reported on ratio of blood levels of n-3/n-6 FAs: a) n=2251; follow-up 6y; age 50-65: Ratio of AA/(DHA + EPA) not associated with global cognitive decline b) n=1389; follow-up 4y; age 63-74: Ratio of n-3/n-6 FAs and DHA/AA significantly associated with lower cognitive decline (OR 0.55, 95% CI 0.33, 0.91; and OR 0.57, 95% CI 0.35, 0.92 respectively). c) n=1214; follow-up 4y; age 74: Ratio of n-6/n-3 FAs and AA/DHA significantly associated with higher dementia risk (HR 1.09, 95% CI 1.01, 1.19; and HR 1.1, 95% CI 1.03, 1.1 respectively).</p> <p>1 cohort study showed higher erythrocyte n-3 and DHA content to be associated with reduced cognitive decline in APOE-ε4 carriers but not in non-carriers (no effect size reported).</p>	

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
Mazereeuw et al., 2012	<p><u>Selection criteria:</u> <i>Inclusion:</i> randomised, double-blind and placebo controlled; n-3 FA supplementation; populations aged ≥ 50 years without diagnosed psychiatric comorbidity; presented measureable results of neuropsychological testing.</p> <p><i>Exclusion:</i> None stated</p>	Immediate recall, delayed recall, recognition, working memory and executive function, attention and processing speed, MMSE score and ADAS-cog score	<p><u>Health at baseline:</u> cognitively healthy; MCI; AD</p> <p><u>Age:</u> >66 years</p>	<p><u>Studies:</u> 10 RCTs (3 in cognitively healthy participants; 4 in participants with MCI; 3 in participants with AD)</p> <p><u>Duration:</u> 12.8 – 108 weeks</p> <p><u>Supplementation:</u> 19.75 – 1670mg/d EPA + 59 – 1550mg/d DHA (most studies supplemented with EPA and DHA) One study also supplemented with 40mg/d AA</p> <p><u>Cognitively healthy</u> No difference between omega-3 supplementation and placebo in composite memory, immediate recall, delayed recall, recognition, working memory and executive function, attention and processing, immediate verbal recall, delayed verbal recall</p> <p><u>MCI</u> Omega-3 supplementation compared with placebo had an effect on immediate recall (Hedge's g (g) 0.16, 95% CI 0.01, 0.32), attention and processing speed (g 0.32, 95% CI 0.03, 0.61), delayed verbal recall (g 0.30, 95% CI 0.01, 0.57). No difference between omega-3 supplementation and placebo in composite memory, delayed recall, recognition, working memory and executive function, MMSE, immediate verbal recall</p> <p><u>AD</u> No difference between omega-3 supplementation and placebo in MMSE, ADAS-Cog</p>	A small but significant benefit of omega-3 supplementation for immediate recall and attention and processing speed in adults with MCI. No benefit for other measures of cognitive function in adults with MCI. No benefit observed for any measure of cognitive function in cognitively healthy adults and adults with AD.
Sydenham & Dangour, 2012	<p><u>Selection criteria:</u> <i>Inclusion:</i> RCTs, pre-screening of participants for dementia and other cognitive impairment, described method of randomisation, participants <60 years of age, intervention of omega-3 PUFA capsules or a placebo or a strictly enforced or provided dietary intervention including omega-3 PUFA supplemented foods in specific proportions,</p>	MMSE, word learning, verbal fluency, digit spans, Wechsler Digit Span Test, Trail Making Test, Stroop Test.	<p><u>Health at baseline:</u> cognitively healthy</p> <p><u>Age:</u> >60 years</p>	<p><u>Studies:</u> 3 RCTs</p> <p><u>Duration:</u> 24 – 40 months</p> <p><u>Supplementation:</u> 500mg/d DHA + 200mg/d EPA; 400mg/d EPA-DHA, 2g/d ALA, both EPA and ALA; 400mg/d EPA/DHA, 1800mg/d EPA/DHA.</p> <p>None of the RCTs assessed incident of dementia.</p>	The available RCTs showed no benefit of omega-3 PUFA supplementation on cognitive function of cognitively healthy adults.

