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Review Article

The effects of flavonoid and other polyphenol consumption on cognitive performance: A systematic research review of human experimental and epidemiological studies

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Abstract. Literature reviews suggest flavonoids, a sub-class of polyphenols, are beneficial for cognition. This is the first review examining the effect of consumption of all polyphenol groups on cognitive function. Inclusion criteria were polyphenol vs. control interventions and epidemiological studies with an objective measure of cognitive function. Participants were healthy or mildly cognitively impaired adults. Studies were excluded if clinical assessment or diagnosis of Alzheimer's disease, dementia, or cognitive impairment was the sole measure of cognitive function, or if the polyphenol was present with potentially confounding compounds such as caffeine (e.g. tea studies) or Ginkgo Biloba. 28 studies were identified; 4 berry juice studies, 4 cocoa studies, 13 isoflavone supplement studies, 3 other supplement studies, and 4 epidemiological surveys. Overall, 16 studies reported cognitive benefits following polyphenol consumption. Evidence suggests that consuming additional polyphenols in the diet can lead to cognitive benefits, however, the observed effects were small. Declarative memory and particularly spatial memory appear most sensitive to polyphenol consumption and effects may differ depending on polyphenol source. Polyphenol berry fruit juice consumption was most beneficial for immediate verbal memory, whereas isoflavone based interventions were associated with significant improvements for delayed spatial memory and executive function. Comparison between studies was hampered by methodological inconsistencies. Hence, there was no clear evidence for an association between cognitive outcomes and polyphenol dose response, duration of intervention, or population studied. In conclusion, however, the findings do imply that polyphenol consumption has potential to benefit cognition both acutely and chronically.

Keywords: Polyphenols, flavonoids, isoflavones, cognitive function, memory, executive function

1. Introduction

Polyphenols are a group of naturally occurring substances which are found in plants and are characterised by the presence of a least one phenol unit per molecule. Polyphenols can be separated into several classes. These include flavonoids, lignans, phenolic acids, and stilbenes. The processes of food fermentation, storage, and cooking can also produce other, unknown polyphenols. Singh et al. [1] suggest it is useful to characterise polyphenols as either flavonoids or non-flavonoids. Flavonoids can be divided into several major sub-classes according to the degree of oxidation

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of the heterocyclic ring; flavonols (e.g. quercetin and kaempferol), flavanols (e.g. catechin and epicatechin) and their polymers (e.g. proanthocyanidins), flavones (e.g. apigenin and luteolin), flavanones (e.g. naringenin and hesperetin), isoflavones (e.g. genistein and daidzein), and anthocyanins (e.g. cyanidin and malvidin).

The main source of polyphenols in our diet is fruits and beverages such as fruit juice, tea, coffee, wine, beer and chocolate. Consumption of vegetables and cereals also contributes to a lesser extent. Average daily intake of total polyphenols has been recently estimated as 1193 mg/d, although the authors suggest this may be a slight underestimate due to insufficient data on the polyphenol content of foods (proanthocyanidins and thearubigins) [2]. The main flavonol in our diet is quercetin which is present in many fruits, vegetables and beverages. Mean intake of quercetin per day has been estimated at 16 mg/day [3]. Anthocyanins are present in red, blue and purple fruits such as berries, grapes and strawberries. Proanthocyanidins are usually present in plants and are found in apples, pears, grapes, red wine, tea, and chocolate [1]. Catechins are the main flavanols, and are abundant in tea. Other sources of catechins are red wine and chocolate [4, 5]. Flavones are less common and are known to be present in red pepper and celery [3]. Stilbenes, (non-flavonoids) are present in a variety of plants and beverages, including wine, dark chocolate, nuts and berries [6], however, their concentrations are lower than other polyphenols. Nevertheless, the stilbene resveratrol found in red wine has received great attention for its anticarcinogenic properties [7], and its neuroprotective effect [8]. One of the main sources of dietary flavanones are citrus fruits and juices [9] with hesperetin, naringenin and eriodictyol being the most common types. Isoflavones are present in the highest amount in soy beans, flaxseed and legumes with genistein, daidzein and glycitein being the most common types. Overall, non-flavonoids account for about a third of total phenols whereas flavonoids account for around two thirds [1].

In normal aging and neurodegenerative disease (e.g. Parkinson's disease and Alzheimer's disease) inflammatory processes within the brain are understood to be partially responsible for cognitive decline [10]. It is thought that polyphenols have antioxidant properties which may reduce inflammatory and neurodegenerative effects (for review see [11–13]). Consequently, there has been an increase in research investigating the effects of polyphenol consumption for cognitive function in humans. A recent review of randomised controlled trials examining the effect of flavonoid consumption on cognitive function concluded that there is some encouraging evidence that flavonoids may be beneficial for cognition [14]. However, to date there has been no recent systematic review including all polyphenol groups. Therefore, the aim of the present paper was to systematically evaluate human studies examining the relationship between polyphenol consumption and cognitive function, in order to suggest recommendations for the design and focus of future research.

2. Method

A systematic review of the literature was performed using the following search strategy.

2.1. Search terms

A search of the literature was conducted using the search terms polyphenol$, flavon$, Flava$, cognit$, isoflavone, proanthocyanidin, anthocyanidin, and memory using the Boolean operator "and". The $ was used for truncation to ensure that key words such as flavanols, flavonols, flavones, cognition and cognitive performance etc. were included. This search returned 845 articles from the databases listed below.

2.2. Databases

A search of the following databases was performed: AMED (Allied and Complimentary Medicine, 1985 to Dec 2011), EMBASE (Excerpta Medica Reviews 1980 to 2011), Food Science and Technology Abstracts, Global Health (1975 to 2011), HMIC (Health Management Information Consortium, 1983 to Dec 2011), Ovid Medline (1950 to Dec 2011), Pubmed (1948 to Dec 2011), PsycInfo (1866 to Dec 2011), Web of Science (1986 to Dec 2011). A hand search of recently published relevant journals and a scan of references from the included studies were also performed.

2.3. Inclusion and exclusion criteria

Studies were included if they examined human participants, employed an objective measure of cognitive function using a reliable and valid test, and administered a polyphenol intervention condition and a

control condition. Only manuscripts written in English were included. Longitudinal observational studies which measured polyphenol consumption over a stated period were also included. Studies were excluded if the primary intervention was Ginkgo Biloba extract or if clinical assessment or diagnosis of Alzheimer's disease or Dementia was the sole measure of cognitive function. Studies of tea were excluded due to the confounding effects of caffeine and theanine [15], and studies of decaffeinated tea were excluded due to expectancy effects [16, 17]. Studies investigating polyphenol consumption exclusively from alcoholic beverages (e.g. wine) were excluded due to the confounding effects of alcohol. Associations between alcohol consumption over the lifespan and cognitive benefits have been observed, possibly due to improved vascular outcomes [18, 19].