Review	Methods	Measures of cognitive function	Population	Results	Comments / Conclusion
	<p>intervention provided for 26 weeks or 180 days or longer.</p> <p><i>Exclusion:</i> studies which included participants with dementia or cognitive impairment, intervention consisted of solely dietary advice, intervention based solely on self-report.</p> <p><u>Outcomes:</u></p> <p><i>Primary:</i> incident of dementia defined by international diagnostic criteria.</p> <p><i>Secondary:</i> Difference between study arms at final follow up in recognised measures of memory and cognitive function, safety of omega-3 PUFA supplementation, adherence to omega-3 PUFA supplementation.</p> <p><u>Analysis:</u></p> <p>Where trials had comparable outcomes mean differences (MD) or standardised mean differences (SMD) with 95% CI were calculated using a fixed-effect model.</p> <p>Statistical heterogeneity assessed using Chi² and I² statistics.</p>			<p>Two studies involving 3221 participants tested MMSE score: Mean difference (MD) -0.07 (95% CI -0.25, 0.10)</p> <p>Two studies involving 1043 participants tested immediate word recall: standardised mean difference (SMD) 0.01 (95% CI -0.11, 0.14)</p> <p>Two studies involving 1043 participants tested delayed word recall: SMD -0.04 (95% CI -0.16, 0.09)</p> <p>Two studies involving 1042 participants tested word recognition: SMD 0.04 (95% CI -0.08, 0.16)</p> <p>Two studies involving 1042 participants tested verbal fluency: SMD 0.06 (95% CI -0.06, 0.18)</p> <p>Two studies involving 1018 participants tested digit span forwards: MD 0.03 (95% CI -0.25, 0.31)</p> <p>Two studies involving 1015 participants tested digit span backwards: MD 0.12 (95% CI -0.12, 0.36)</p>	

Abbreviations: AD, Alzheimer's Disease; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; AA, arachidonic acid; BVRT Benton's visual retention test; CI, confidence Interval; CIND, cognitive impairment but not dementia; CASI, Cognitive Abilities Screening Instrument; CAT, Continuous Attention Task; CESD, The Center for Epidemiological Studies Depression Scale; DHA, docosahexaenoic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; EPA, eicosapentaenoic acid; DSST, Digital Symbol Substitution Test; FCRT, Four Choice Reaction Time; n-3 FA, omega-3 fatty acids; HRT, hormone replacement therapy; MD, Mediterranean diet; MMSE, Mini-Mental State Examination; IST "Isaacs" set test; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NOSGER, Nurses' Observation Scale for Geriatric patients; NPE, Neuropsychological Evaluation; OR, odds ratio; POMS, The Profile of Mood State Questionnaire; PS, phosphatidylserine; RAVLT, The Rey Auditory Verbal Learning Test; RCT, randomized controlled trial; RR, relative risk; RMT, Randt Memory Test; SD, standard deviation; SMD standardised mean difference; SMS, Scanning Memory Sets; SB, Social Behaviour; TICS-M, the Modified Telephone Interview for Cognitive Status; TMT, Trail Making Test; y, years; ZCT Zazzo's cancelation test.

Annex 6: Other dietary components – Summary of meta-analysis and systematic reviews

Table 12: Results of systematic reviews and meta-analyses on polyphenol intake and cognition

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
Lamport et al. (2012)	<p><u>Selection criteria:</u> <i>Inclusion:</i> Studies that examined human participants, employed an objective measure of cognitive function using a reliable and valid test, administered a polyphenol intervention condition and a control condition, longitudinal observational studies which measured polyphenol consumption over a stated period, written in English.</p> <p><i>Exclusion:</i> Studies where the primary intervention was Ginkgo Biloba extract, tea, decaffeinated tea or alcoholic beverages (e.g. wine); clinical assessment or diagnosis of Alzheimer's disease or Dementia was the sole measure of cognitive function.</p> <p><u>Analysis:</u> No statistical analysis conducted, studies narratively analysed</p> <p><u>Exposure:</u> Polyphenol intake</p> <p><u>Outcome:</u> Cognitive function</p> <p><u>Control of confounding:</u> The cohort study controlled for age, gender, education, depression, cardiovascular disease, hypertension, BMI, energy intake, diabetes, smoking, and alcohol intake</p> <p>The cross-sectional study controlled for sex, education, vitamin supplement use, smoking status, history of CVD, diabetes and total energy intake.</p>	<p><u>Berry Juice trials:</u> CVLT, Internal Memory test, Selective Reminding Test, Spatial Paired Associated Learning Test., Stroop Color and Word Test, Trail Making Test (parts A and B), Verbal Paired Associated Learning Test., Wechsler Adult Intelligence Scale- III Digit Symbol-Coding subtest, Wechsler Memory Scale-III Faces I and Faces II subtests, Word Fragmentation Test</p> <p><u>Resveratrol RCT:</u> Rapid Visual Information Processing, Serial threes and sevens subtraction</p> <p><u>Cohorts study:</u> Forward and backward DigitSpan, Trail Making Test, Word recall (RI-48), Verbal Fluency.</p> <p><u>Cross-sectional study:</u> Block Design, Controlled OralWord Association Test, Digit Symbol Test, Kendrick Object Learning Test, Trail Making</p>	<p><u>Intervention studies</u></p> <p><i>Polyphenols in berry juice:</i> 4 trials – 2 reported significantly better immediate verbal recall in the berry juice groups (after 12 weeks), 2 reported no significant effect on cognition (after 1 day and 6 weeks respectively).</p> <p><i>Resveratrol supplement</i> 1 RCT, reported no significant effect on cognition (after 45 mins)</p> <p><u>Epidemiological studies:</u> 1 PCS (n=2574) - reported that higher polyphenol intake was associated with better language and memory performance and worse executive function after 13 years of follow-up.</p> <p>1 cross-sectional study (n=2031) – reported on the consumption of polyphenol rich foods. Of 5 cognitive function tests, wine consumption showed a beneficial associated with 4 tests, tea consumption with 3 tests and chocolate consumption with 1 test.</p>	The identified evidence base on the relationship between polyphenols and cognition is limited and inconsistent.