3. Results

As shown in Table 1, the search strategy identified twenty eight articles after removal of duplicates and application of inclusion and exclusion criteria.

3.1. Berry juice studies

Table 1 shows that only four studies have been conducted which specifically examine the cognitive impact of polyphenols in the form of berry fruit juice. A relatively short 6 week intervention with older adults (aged >59) failed to find any effects of cranberry juice consumption on a range of cognitive outcomes [23]. The exact polyphenol dose was not stated, there was no consideration of habitual polyphenol consumption, and no details were provided regarding cognitive test procedures such as time of day of testing. In contrast, two 12 week intervention studies with grape juice or blueberry juice in adults with mild cognitive impairment (MCI) reported benefits for immediate verbal and spatial memory [20, 22]. However, both of these between group comparisons had very small sample sizes with only five participants in the grape polyphenol condition [20] and nine participants in the blueberry condition [21]. Given the small sample size, it is possible that the observed effects in the grape juice study may be partly explained by the older age of the control group (80 years) relative to the grape juice group (75 years). A five year age difference at the extremes of the lifespan can be associated with substantial differences in cognitive performance [47]. Similarly, the blueberry group were four years younger than the control group (76 years). Furthermore, the control group, which consumed a placebo designed for the grape study, was also used for the blueberry study (i.e. a new control group was not recruited nor blueberry juice placebo utilized). This suggests the findings from these two studies are perhaps better considered as a three condition study and should have been analysed accordingly, although this would result in a loss of power from the increased number of comparisons. It is also of interest to note that these two studies attempted to control for baseline cognitive performance by adding baseline as a covariate with post intervention cognition as the cognitive outcome. Finally, Krikorian et al. [20] did not report the specific dosage of polyphenol per day consumed.

These are the only three studies to date which have examined the cognitive effects of a long term polyphenol intervention in the form of berry fruit juice, all of which have recruited older adults (aged >60). An acute study in young adults reported that consuming grape juice with a standardised lunch did not affect cognition over the afternoon [22]. It is possible that any effects of the grape juice were obscured by the concomitant consumption of lunch. In addition, habitual polyphenol consumption was not assessed, although participants who consumed polyphenol supplements were excluded. Overall, these studies suggest that polyphenol consumption in the form of berry fruit juice over a period of 12 weeks has some potential for cognitive benefits, particularly for verbal memory, at least in older adults or those with mild cognitive impairment (MCI).

3.2. Cocoa studies (flavonoid-rich)

Both a 6 week cocoa intervention using chocolate bars in healthy older adults (mean age 69) [26] and a 5 day chocolate drink intervention in younger adults (aged 18–30) [27] showed no effects on cognitive performance. In contrast, two acute studies have shown consistent beneficial effects of cocoa flavanol consumption on working memory and attention. Scholey et al. [25] reported improved working memory and attention over a period of 90–150 minutes after consumption of chocolate drinks containing 520 mg and 994 mg flavanols relative to a 46 mg control, and Field et al. [24] reported improved spatial working mem-

Table 1

Summary of studies examining the relationship between polyphenol consumption and cognitive performance (sponsor/source of product in brackets where available)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Berry juice Krikorian et al. 2010a [20]	8 males 4 females mean age 78 (sd 5). All scored mild impairment on the Clinical Dementia Rating scale	Concord Grape Juice (Welch's). 6–9 ml per kg divided over 3 servings a day. Details of polyphenols not given. Placebo matched for appearance, taste, carbohydrate, and energy	12 week, parallel groups, placebo controlled, randomised, double blind. $n = 5$ for grape juice, $n = 7$ for placebo	Tested at baseline and 12 weeks. CVLT, Spatial Paired Associated Learning Test. Baseline performance included as a covariate	Significantly better verbal memory acquisition (CVLT) at 12 weeks in grape juice group. No sig. effect on delayed verbal memory or spatial memory
Berry juice Kirkorian et al. 2010b [21]	5 males 4 females mean age 76 (sd 5). All scored mild impairment on the Clinical Dementia Rating scale	Wild Blueberry juice (Van Dyke's Health Juice Products). 2.38 g Galic acid/L. Hydroxycinnamic acid ester, chlorogenic acid, at approximately 734 mg/L, and flavonoid anthocyanins at 877 mg of cyanidin 3-glucoside equiv/L. 6–9 ml per kg divided over 3 servings a day. Mean 1.78 g/d polyphenols	12 week, parallel groups, single blind. Data from placebo group ($n = 7$) from Krikorian et al. 2010a. Therefore, placebo not matched with blueberry condition for kcal and macronutrient composition	Tested at baseline and 12 weeks. CVLT, Verbal Paired Associated Learning Test. Baseline performance included as a covariate	Significantly better verbal paired associate learning at 12 weeks in the blueberry juice group. No sig. effect on CVLT (also a test of verbal memory)
Berry juice Hendrickson & Mattes 2008 [22]	17 males and 18 females mean age 26 (sd 7.5)	Concord Grape Juice (Welch's). Containing 2,100 mg/l total phenolics as gallic acid equivalents. For 70 kg person = 1.47 g polyphenol. 10 ml/kg body weight administered. Placebo matched for energy, fructose, glucose, acidity, taste, colour and aroma	Acute, crossover, placebo controlled, double blind. Test drink (placebo or grape juice) administered with standardised lunch. Participants ate similar breakfast (self reported) on each day, and fasted for 3 hours before arrival	Tested before and after drink. Internal Memory test, Word Fragmentation Test	No effect of grape juice on performance relative to placebo. Baseline was not included as a covariate in the analyses. It is of note that the grape juice group were significantly better than the placebo group at baseline
Berry Juice Crews et al. 2005 [23]	50 adults aged $\geq$60 mean age 69 (sd 6)	Cranberry juice. 32 ounces/day of a beverage containing 27% cranberry juice per volume (Ocean Spray Cranberries, Inc). 16 ounces consumed twice a day. No details of polyphenol dose. Placebo matched for appearance, taste, smell and vitamin C	6 week, parallel groups, placebo controlled, randomised, double blind. $n = 25$ for cranberry juice and $n = 25$ for placebo	Tested at baseline and 6 weeks. Selective Reminding Test, Stroop Color and Word Test, Trail Making Test (parts A and B), Wechsler Adult Intelligence Scale- III Digit Symbol-Coding subtest, Wechsler Memory Scale-III Faces I and Faces II subtests	No significant effects of cranberry juice

Table 1
(*Continued*)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Cocoa Field et al. 2011 [24]	8 males and 22 females aged 18–25 (no mean provided)	Cocoa flavanols. Commercially available dark chocolate (CHOIX+) with 773 mg flavanol and white chocolate control (Waitrose own brand) with a flavanol trace	Acute, crossover, experimenter blind, randomised. Chocolate consumed at 9am. Participants consumed a self administered "light breakfast" prior to arrival	Testing commenced 2 hours post consumption. Choice reaction time, Visual Spatial Working Memory Test	Significantly better spatial working memory and choice reaction time in the flavanol condition. The spatial memory effect was driven by the group who consumed the control first
Cocoa Scholey et al. 2009 [25]	13 males and 17 females aged 18–35 (mean 22, se 0.6)	Cocoa flavanols. 3 dairy based flavanol drinks: 46 mg (control), 520 mg, 994 mg (Mars)	Acute, crossover, placebo controlled, randomised, double blind. Drink consumed at laboratory in the morning. Participants consumed the same (personal, self reported) breakfast before each visit	Testing commenced 90 minutes post drink consumption. Rapid Visual Information Processing Task (RVIP), Serial threes subtraction, Serial sevens subtraction	Significantly better performance on serial threes following 520 and 994 mg drinks compared to 46 mg drink. The 994 mg drink associated with improved RVIP
Cocoa Crews et al. 2008 [26]	41 males and 60 females mean age 69 (sd 8)	Flavanoid and procyanidin rich dark chocolate bars and beverages. (The Hershey Company). One 37 g chocolate bar containing 397 mg proanthocyanins (powder) and 12 g drink containing 357 mg total proanthocyanins consumed per day. Placebo matched for appearance, smell, taste and energy	6 week, parallel groups, placebo controlled, randomised, double blind. $n = 51$ for cocoa group and $n = 50$ for placebo group	Tested at baseline and 6 weeks. Selective Reminding Test, Stroop Test, Trail Making Test, Wechsler Adult Intelligence Scale-III Digit Symbol-Coding Subtest, Wechsler Memory Scale-III Faces I and Faces II subtests	No differences in performance between placebo and polyphenol groups
Cocoa Francis et al. 2006 [27]	16 females aged 18–30 years (no mean provided)	Flavanol cocoa drink. (Cocoaprot cocoa, Mars). High flavanol drink (172 mg per day) and low flavanol drink (13 mg per day) consumed daily, 5 days before testing	5 day/acute, crossover, randomised, double blind. No data on whether participants were fasted or time of day of testing	Two test days a minimum of 14 days apart. Testing commenced 90 minutes post consumption of final drink. Main outcome was fMRI scan. Attention switching task also assessed	No difference in attention switching performance between the low and high flavanol conditions
Resveratrol Supplement Kennedy et al. 2010 [28]	4 males and 20 females aged 18–25 (mean 20)	Resveratrol – a phytoalexin polyphenol (Biotivia Bioceuticals). 3 conditions; 250 mg, 500 mg trans-resveratrol & placebo	Acute, crossover, placebo controlled, randomised, double blind. Participants arrived fasted between 8–10 am	Tested 45 minutes post consumption on 3 mornings separated by 7 days. Rapid Visual Information Processing, Serial threes and sevens subtraction	No significant effects on cognition

Table 1
(*Continued*)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Flavonoid Supplement Pipingas et al. 2008 [29]	42 males mean age 58 (sd 4)	Enzogenol® contains approximately 80% total proanthocyanidins and other water-soluble flavonoids, flavonoid-conjugates and phenolic acids. 4 capsules administered daily. Total 960 mg of Enzogenol® and 120 mg of vitamin C	5 week, parallel groups, vitamin C controlled, randomised, double blind. Fasted from caffeine 2 hours prior to testing	Tested at baseline and 5 weeks. Complex Visual Vigilance, Contextual Memory, Immediate and Delayed Recognition, Simple and Choice Reaction Time, Spatial Working Memory, Visual Vigilance	Polyphenol supplement associated with faster spatial working memory and faster word recognition
Flavonoid Supplement Ryan et al. 2008 [30]	46 males and 55 females mean age 68 years (sd 6)	150 mg flavonoid Pycnogenol® (Horphag Research Ltd). 2 pills consumed at breakfast and 1 pill at evening meal. Each pill contained 50 g Pycnogenol®. Placebo matched for appearance	3 month, parallel groups, placebo controlled, randomised, double blind. $n = 49$ for flavonoid, $n = 52$ for placebo	CDR cognitive battery tested at baseline, 1, 2 and 3 months. Digit Vigilance, Immediate and Delayed Word Recognition, Simple and Choice Reaction Time, Spatial and Numerical Working Memory	Spatial working memory significantly better in the supplement group at 3 months only
Isoflavone Supplement Basaria et al. 2009 [31]	93 post menopausal females aged 47–76 (mean 56, se 1.6)	20 g soy protein powder mixed with beverages consisting of 160 mg Isoflavones (64 mg genistein, 63 mg diadsein, & 34 mg glycitein). Placebo: 20 mg milk protein (Physicians Pharmaceuticals, Inc.). Supplement consumed daily	12 week, parallel groups, placebo controlled, randomised, double blind. $n = 38$ for Isoflavone group and $n = 46$ for placebo group	Tested at baseline and 12 weeks. Cube Comparisons Test, Grooved Peg Board, Identical Pictures Test, Trail Making Test (parts A and B), Verbal Fluency Test	No significant differences between the Isoflavone and placebo groups at baseline or 12 week follow up
Isoflavone Supplement Gleason et al. 2009 [32]	15 males and 15 females aged >60 (mean 73, sd 6)	1 capsule per day consumed containing 100 mg/day of purified glycosidic Isoflavones; 85% daidzein and genistein or placebo containing maltodextrine (Novasoy®, Archer Daniels Midland Co.)	6 month, parallel groups, placebo controlled, randomised, double blind. $n = 15$ for Isoflavone and $n = 15$ for placebo	Tested at baseline, 1, 3 and 6 months. Buschke Selective Reminding Test, Boston Naming Test, Grooved Peg Board, Paragraph recall, Rey Complex Figure Test, Stroop Test, Trail Making Test, Verbal Fluency, Visual Spatial Learning Test	Isoflavone group showed better performance on Rey Complex Figure Test, Category Fluency, and Grooved Peg Board. Placebo group better at Trail Making and Stroop. Placebo group better on the VSLT at detecting stimuli, but the isoflavone group better at detecting incorrect designs