Table 13: Results of systematic reviews and meta-analyses on flavonoids

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Cao et al. (2016)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> Cohort studies on anti-oxidant intake and dementia risk; white subjects; follow-up >= 1 year; risk ratio and 95%CI available, or data from which these can be calculated; exposure: dietary pattern; outcome.</p> <p><i>Exclusion:</i> Cross-sectional studies; non-original research (e.g. reviews); duplicated studies.</p> <p><u>Analysis:</u> Meta-analysis</p> <p><u>Exposure:</u> Flavonoids intake</p> <p><u>Outcome:</u> Dementia risk</p> <p><u>Control of confounding:</u> Study 1 adjusted for age, sex, MMSE baseline, alcohol intake, education, smoking habits and pack-years, body mass index, total energy intake, presence of carotid plaques, and antioxidative supplements</p> <p>Study 2 adjusted for age, gender, education, weight and vitamin C intake</p>	<p>Dementia risk DSM-III-R MMSE NINCDS-ADRDA</p>	<p><u>2 PCS</u></p> <ul style="list-style-type: none"> • Meta-analysis showed no significant association RR=0.97 (95% CI 0.65–1.46); • For both studies n is not stated; mean age = > 55 and >65; follow-up = 5y and 6y. 	<p>A meta-analysis of 2 PCS showed no significant association of flavonoid intake and dementia risk.</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Crichton et al. (2013)</p>	<p><u>Selection criteria:</u> <i>Inclusion</i> : Cross-sectional, prospective cohort and longitudinal studies; report an association between dietary antioxidant intake (incl. flavonoids) and cognitive function; only studies that included a quantitative assessment of dietary antioxidant intake; provide measures for at least one aspect of cognitive function obtained from neuropsychological testing or provide an estimate of probable dementia, including AD. <i>Exclusion</i>: Studies on wholefoods or beverages (e.g. fruits, vegetables, chocolate, tea), antioxidant supplements and blood levels of antioxidants; studies that used self-reported cognitive function.</p> <p><u>Analysis:</u> No meta-analysis was undertaken</p> <p><u>Exposure:</u> Flavonoids intake</p> <p><u>Outcome measures:</u> Cognitive function and risk of dementias</p> <p><u>Control of confounding:</u> <i>Cross-sectional study</i> : Age, gender, energy intake, socio-economic group, smoking, education, APOE e4, childhood IQ <i>Longitudinal study</i> : Of the 6 studies, 6 adjusted for education (x 6), smoking (x 5), Age (x 5), total energy (x 4), BMI (x 4), Alcohol (x 4), gender (x 3), antioxidant supplement use (x 3), baseline MMSE (x 2), APOE e4 (x 2), weight (x 1), presence of carotid plaques (x 1), physical activity (x 1), CVD history (x 1), Cholesterol (x 1), BP (x 1), birth year (x 1)</p>	<p><u>Cross-sectional study:</u> National Adult Reading Test</p> <p><u>Longitudinal studies:</u> MMSE; clinical evaluations and standardised diagnostic criteria of dementias</p>	<p><u>1 Cross-sectional study</u></p> <ul style="list-style-type: none"> Butchart et al. (2011) (n=1091; age 70) reported significant association of flavone intake with higher NART score <p><u>6 PCS</u></p> <ul style="list-style-type: none"> Kalmijn et al. (1997) (n=1091; age 68-69; follow-up 3y) reported no significant association with cognitive impairment or decline. Commenges et al. (2000) (n=1367; age ≥65; follow-up 5y) reported significant association of flavonoids intakes >11.5 mg/d and reduced dementia risk (RR=0.49, 95 % CI: 0.26–0.92, p=0.04). Engelhart et al. (2002) (n=5395; age ≥55; follow-up 6y) reported no association of flavonoid intake and AD risk. Laurin et al. (2004) (n=2459; age 45-68; follow-up 30y) reported no association of flavonoid intake and risk of dementia, AD or vascular dementia. Letenneur et al. (2007) (n=1640; age ≥65; follow-up 10y) reported flavonoid intakes >13.6 mg/d to be associated with a reduced rate of cognitive decline. Devore et al. (2010) (n=5395; age ≥55; follow-up 9.6y) reported no association of flavonoid intake and risk of dementia or AD. 	<p>The authors concluded that flavonoids do not appear to be associated with a reduced risk of dementia or AD.</p>