Table 1
(*Continued*)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Isoflavone Supplement Thorp et al. 2009 [33]	34 males aged 30–80 (mean 49, se 10)	Soy Isoflavones (Frutarom). Total intake per day: 116 mg total isoflavones of which 68 mg was daidzein, 127 mg was genistein and 36 mg glycitein. 4500 mg Soy Life® capsules per day. 2 capsules in the morning and 2 at night. Placebo contained 30 mg raftilose and fibre	6 week, crossover, placebo controlled, randomised, double bind. Participants fasted for 6 hours from food and 2 hours from caffeine prior to testing	Tested at baseline and 6 weeks. Backward Digit Span, Letter-Number Sequencing, Letter Fluency, Mental Rotation Task, Novel-Spatial Working Memory, Paired Associates Learning, Rey AVLT, Trail Making Test	Performance significantly better on the Novel Spatial Working Memory task following isoflavones. No significant effects for other tests
Isoflavone Supplement & Soy milk Fournier et al. 2007 [34]	79 post menopausal females aged 48–65 (mean 56, se 0.8)	Isoflavones supplement & soy milk. 3 conditions: cow's milk and placebo (control), soy milk and placebo (soy), cow's milk and supplement (supplement). Supplement contained 70 mg per day (30 mg daidzein, 33 mg genistein, and 7 mg glycitein, Archer Daniels Midland Co. (Novasoy®). 353 ml of milk consumed in evening & morning. Maltodextrin placebo	16 week, parallel groups, placebo controlled, randomised, double blind. $n = 27$ for control, $n = 25$ for soy milk, $n = 27$ for supplement	Tested at baseline and 16 weeks. Benton Visual Retention Test, Colour Matching, Corsi Block Tapping Test, Digit Ordering, Forward Digit Span, Stroop Test, Visual Pattern Recognition	No effects of soy isoflavones on any cognitive measures
Isoflavone Supplement Ho et al. 2007 [35]	168 females aged 55–76 (mean 63, se 6)	Soy Isoflavone capsule (Acatris Holding B.V.). 80 mg Isoflavones per day. Starch placebo	6 month, parallel groups, placebo controlled, randomised, double blind. $n = 80$ for Isoflavone, $n = 88$ for placebo	Tested at baseline and 6 months. Boston Naming Test, Digit Span, Digit Vigilance, Finger Tapping Test, Hong Kong List Learning Test, Immediate Verbal Recall (WMS-R) Rey-Osterreith Complex Figure, Trail Making Test, Verbal Fluency	No effects of isoflavone supplement on any cognitive measures
Isoflavone Supplement Vanata & Metzger 2007 [36]	37 males and 13 females, mean age 20 (sd 2.9)	54 mg soy Isoflavones diluted in 400 ml water. Placebo 50 g whey protein in 400 ml water (Cargill Health and Food Technologies)	Acute, parallel groups, placebo controlled, randomised, single blind. $n = 25$ for Isoflavone, $n = 25$ for placebo. Participants arrived fasted for 8 hours	Tested at baseline before drink consumption and 1.75 hours post drink consumption. Visual Spatial Memory, Word List Recall, Word Recognition	No cognitive effects

Table 1
(*Continued*)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Isoflavone Supplement Casini et al. 2006 [37]	78 females mean age 50 (sd 4)	Soy isoflavones (aglycone) 60 mg per daily supplement (40%–45% in genistein, 40%–45% in diadzein, and 10%–20% in glycitein). Placebo matched for appearance	6 month, crossover, placebo controlled, randomised, double blind	Tested at baseline and 6 months. Digit Span, Digit Symbol Test, Visual Scanning Test. Assessed after each condition	Isoflavone associated with significantly better performance on the Digit Symbol Test and backwards digit span
Isoflavone Supplement File et al. 2005 [38]	50 post menopausal females aged 50–66 (mean 58, sd 0.8)	Soy Isoflavone supplement 60 mg per day ($n = 25$) or matching placebo ($n = 25$) (Novasoy®)	6 week, parallel groups, placebo controlled, randomised, double blind	Tested at baseline and 6 weeks. CANATB Delayed Matching to Sample test, CANTAB IDED test, Paragraph recall, PASAT, Stockings of Cambridge, Verbal fluency	Isoflavone associated with greater improvement in short term non-verbal memory (DMST) and tests of executive functioning
Isoflavone Supplement Howes et al. 2004 [39]	28 females aged >60 (mean 68, sd 6.6)	Red clover Isoflavones, 55 mg per day. 2 tablets per day each containing approximately 25 mg of formononetin, 2.5 mg of biochanin and less than 1 mg of genistein and daidzein (Rimostil®, Novogen). Placebo matched for appearance and taste	6 month, crossover, placebo controlled, randomised, double blind	Tested at baseline and 6 months. Arithmetic Test, Block Design Test, Boston Naming Test, Digit Recall Digit Symbol, Paragraph Recall, Similarities Test, Trail Making (parts A & B), Verbal Fluency, Visual Memory, Word Recall	No significant effects following corrections for multiple comparisons
Isoflavone Supplement Kreijkamp-Kaspers et al. 2004 [40]	175 females aged 60–75 (mean 67, sd 5)	25.6 g of soy protein (52 mg genistein, 41 mg daidzein, and 6 mg glycitein (aglycone weights) in 36.5 g of powder (Solae, Solae Co, St Louis, Mo) that could be mixed with food or beverages. 25.6 g milk protein placebo matched for appearance, taste and nutrients. One supplement per day	12 month, parallel groups, placebo controlled, randomised, double blind. $n = 88$ for Isoflavone, $n = 87$ for placebo	Tested at baseline and 12 months. Boston Naming Test, Digit Span, Digit Symbol Substitution, Doors Test, Rey AVLT, Trail Making A and B, Verbal and Category Fluency	No significant effects of isoflavone supplement
Isoflavone Supplement Duffy et al. 2003 [41]	33 post menopausal females aged 50–65 (mean 58, sd 1.1)	Soy Isoflavone supplement: Solgen 40 (Solbar Plant Extracts). Each capsule 30 mg total isoflavone equivalents. 2 capsules per day consumed. Lactose placebo matched for appearance	12 week, parallel group, placebo controlled, randomised, double blind. $n = 18$ for Isoflavone, $n = 15$ for placebo	Tested at baseline and 12 weeks. Paragraph recall, Delayed Matching to Sample test, category fluency, two tests of frontal lobe function from CANTAB, Paced Auditory Serial Addition Test	Isoflavone group showed significantly greater improvement in paragraph recall and the delayed matching to sample test, the stockings of Cambridge test, the IDED test and the PASAT

Table 1
(*Continued*)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Isoflavone Supplement Kritz-Silverstein et al. 2003 [42]	53 post menopausal females aged 54–75 (mean 60, sd 5)	110 mg daily soy Isoflavones. 55 mg soy isoflavones per supplement. 2 supplements consumed daily (Personal Products Company, McNeil-PPC Inc.). Placebo matched for appearance	6 month, parallel groups, placebo controlled, randomised, double blind. $n = 27$ for Isoflavone, $n = 26$ for placebo	Tested at baseline and 6 months. Category Fluency, Immediate and Delayed Paragraph Recall, Trail Making Test (parts A& B)	Greater improvement in the isoflavone group for category fluency. For younger women only 50–59 years, isoflavone was associated with greater improvement for Trails B
Isoflavone containing foods File et al. 2001 [43]	15 males and 12 females, mean age 25 (se 2.6)	Soy isoflavones. Diet intervention using rotating menu eaten at lab. 100 mg/day (high soy) or 0.5 mg/day (low soy control) matched for macronutrients and energy	10 week, parallel groups, randomised. Sample size for each group not reported	Tested at baseline and 10 weeks. Category fluency, Digit Cancellation, Digit Symbol Substitution, Paragraph Recall, PASAT, Spatial memory from CANTAB, tests of frontal lobe function from CANTAB	Isoflavone diet associated with greater improvement in paragraph recall, spatial memory, and two tests of executive function (IDED test and the Stockings of Cambridge test)
Epidemiological survey Kesse-Guyot et al. 2012 [44]	1413 males and 1161 females mean age 66 (se 4.6)	Dietary intake over 1 year assessed with a 24 hour food diary completed every 2 months. Polyphenol consumption estimated with Phenol-explorer database	Longitudinal study. Cognitive performance at 13 year follow up compared between quartiles of baseline polyphenol intake	Forward and backward Digit Span, Trail Making Test, Word recall (RI-48), Verbal Fluency. These tests were grouped into 2 categories using factor analysis	Higher polyphenol intake associated with better language and memory performance but worse executive function
Epidemiological survey Butchart et al. 2011 [45]	425 males and 457 females aged >60 (mean 70)	Flavonoid intake over the past 3 months measured using the Scottish Collaborative Group Food Frequency Questionnaire. Intake of the flavonoid subclasses was estimated using a UK flavonoids database (unspecified)	Cross-sectional flavonoid intake survey	Cognitive performance assessed at a clinic visit. These tests were analysed together as 'Memory': Forward and Backward Spatial Span, Letter-Number Sequencing, Paragraph Recall, Verbal Paired Associates. These tests were analysed together as 'Fluid Intelligence': Backward Digit Span, Block Design, Digit Symbol Coding, Letter-Number Sequencing, Matrix Reasoning, Symbol Search. Verbal fluency also assessed separately	A regression model showed no associations between flavonoid intake and memory, fluid intelligence or verbal fluency after adjusting for gender, childhood IQ, smoking, socio-economic status, education and the apoE 14 allele

Table 1
(*Continued*)

Type/author	Participants	Polyphenol source	Design	Cognitive tests	Key findings
Epidemiological survey Nurk et al. 2009 [46]	2031 from Norwegian health study (HUSK) all aged 72 years	Self report food frequency questionnaire completed retrospectively for the previous year. Consumption of chocolate, wine and tea calculated in grams	Cross-sectional food intake survey (for previous year) regressed against cognitive performance at a one off test session	Block Design, Controlled Oral Word Association Test, Digit Symbol Test, Kendrik Object Learning Test, Trail Making Test A	When adjusted for various covariates increased wine consumption was associated with better performance on 4 tests KOLT, TMT-A, DST, and word association), increased tea intake associated with better performance on 3 tests (TMT-A, DST, and word association), and increased chocolate associated with better word association performance
Epidemiological survey Letenneur et al. 2007 [47]	692 males 948 females (mean age 77, sd 6)	Flavonoid. Five major flavonoids were described: quercetin, kaempferol, myricetin, luteolin, and apigenin	Longitudinal study. Flavonoid intake estimated from a food frequency questionnaire at 3 years	Tested at 3, 5, 8, and 13 years. Benton Visual Retention Test, Isaacs Set Test, Mini Mental State Examination	Higher flavonoid intake associated with less decline in performance over 10 years (all cog tests in one regression model)

ory and attention 120 minutes after consumption of dark chocolate containing 773 mg flavanols relative to a white chocolate control. Interestingly, in the latter study there was an interaction between treatment order and condition, such that improvement in spatial memory was only observed when the flavanol condition followed the control condition rather than vice versa. Given that there was no main effect of treatment order, it can be speculated that consumption of flavanol at week one enhanced performance to a level that was maintained at week two when no flavanol was consumed, suggesting that the effects of acute flavanol consumption are maintained for at least seven days. This is indicative of an inadequate washout duration, resulting in carry-over effects. Crews et al. [26] do not provide any information regarding the conditions under which cognitive testing took place, i.e. time of day and whether participants were fasted prior to chocolate (or placebo) consumption. Therefore, any subtle cognitive effects of flavanol consumption could have been masked by other nutritional intake or time of day effects. Both studies which reported significant effects of cocoa flavanol on cognition standardised the time of day of testing and any nutritional consumption prior to consumption of the cocoa polyphenols by either asking participants to consume the same self reported breakfast before each arm [25] or to consume a "light breakfast" excluding foods high in polyphenols prior to arrival [24].

The primary outcome in the 5 day study [27] was fMRI rather than cognition, and only one test of attention was used to assess cognition. Furthermore, participants were not asked to refrain from consuming polyphenol containing foods prior to or during the study, and there was no assessment of habitual polyphenol consumption. However, in a parallel study with four participants, Francis et al. [27] reported greater mean cerebral blood flow following consumption of 516 mg compared to 39 mg of flavanol. Interestingly, the difference in cerebral blood flow between the low (39 mg) and high (516 mg) flavanol conditions peaked two hours post ingestion, with this difference steadily decreasing thereafter up to six hours post consumption when no difference was observed. In the 5 day intervention assessing cognitive function, the fMRI scan and 18 minute attention switching task commenced 90 minutes after consumption of the low (13 mg) and high (172 mg) flavanol drinks, therefore, the timing of the attention task did not coincide with the peak increase in cerebral blood flow observed at two hours post consumption in the parallel study. Moreover, the flavanol dose in the 5 day intervention (172 mg) was considerably smaller than the flavanol dose associated with increased cerebral blood flow in the parallel study. Therefore, the flavanol dose may not have been of sufficient magnitude to benefit performance on the attention switching task.

There is no evidence of a dose-response relationship; Field et al. [24] and Scholey et al. [25] reported improved performance following acute flavanol doses between 520 mg and 994 mg, however, a relatively large 6 week daily dose of 754 mg [26] or a small 172 mg dose [27] were not associated with improvements in cognitive performance. Moreover, Scholey et al. [25] reported that mean scores on a serial threes working memory task were higher following a 520 mg dose compared to a 994 mg dose (although not significantly). Overall, the evidence suggests that flavonoid-rich cocoa can have an acute effect on working memory and attention, possibly via increased cerebral blood flow. However, there is currently no evidence to suggest that long term cocoa interventions are associated with cognitive benefits.

3.3. Isoflavone studies

Table 1 shows that the majority of polyphenol studies have been conducted with isoflavones (thirteen studies). Within these studies eleven were conducted with soy protein or soy isoflavone supplements, one included both soy isoflavone supplement and soy milk as treatments [34], one included soy based foods [43] and one included red clover isoflavones in a supplement [39]. Typically these studies use randomised, double-blind procedures. Interventions ranged between 6 weeks and 12 months, and there was one acute study which showed that isoflavone consumption 1.75 hours prior to testing had no effect on cognitive functioning [36]. Age and gender of participants may be of particular importance in isoflavone studies [49, 50].