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<p>Rafnsson et al. (2013)</p>	<p><u>Selection criteria:</u> <u>Inclusion:</u> Original primary studies; population-based cohort studies; at least a single baseline measurement of one or more major antioxidant nutrients, including, flavonoids; assessment of cognitive function with standardized tests on at least two different occasions; English language reports only.</p> <p><u>Exclusion:</u> Non-human studies; other study designs; hospital inpatients or patient samples; studies without appropriate antioxidant nutrient data; studies without information on cognitive performance assessed on more than one occasion.</p> <p><u>Analysis:</u> No statistical analysis was undertaken</p> <p><u>Exposure:</u> Flavonoids intake</p> <p><u>Outcome:</u> Cognitive decline</p> <p><u>Control of confounding:</u> Age (x 2, i.e. in 2 studies), education (x 2), sex, smoking, alcohol consumption, energy intake, polyunsaturated fatty acids, and baseline cognitive function.</p>	<p>Global cognitive function (MMSE); visual memory (BVRT); verbal fluency (IST); visuospatial attention (ZCT); psychomotor speed (DSST)</p>	<p><u>2 PCS</u></p> <ul style="list-style-type: none"> • Kalmijn et al. (1997) (n=1091; age 68-69; follow-up 3y); no significant association (OR = 0.86; 95 % CI = 0.39–1.89). • Letenneur et al. (2007) (n=1640; age ≥65; follow-up 10y); significant association for 4th (p=0.001) and 3rd (p=0.046) quartiles of flavonoid intakes. 	<p>Of two identified PCS, one showed no association and one showed higher flavonoid intakes to be associated with slower rate of cognitive decline.</p>

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<p>Lampport et al. (2012)</p>	<p><u>Selection criteria:</u> <i>Inclusion:</i> Studies that examined human participants, employed an objective measure of cognitive function using a reliable and valid test, administered a polyphenol intervention condition and a control condition, longitudinal observational studies which measured polyphenol consumption over a stated period, written in English.</p> <p><i>Exclusion:</i> Studies where the primary intervention was Ginkgo Biloba extract, tea, decaffeinated tea or alcoholic beverages (e.g. wine); clinical assessment or diagnosis of Alzheimer's disease or Dementia was the sole measure of cognitive function.</p> <p><u>Analysis:</u> No statistical analysis was undertaken studies</p> <p><u>Exposure:</u> Flavonoids intake</p> <p><u>Outcome:</u> Cognitive function</p> <p><u>Control of confounding:</u> not stated</p>	<p><u>Flavonoids in cocoa:</u> Attention switching task also; Choice reaction time; Memory Test; Rapid Visual Information Processing; Scale-III Digit Symbol-Coding Subtest; Scale-III Faces I and Faces II Subtests; Selective Reminding Test; Serial sevens subtraction; Serial threes subtraction; Stroop Test; Task (RVIP), ; Trail Making Test; Visual Spatial Working; Wechsler Adult Intelligence; Wechsler Memory;</p> <p><u>Flavonoid supplements:</u> Complex Visual Vigilance Contextual Memory Digit Vigilance Immediate and Delayed Recognition, Simple and Choice Reaction Time Spatial and Numerical Working Memory Visual Vigilance</p>	<p>The effect sizes of primary studies were not reported by Lampport et al. (2012).</p> <p><u>4 RCTs on flavonoids in cocoa</u></p> <ul style="list-style-type: none"> Field et al. (2011) (n=30; age 18-25y; intervention: flavanols in cocoa; cognitive tests after 2hrs) Significantly better spatial working memory and choice reaction time in intervention. Scholey et al. (2009) (n=30; age 18-35y; intervention: flavanols drink at two doses (low and high); cognitive tests after 1.5hrs) Significantly better in serial threes subtraction (high and low dose) and Rapid Visual Information Processing Task (RVIP) (high dose), but not for serial sevens subtraction (high and low dose) and RVIP (low dose). Crews et al. (2008) (n=101; mean age 69y; intervention: flavonoids in dark chocolate; 6w intervention period); No significant difference in 6 cognitive tests (Selective Reminding Test, Stroop Test, Trail Making Test, Wechsler Adult Intelligence Scale-III Digit Symbol-Coding Subtest, Wechsler Memory Scale-III Faces). Francis et al. (2006) (n=16; age 18-30y; intervention: flavanols in cocoa drink; 5d intervention period) no significant difference in attention switching performance. <p><u>2 RCTs with flavonoid supplements</u></p> <ul style="list-style-type: none"> Pipingas et al. (2008) (n=42; mean age 58y; intervention period: 5 weeks); 2 of 8 cognitive tests were significantly better (faster spatial working memory and faster word recognition). Ryan et al. (2008) (n=101; mean age 68y; intervention period: 3 months); 1 of 7 cognitive test were significantly better at 3 months, but not at 1 or 2 months (spatial working memory). 	<p>Of 4 RCT's reporting on flavonoids in cocoa; 2 showed significantly better cognition 1.5 and 2 hrs after cocoa consumption, while the two longer-term RCTs showed no association after 5 days and 6 weeks.</p> <p>Two RCTs with flavonoid supplements showed a significant association with better cognition.</p> <p>Of 13 RCTs that reported on isoflavone supplementation 6 showed significantly better cognition in the intervention group, while 6 RCTs reported no association and one RCT reported mixed results.</p> <p>One PCS of flavonoid intake showed less cognitive decline over 10 years.</p>