Overall, the data from the isoflavone studies is inconclusive – where significant effects are reported (six studies) these are in the cognitive domains of memory or executive function. For example, five studies showed significant improvements for spatial memory [32, 33, 38, 41, 43], and five studies showed significant improvements for tests of executive function [32, 38, 41–43]. There was no consistent association

between duration of trial, or size of isoflavone dose and cognitive benefits. These equivocal findings could be explained by inconsistency in the cognitive testing procedure. A major limitation of the isoflavones studies is that only one study provided details of the time of cognitive testing [33], and the conditions under which testing took place, e.g. if participants were fasted or the nature and time of the last meal [36]. In addition, several studies did not control for habitual isoflavone consumption prior to the trial or during the trial [31, 37, 40, 42, 43]. Whilst there was some evidence that isoflavone consumption may benefit memory and executive function, it is clear that a greater degree of clarity is required regarding the cognitive test procedures.

3.4. Polyphenol capsule supplement studies

Two long term intervention studies show benefits for either spatial or working memory following consumption of supplements containing approximately 768 mg of proanthocyanidins, other water-soluble flavonoids, flavonoid-conjugates and phenolic acids [29] and supplements containing 150 mg of the flavonoid antioxidant Pycnogenol® [30]. This supports the findings from the isoflavone studies that memory can be sensitive to polyphenol consumption. However, Pipingas et al. [29] did not consider habitual polyphenol consumption before or during the trial, whereas Ryan et al. [30] controlled for this via stratified sampling using data from a general food frequency questionnaire (FFQ) of 126 items to ensure that habitual intake of antioxidants and vitamins was matched at baseline between the polyphenol and control groups. No details were provided regarding time of day of cognitive testing or whether participants were fasted prior to cognitive testing, for either of these long term intervention studies, however, Pipingas et al. [29] ensured caffeine or alcohol was not consumed 2 hours and 24 hours (respectively) prior to testing. An acute study showed no effects on tests of attention and working memory 45–80 minutes after consumption of a 250 mg or 500 mg resveratrol dose at breakfast [28]. It is possible that cognitive function is more sensitive to consumption of flavonoids than non-flavonoids such as resveratrol, however, long term interventions with the latter are required to examine this. Evidence from rodent research suggests resveratrol can protect against cognitive decline associated with ageing and neurodegenerative diseases [51]. Acute and chronic studies of resveratrol are required to examine whether these effects are observed in humans. To date, cognitive effects of resveratrol supplementation have only been examined in young healthy adults [28]. Despite no cognitive effects of resveratrol, Kennedy et al. [28] observed dose dependent increases in blood flow in the prefrontal cortex during the cognitive tasks. This suggests that increases in cerebral blood flow are not always associated with cognitive benefits, a finding also reported by Francis et al. [27] following daily consumption of 172 mg cocoa flavanols for 5 days (see above).

3.5. Epidemiological studies

Evidence for the effects of polyphenol consumption on cognition from four epidemiological studies is encouraging. Using general FFQs both Nurk et al. [46] and Letenneur et al. [47] demonstrated that increased dietary polyphenol consumption is associated with better cognitive outcomes over periods of 1 year and 10 years respectively. Nurk et al. [46] reported significant associations between chocolate, wine and tea consumption with memory and executive function after controlling for sex, education, vitamin supplement use, smoking status, history of CVD, diabetes, and total energy intake. Similarly, Letenneur et al. [47] reported associations between total polyphenol consumption and a measure of global cognitive function combining three tests (see Table 1) after controlling for age, sex, education, tobacco use, and body mass index. Letenneur et al. [47] also employed measurements from several other cognitive tests, but did not perform analyses due to missing data. There was no indication that polyphenol consumption was associated with performance on any of the tests individually, apart from the Mini Mental State Examination (MMSE). However, the MMSE is better considered as a test of dementia rather than a sensitive test of nutrient induced changes in cognitive function. Whilst both of these studies assessed education there was no measure of IQ taken.

IQ was included as a covariate in a regression model by Butchart et al. [45] who failed to find any associations between flavonoid intake over the previous three months as assessed by a general FFQ and cognition in adults over 70 years. However, data from the eleven cognitive tests was combined into two groups (memory and fluid intelligence) which could have

masked any associations between flavonoid intake and performance on individual cognitive tests. Furthermore, the FFQ (Scottish Collaborative Group FFQ) required participants to retrospectively report their dietary consumption of 168 foods and drinks for a period of three months. In contrast to FFQs, Kesse-Guyot et al. [44] reported associations between polyphenol intake at baseline assessed using six 24 hour food diaries completed every 2 months and cognitive performance at a 13 year follow-up. This is the only epidemiological study to show associations between specific subclasses of flavonoids and non-flavonoids and cognition. After inclusion of several covariates (including age, gender, education, depression, cardiovascular disease, hypertension, BMI, energy intake, diabetes, smoking, and alcohol intake but not IQ) better language and memory scores were associated with higher consumption of total polyphenols, total flavonoids, catechins, theaflavins, flavonols, and hydroxybenzoic acids. However, increased consumption of some polyphenols (dihydrochalcones, catechines, proanthocyanidins, and flavanols) was unexpectedly associated with worse executive function scores.

It can be speculated the effects of polyphenols on cognition are most likely to be observed after long periods of sustained habitual intake such as one to thirteen years, as demonstrated by Nurk et al. [46], Letenneur et al. [47] and Kesse-Guyot et al. [44]. Comparisons between epidemiological studies are hampered by variation in the types of FFQs employed, and inconsistencies in the methods by which polyphenol intake is calculated. Butchart et al. [45] estimated flavonoid intake using an unspecified UK flavonoids database of 396 foods, whereas, Letenneur et al. [47] employed published flavonoid composition tables [52]. In further contrast to this, Nurk et al. [46] estimated weight and energy intake of only three food groups (wine, tea, and chocolate) using portion size estimates from a FFQ, whereas Kesse-Guyot [44] used the Phenol-Explorer database to estimate intake of 502 flavonoids and non-flavonoids from 24 hour food diaries. A standardised method for estimating dietary polyphenol intake would be of value. Finally, a notable shortcoming of all four epidemiological studies is the absence of detail regarding cognitive test procedures. Caution is needed when generalising findings from these epidemiological survey studies due to sample bias. The samples may reflect participants who are particularly health conscious and compliant in completing FFQs, food diaries and other experimental procedures.

4. Discussion

Overall, 16 studies report significant associations between polyphenol consumption and cognition and 12 studies report no association. Therefore, there is evidence that consuming additional dietary polyphenols can lead to cognitive benefits. However, these findings should be interpreted with caution. Inspection of the number of cognitive tests examined suggests that any observed cognitive benefits associated with polyphenol consumption are likely to be small. Table 2 shows that 165 cognitive outcomes were analysed, of which 44 showed significant effects (27%). Furthermore, 80 different types of cognitive test were applied across 28 studies. This demonstrates a lack of consistency regarding cognitive test selection, which hampers comparisons between studies. Future research should provide a strong rationale for test selection and assess only the cognitive domains for which effects are hypothesised.

There is evidence that the polyphenol source may differentially impact upon cognition. Immediate spatial memory is most likely to benefit from polyphenol consumption in the form of berry fruit juice, cocoa, and other non-isoflavones, with 50% of tests (4/8) showing significant effects (see Table 2). Given this finding it is surprising that delayed spatial memory has been assessed on only one occasion in the juice and cocoa studies. Immediate verbal memory may be particularly sensitive to polyphenol berry fruit juice consumption, with 2/4 tests showing significant effects, however, few other cognitive domains were assessed. Spatial memory is also the domain most likely to benefit from isoflavone consumption. Three of four tests of delayed spatial memory showed significant effects, whilst this figure was 27% (4/15) for immediate spatial memory. There is also some consistent evidence that executive function (28%, 7/25) and psychomotor speed (29%, 4/14) can benefit from isoflavone consumption. Overall, the evidence implies that declarative memory is most sensitive to polyphenol consumption. This is consistent with numerous rodent studies showing polyphenol supplementation can reverse age related deficits in spatial memory [54–60].

There is little evidence for dose response effects or an association between dose, duration of intervention and cognitive performance (see Table 3). This could be due to the wide range of specific polyphenols present in the sources examined, the large variation in other methodological features between studies such as the

Table 2
Summary of cognitive tests performed in polyphenol intervention trials and epidemiological studies, reported as significant findings ($p < 0.05$/ applications of cognitive test) (tests are categorised according to [53])

Cognitive domain	Cognitive test	Isoflavone intervention studies	Berry juice/Cocoa/ Resveratrol/Pine Bark intervention studies	Epidemiological studies
Verbal memory immediate	Common objects recall test	1/1	–	–
	CVLT	–	1/2	–
	Hong Kong list learning test	0/1	–	–
	RAVLT	0/2	–	–
	RI-48 (word recall)	–	–	1/1
	Selective reminding	0/1	0/2	–
	VPAL	0/1	1/1	–
	WMS memory 1 test	0/1	–	–
	WMS paragraph recall	2/6	–	0/1
	WMS verbal paired associates	–	–	0/1
	Word list recall	0/1	–	–
	Word presentation (CDR)	–	0/1	–
	Word recognition (CDR)	0/1	0/1	–
		3/15	**2/7**	**1/3**
Verbal memory delayed	CVLT	–	0/1	–
	Hong Kong list learning test	0/1	–	–
	RAVLT	0/2	–	–
	Selective reminding	0/1	0/2	–
	WMS memory 2 test	0/1	–	–
	WMS paragraph recall	0/4	–	–
	Word recognition (CDR)	–	0/1	–
		0/9	**0/4**	–
Spatial memory immediate	Benton visual retention test	0/1	–	0/1
	Colour matching	0/1	–	–
	Contextual memory task	–	0/1	–
	Corsi block tapping test	0/1	–	–
	CANTAB DMST	1/3	–	–
	Doors test	0/1	–	–
	Faces (WMS-III)	–	0/2	–
	Identical pictures test	0/1	–	–
	Kendrick object learning test	–	–	1/1
	Novel spatial working memory	1/1	–	–
	Rey complex figure test	1/2	–	–
	SPAL	–	0/1	–
	Spatial pattern recognition	–	1/1	–
	Spatial working memory	–	1/1	–
	Spatial working memory (CDR)	–	1/1	–
	Visual pattern recognition	0/1	–	–
	Visual spatial learning test	1/1	–	–
	Visual spatial memory	0/1	1/1	–
	WMS visual 1 test	0/1	–	–
		4/15	**4/8**	**1/2**
Spatial memory delayed	Long term episodic memory	2/2	–	–
	Rey complex figure test	1/1	–	–
	Spatial pattern recognition	–	0/1	–
	WMS visual 2 test	0/1	–	–
		3/4	**0/1**	–

Table 2
(Continued)

Cognitive domain	Cognitive test	Isoflavone intervention studies	Berry juice/Cocoa/ Resveratrol/Pine Bark intervention studies	Epidemiological studies
Executive function	Boston naming test	0/4	–	–
	Category generation task	0/1	–	–
	Controlled oral word association	–	–	1/1
	Cube comparisons test	0/1	–	–
	IDED (CANTAB)	3/3	–	–
	Isaacs set test (verbal fluency)	–	–	0/1
	Mazes	0/1	–	–
	Mental rotation task	0/1	–	–
	Stockings of Cambridge (CANTAB)	3/3	–	–
	Stroop colour test	1/2	0/2	–
	Verbal fluency	2/10	–	1/2
	Visual scanning	0/1	–	–
	WAIS block design	0/1	–	1/2
	WAIS matrix reasoning	–	–	0/1
	WAIS similarities test	0/1	–	–
	Word fragmentation completion	–	0/1	–
		9/29	**0/3**	**3/7**
Working memory	Digit ordering	0/1	–	–
	Digit span	1/6	–	1/2
	Numeric working memory (CDR)	–	0/1	–
	Serial subtraction 3s	–	1/2	–
	Serial subtraction 7s	–	0/2	–
	Spatial span	–	–	0/1
	WMS arithmetic test	0/1	–	–
	WMS letter number sequencing	–	–	0/1
		1/8	**1/5**	**1/4**
Attention	Attention switching	–	0/1	–
	Choice reaction time	–	1/3	–
	Digit cancellation	0/1	–	–
	Digit vigilance	0/1	0/1	–
	Paced auditory serial addition	1/3	–	–
	RVIP	–	1/3	–
	Simple reaction time	–	0/2	–
	Visual vigilance	–	0/1	–
	WAIS letter-number sequencing	0/1	–	–
	Zazzo'z cancellation test	–	–	1/1
		1/6	**2/11**	**1/1**
Psycho-motor skill	Finger tapping test	0/1	–	–
	Grooved pegboard	1/2	–	–
	Trail making test A & B	2/7	0/2	1/2
	WAIS digit symbol	1/4	0/2	2/3
		4/14	**0/4**	**3/5**

Abbreviations. CANTAB: Cambridge Neuropsychological Test Automated Battery. CVLT: California Verbal Learning Test. DMST: Delayed Matching to Sample Test. RAVLT: Rey Auditory Verbal Learning Test. SPAL: Spatial Paired Associate Learning. VPAL: Verbal Paired Associate Learning. WMS: Wechsler Memory Scale. WAIS: Wechsler Adult Intelligence Scale. CDR: Cognitive Drug Research Battery.

cognitive test procedures (e.g. time of day of testing and fasting period), and the degree to which habitual polyphenol consumption is controlled before and during studies. It is crucial that future studies carefully consider these issues and document the methodologies/procedures used. Furthermore, there is no clear association between the age of the population and the likelihood of cognitive benefits. It is noticeable that the