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
		<p><u>Isoflavone supplements:</u></p> <p>Arithmetic Test; Backward Digit Span; Benton Visual Retention Test; Block Design Test; Boston Naming Test; Buschke Selective Reminding Test; CANATB Delayed Matching to Sample test; CANTAB IDED test; CANTAB Spatial memory; CANTAB tests of frontal lobe function; Category Fluency; Colour Matching; Corsi Block Tapping Test; Cube Comparisons Test; Delayed Matching to Sample test; Digit Cancellation; Digit Ordering; Digit Recall Digit Symbol; Digit Span; Digit Symbol Substitution; Digit Symbol Test; Digit Vigilance; Doors Test; Finger Tapping Test; Grooved Peg Board; Hong Kong List Learning Test; Identical Pictures Test; Immediate and Delayed Paragraph Recall; Immediate Verbal Recall (WMS-R); Letter Fluency; Letter-Number Sequencing; Mental Rotation Task; Novel-Spatial Working Memory; Paced Auditory Serial Addition Test; Paired Associates Learning; Paragraph Recall;</p>	<p><u>13 RCTs with isoflavone supplements</u></p> <ul style="list-style-type: none"> Basaria et al. (2009) (n=93; mean age 56y; intervention period: 12 weeks) No significant difference in 6 cognitive function tests. Gleason et al. (2009) (n=30; mean age 73y; intervention period: 6 months) 10 cognitive function tests: intervention significantly better in 4 tests; placebo group significantly better in 3 tests. Thorp et al. (2009) (n=34; mean age 49y; intervention period: 6 weeks) intervention group significantly better in 1 of 8 cognitive function tests. Fournier et al. (2007) (n=79; mean age 56y; intervention period: 16 weeks) no significant difference in 7 cognitive function tests. Ho et al. (2007) (n=168; mean age 63y; intervention period: 6 months) no significant difference in 9 cognitive function tests. Vanata & Metzger (2007) (n=50; mean age 20y; cognitive assessment 1.75hrs post intervention) no significant difference in 3 cognitive function tests. Casini et al. (2006) (n=78; mean age 50y; intervention period: 6 months) intervention group significantly better in 2 of 3 cognitive function tests. File et al. (2005) (n=50; mean age 58y; intervention period: 6 weeks) intervention group showed greater improvement in 4 of 6 cognitive function tests. Howes et al. (2004) (n=28; mean age 68y; intervention period: 6 months) no significant difference in 11 cognitive function tests. Kreijkamp-Kaspers et al. (2004) (n=175; mean age 67y; intervention period: 12 months) no significant difference in 9 cognitive function tests. 	

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
		<p>PASAT; Rey AVLT; Rey Complex Figure Test; Similarities Test; Stockings of Cambridge; Stroop Test; Trail Making A and B; Verbal Fluency; Visual Memory; Visual Pattern Recognition; Visual Scanning Test; Visual Spatial Learning Test; Visual Spatial Memory; Word Recall; Word Recognition</p> <p><u>Flavonoids (cohort):</u></p> <p>Benton Visual Retention Test; Isaacs Set Test; Mini Mental State Examination</p>	<ul style="list-style-type: none"> • Duffy et al. (2003) (n=33; mean age 58y; intervention period: 12 weeks) intervention group showed significantly greater improvement in 5 of 7 cognitive function tests. • Kritz-Silverstein et al. (2003) (n=53; mean age 60y; intervention period: 6 months) intervention group showed greater improvement in 1 of 5 cognitive function tests. • File et al. (2001) (n=27; mean age 25y; intervention period: 10 weeks) intervention group showed greater improvement in 5 of 11 cognitive function tests. <p><u>1 PCS of flavonoid intake</u></p> <p>Letenneur et al. (2007) (n=1640; mean age 77; follow-up 10y) higher flavonoid intake associated with less cognitive decline over 10 years.</p>	

Review	Methods	Measures of cognitive function	Results	Comments / Conclusion
<p>Clement et al. (2011)</p>	<p><u>Selection criteria</u> <u>Inclusion:</u> Double-blind RCTs in post-menopausal women; intervention period at least 4 weeks; outcome had to be validated measure of cognitive function.</p> <p><u>Exclusion:</u> Open label trials; less than 4 weeks duration.</p> <p><u>Analysis:</u> No statistical analysis was undertaken.</p> <p><u>Exposure:</u> Isoflavone supplementation.</p> <p><u>Outcome:</u> Cognitive function.</p> <p><u>Control of confounding:</u> not stated</p>	<p>Attention; Category fluency; Category generation; Cognitive & perceptual speed; Digit Span Test; Digit Symbol Test; Episodic memory; Executive function; Frontal lobe function; Logical memory and recall; MMSE; Selective attention; Short-term visuo-spatial memory; Sustained attention; Trials A; Trials B; Verbal competence & semantic retrieval; Verbal episodic memory; Verbal fluency; Visual long-term memory; Visual memory; Visual perception and constructional ability; Visual reproduction; Visual Scanning Test; Visuo-spatial working memory</p>	<p>The effect sizes of primary studies were not reported by Clement et al. (2011).</p> <p><u>8 RCTs</u></p> <ul style="list-style-type: none"> • Kreijkamp-Kaspers et al. (2004) (n=175; age 60 to 75y; intervention period: 12 months) no significant difference between groups. • Duffy et al. (2003) (n=33; age 50 to 60y; intervention period: 12 weeks) intervention group showed significant improvements in 4 cognitive function tests. • Basaria et al. (2009) (n=84; age 46 to 76y; intervention period: 12 weeks) no significant difference between groups. • Fournier et al. (2007) (n=79; age 48 to 65y; intervention period: 16 weeks) no significant difference between groups. • Ho et al. (2007) (n=176; age 55 to 76y; intervention period: 6 months) no significant difference between groups. • Kritz-Silverstein et al. (2003) (n=56; age 55 to 74y; intervention period: 6 months) intervention group showed significant improvement in 1 of 5 cognitive function tests. • File et al. (2005) (n=50; age 51 to 66y; intervention period: 6 weeks) intervention group showed significant improvement in tests assessing frontal lobe function. • Casini et al. (2006) (n=78; age range ~50y; intervention period: 6 months) significant improvement in 2 of 3 cognitive function tests. 	<p>Authors concluded that evidence failed to conclusively demonstrate a beneficial effect of isoflavone supplementation on cognition in postmenopausal women.</p>

Table 14: Caffeine intake and cognition: PCS included in considered reviews

Citation	Assessed outcome	Systematic review (SR) or meta-analysis (MA)	Noguchi-Shinohara et al. (2014)	Wang et al. (2014)	Vercambre et al. (2013)	Feng et al. (2012)	Arab et al. (2011)	Gelber et al. (2011)	Corley et al. (2010b)	Ritchie et al. (2010)	Santos et al. (2010b)	Eskelinen et al. (2009)	Laitala et al. (2009)	Ng et al. (2008)	Ritchie et al. (2007)	van Gelder et al. (2006)	(Dai et al., 2006)	Lammi et al. (1989)	van Boxtel et al. (2003)	Lindsay et al. (2002)	Tyas et al. (2001)	Laurin et al. (2004)
Kim et al. (2015)	AD, cognitive impairment, and cognitive decline	MA	✓	✓							✓	✓	✓	✓	✓		✓			✓		
Panza et al. (2015)	MCI, AD, unspecified dementia, cognitive impairment/decline	SR			✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Beydoun et al. (2014)	Normal progressing to dementia, AD, cognitive function, cognitive decline or cognitive impairment (including MCI)	SR				✓	✓	✓	✓	✓	✓	✓	✓	✓		✓			✓			
Arab et al. (2013)	Cognitive decline	SR					✓				✓		✓	✓	✓				✓			
Santos et al. (2010a)	Cognitive decline	MA									✓	✓	✓	✓	✓	✓		✓		✓	✓	

Table 15: Results of systematic reviews and meta-analyses on caffeine intake and cognition (cohort studies and RCTs only)

Study	Methods	Measures of cognitive function	Results	Conclusion/comments
Kim et al. (2015)	<p><u>Selection criteria</u> <i>Inclusion:</i> Cohort studies (case control and cross-sectional also included but not reported here); Human studies only.</p> <p><i>Exclusion:</i> Studies reporting intake of caffeine-containing pill supplements; Studies with insufficient data.</p> <p><u>Exposure:</u> Caffeine consumption from coffee or tea intake.</p> <p><u>Outcome:</u> Cognitive disorders such as AD, cognitive impairment, and cognitive decline.</p> <p><u>Control of confounding:</u> Age, sex, education.</p>	DSM-IVE TELE NINCDS-ADRDA MMSE	<p><u>9 PCS</u> n=223-7017; follow-up: 1.3-28y; mean age: $\geq 55 - \geq 65$.</p> <p>Summary estimate for the association between intake and cognitive disorders combined (AD, dementia and cognitive decline).</p> <p><i>Caffeine</i> RR 0.96 (95%CI 0.73, 1.28) $I^2=58.8\%$</p> <p><i>Coffee</i> RR 0.90 (95%CI 0.59, 1.36) $I^2=60.0\%$</p> <p><i>Tea</i> RR 1.04 (95%CI 0.74, 1.46) $I^2=50.2\%$</p>	Meta-analysis showed no association between the intakes of either caffeine, coffee or tea and the risk of cognitive disorders.
Panza et al. (2015)	<p><u>Selection criteria</u> <i>Inclusion:</i> Cohort studies (cross-sectional and case-control studies also included but are not reported here); Provision of a description of the assessment of coffee, tea, or caffeine intake/plasma caffeine levels. Provided diagnostic criteria for MCI, AD, unspecified dementia, or the neuropsychological tools used to define late-life cognitive impairment/decline; Presentation of original data; Only human subjects.</p> <p><i>Exclusion:</i> Covering irrelevant topic; No original data; Comments/editorials/reviews.</p>	MSQ MMSE VVLT MCRT LDST CF CST SCWT MMSE BVRT TELE TICS Isaac's Set test DSM-III-R NINCDS/ADRDA CADDTC	<p><u>16 PCS</u> n=124-7139; follow-up: 2-30.2 y; mean age: 50.2-91.4y.</p> <p><i>Caffeine (5 PCS)</i> Higher caffeine intake associated with less cognitive decline in women but not men (two studies) and all-male participants (1 study). Higher caffeine intake was associated with less decline in complex motor speed (1 study). n=716-7017; f/u=4-25y; mean age=24->65y.</p> <p>Caffeine intake not associated with AD, dementia, or cognitive impairment (1 study). n=3734; f/u=25y; mean age=52y.</p> <p>Plasma caffeine levels greater than 1200 ng/ml in MCI subjects were associated with no conversion to dementia (1 study). n=124; f/u=2-4y; mean age=65y Miami cohort, 88y Tampa cohort.</p>	The authors conclude that some evidence suggests a protective effect of caffeine, coffee, or tea consumption against cognitive impairment, decline and dementia, with a stronger association in women than men. However, there was no distinct dose-response relationship.

Study	Methods	Measures of cognitive function	Results	Conclusion/comments
	<p><u>Exposures:</u> Tea / coffee / caffeine</p> <p><u>Outcomes:</u> MCI, AD, unspecified dementia, cognitive impairment/decline.</p>		<p><i>Coffee (9 PCS)</i> Higher coffee intake associated with less AD (2 studies). Two studies found higher coffee intake associated with better cognitive function in women but not men. 1 all-male cohort found a protective effect on cognitive function with higher coffee intake, and another found a significant J-shaped curve in 1 study with coffee intake and cognitive decline (male population). <i>n = 676-4809; f/u=5-25y; mean age=50.2->65y.</i></p> <p>No associations between coffee intake and cognitive performance (1 study), cognitive impairment (1 study), and AD (1 study). <i>n = 1039-3734; f/u=1.3-28y; mean age=55-73.6y (1 NR).</i></p> <p><i>Tea (8 PCS)</i> Higher tea intake was associated with better cognitive function (1 study), and decreased cognitive decline (1 study), and reduced cognitive decline in women only (1 study). <i>n = 1039-7139; f/u=1.3-7y; mean age=55-91.4y (1 NR).</i></p> <p>Tea was not associated with AD (4 studies) or dementia (2 studies). <i>n = 1836-4615; f/u=5-30.2y; mean age=50.4-52y (2 NR).</i></p>	
Beydoun et al. (2014)	<p><u>Selection criteria</u> <i>Inclusion:</i> Study sample size > 300; Cohort study (cross-sectional studies also selected but not included here).</p> <p><i>Exclusion:</i> Case-control studies, review articles, commentaries, and basic science papers.</p> <p><u>Outcomes:</u> Dementia, AD, cognitive function, cognitive decline or cognitive impairment (including MCI).</p>	Hachinski Ischemic Score ICD-10 DSM-IV ADDTc NINCDS-ADRDA other clinical features / symptoms.	<p><u>11 PCS</u> <i>n=641-7139; follow-up: 1.3-28y; mean age: 54-91.4y (one study reported only age range: 24-81y).</i></p> <p>Positive findings (i.e. caffeine improved cognitive performance) in 3 studies: coffee (1 study), tea (2 studies). Two additional studies found positive findings for coffee but not tea.</p> <p>5 studies detected this association only among women.</p> <p>3 studies did not find an association between caffeine intake and cognitive change.</p> <p>Multiple logistic regression results (study level predictors of study finding): Caffeine OR 0.18; [95%CI 0.04;0.84];p=0.029</p>	Beydoun et al. (2014) do not draw any conclusion on the association between caffeine intake and cognitive outcomes, commenting that the evidence is too limited.

Study	Methods	Measures of cognitive function	Results	Conclusion/comments
Arab et al. (2013)	<p><u>Selection criteria:</u> <u>Inclusion:</u> Studies with a cohort design that addressed the relation between caffeine consumption through coffee and/or tea regardless of assessment of other dietary sources of caffeine.</p> <p><u>Exclusion:</u> Reviews; Did not study humans; Did not measure caffeine, tea, or coffee; Articles in which cognitive decline was not measured or measured through Alzheimer's disease or dementia; Analyses with dichotomous outcomes; Cross-sectional studies.</p> <p><u>Exposures:</u> Caffeine consumption through coffee and/or tea.</p> <p><u>Outcome:</u> Cognitive decline.</p> <p><u>Confounding:</u> Age, education (all studies); Smoking, sex, other health variables (5 studies).</p>	MMSE 3MS Benton Visual Retention Test Isaacs Set tests Visual Verbal Learning Test Motor Choice Reaction Test Concept Shifting Test Letter Digit Substitution Test Fluency Test Stroop Colour Word Test	<p><u>6 PCS</u> n=309-7017; follow-up: 1.3-10 years; mean age: ≥ 55 - ≥ 65y.</p> <p><i>Caffeine</i> Higher caffeine intake was significantly associated with a reduction in cognitive decline in 3 studies, in women only not men. One study found a significant association between MCRT and higher caffeine intake.</p> <p><i>Coffee</i> 1 study found a significant J-shaped curve with the least amount of cognitive decline for 3 cups of coffee per day.</p> <p><i>Tea</i> Significant trend with increasing tea intake associated with less cognitive decline (1 study). Significant association between higher tea intake and lower cognitive decline only when high tea consumption was compared with no consumption in women (1 study).</p>	Arab et al. (2013) conclude that although there is no dose-response relationship, cognitive decline tended to be lower in caffeine, coffee, and/or tea consumers, with a stronger association in women than men.
Santos et al. (2010a)	<p><u>Selection criteria:</u> <u>Inclusion:</u> Cohort studies (case-control and cross-sectional also selected but not included here). Only studies that addressed the relation between caffeine consumption, through coffee and/or tea intake regardless of assessment of other dietary sources of caffeine, and different forms of dementia, cognitive impairment, or cognitive decline (all diagnostic criteria were considered).</p> <p><u>Exclusion:</u></p>	MSQ, 3MS test, NINCDS-ADRDA, DSM-IV, MMSE, BVRT, Isaacs Set test, DSM-IV	<p><u>9 PCS</u> n=309-7017, follow-up: 1.3-28 years; mean age: not reported.</p> <p>Meta-analysis for the association between caffeine intake and combined measures of cognitive impairment/decline was not significant: RR 0.93 (CI: 0.83, 1.04 $I^2=0.0\%$)</p> <p>One study (Ritchie et al. (2007)) is highly influential, with a weight of 60% in the overall RR estimate. When excluded, the summary RR for cohort studies was RR 0.85 (95%CI 0.71, 1.01, $I^2=0.0\%$).</p>	No significant association was shown, between caffeine intake and a combined measure of cognitive impairment, decline, and dementia.

Study	Methods	Measures of cognitive function	Results	Conclusion/comments
	<p>Cross-sectional studies or analyses relying on retrospective assessment of exposure when cognitively impaired subjects were the informants for estimation of their own caffeine intake.</p> <p><u>Outcome:</u> Cognitive decline.</p> <p><u>Control of confounding:</u> Age, sex, education, depressive symptoms.</p>			