Table 3
Summary of significant effects on cognitive performance in polyphenol intervention trials and epidemiological studies ranked by polyphenol dose

Authors	Polyphenol concentration mg/day	Polyphenol source	Intervention	Significant effects
Krikorian et al. [21]	1780	Blueberry Juice	6 weeks	Yes
Hendrickson & Mattes [22]	1470	Grape Juice	Acute	No
Scholey et al. [25]	994 & 520	Cocoa	Acute	Yes
Pipingas et al. [29]	768	Flavonoid Supp.	5 weeks	Yes
Field et al. [24]	773	Cocoa	Acute	Yes
Crews et al. [26]	754	Cocoa	6 weeks	No
Kennedy et al. [28]	500 & 250	Resveratrol Supp.	Acute	No
Francis et al. [27]	172	Cocoa	5 days	No
Basaria et al. [31]	160	Isoflavone	12 weeks	No
Ryan et al. [30]	150	Flavonoid Supp.	3 months	Yes
Thorp et al. [33]	116	Isoflavone	6 weeks	Yes
Kritz-Silverstein et al. [42]	110	Isoflavone	6 months	Yes
Gleason et al. [32]	100	Isoflavone	6 months	Yes
Kreijkamp-Kaspers et al. [40]	100	Isoflavone	12 months	No
File et al. [43]	100	Isoflavone	10 weeks	Yes
Ho et al. [35]	80	Isoflavone	6 months	No
Fournier et al. [34]	70	Isoflavone	16 weeks	No
Casini et al. [37]	60	Isoflavone	6 months	Yes
File et al. [38]	60	Isoflavone	6 weeks	Yes
Duffy et al. [41]	60	Isoflavone	12 weeks	Yes
Howes et al. [39]	55	Isoflavone	6 months	No
Vanata & Metzger [36]	54	Isoflavone	Acute	No
Krikorian et al. [20]	Not stated	Grape Juice	6 weeks	Yes
Crews et al. [23]	Not stated	Cranberry Juice	6 weeks	No
Kesse-Guyot et al. [44]	Habitual intake (Diary)	Epidemiological	13 years	Yes
Butchart et al. [45]	Habitual intake (FFQ)	Epidemiological	3 months	No
Nurk et al. [46]	Habitual intake (FFQ)	Epidemiological	1 year	Yes
Letenneur et al. [47]	Habitual intake (FFQ)	Epidemiological	1 year	Yes

majority of studies have been conducted in populations aged 50 and over, and there are no studies specifically focusing on adults aged between 30 and 45 years. It can be hypothesised that polyphenol based interventions will be most effective in populations who are at increased risk of cognitive decline such as malnourished or ageing adults and populations with vascular and metabolic disorders such as type 2 diabetes, cardiovascular disease and hypertension. Research directly comparing cognitive outcomes following polyphenol consumption in populations with and without the presence of these risk factors would be of value to examine this hypothesis. The findings presented here suggest that cognitive benefits from polyphenol consumption are more likely to be observed over longitudinal interventions than over acute periods of 1-2 hours following consumption. Four of six acute studies failed to find any effects. It is likely that different underlying mechanisms account for chronic and acute effects. For example, cerebrovascular outcomes such as increased blood flow to the brain may underlie acute effects, whereas chronic effects are more likely to be mediated by neuroprotective actions and enhancement of neuronal growth.

4.1. Mechanisms of action

Historically, it has been argued that the effect of polyphenols on cognitive performance and the brain are due to their ability to exert antioxidant actions [61]. However, research *in vivo* shows that polyphenols and their metabolites are found at lower concentrations in the brain than other antioxidants such as ascorbate [62], and therefore, it is unlikely that purely antioxidant actions can account for cognitive effects. More recently, it has been suggested that polyphenol effects on the brain are mediated by protection of neurons,

enhancement of neuronal function and growth, and effects on the cerebrovascular system such as increased blood flow in the brain. Flavonoids may exert neuroprotective actions via interaction with specific proteins central to intracellular signalling cascades [59] which are crucial for neuronal survival and long term potentiation (LTP). The pathways that are affected appear to be protein kinase and lipid kinase signalling cascades [63, 64]. These signalling cascades are also responsible for neuroinflammation. Neuroinflammatory processes are thought to play a major role in the development of Alzheimer's disease and Parkinson's disease. Research shows that flavonoids present in blueberry can inhibit neuroinflammatory processes [65] and show cognitive benefits in aged rodents [66]. These effects appear to be mediated by protection of protein kinase and lipid kinase signalling pathways [11, 12]. There is also some evidence that polyphenols can delay the progression of brain pathologies such as Alzheimer's disease and Parkinson's disease [13]. It has been suggested this is partly due to polyphenols having an inhibitory effect on acetylcholinesterase activity [67], which may enhance cognition in conditions associated with a cholinergic deficit (e.g. Alzheimer's disease). Studies also show green tea can reduce the effects of Parkinson's disease [68], and Gingko Biloba extract has been shown to protect hippocampal neurons against oxidative stress and neuroinflammation [69].

In addition to neuroprotective actions, it is thought that polyphenols have the potential to induce new protein synthesis in neurons which could have a direct effect on cognitive performance, particularly memory [11, 12]. Rodent data indicated that fruit polyphenols can increase neuronal communication efficiency and dendrite morphology [59]. Other research shows that blueberry supplementation may increase synaptic plasticity via changes in the genetic expression of neurons [70]. Flavonoids are now well known to modulate neural signalling pathways that induce synaptic plasticity [71]. For example, research with mice has shown that certain fruit based flavonoids (fisetin) can improve LTP and object recognition [72, 73]. Rats fed with a diet supplemented with blueberries showed increased hippocampal neurogenesis, increased activation of extracellular kinase receptors, and increases in insulin like growth factor and its receptor [74]. These increases were correlated with improved spatial memory performance as assessed by a Morris water maze. Furthermore, various anthocyanins present in blueberries and other fruits have been detected in the cortex, hippocampus, striatum, and cerebellum of rats fed with a blueberry supplemented diet [54, 59]. These brain areas are associated with memory function. The findings demonstrate that polyphenolic compounds can cross the blood brain barrier and localise in brain regions associated with memory function. This could provide a mechanism for the findings from the present review that polyphenol consumption in humans is most likely to be associated with improvements in spatial memory (see Table 2). However, data supporting these mechanisms relies heavily on animal research. There is clear need for mechanistic research with humans.

Research with humans suggests polyphenols can improve vasodilatation [75], blood flow [76], blood pressure [77], insulin resistance and glucose tolerance [78]. *In vitro* experiments show that grape polyphenols can induce endothelium dilation which is beneficial for cardiovascular function [79]. Improvements in vascular function and increased blood flow in the brain could lead to cognitive benefits, thus offering a mechanism for the association between polyphenol consumption and acute cognitive benefits. fMRI research has shown correlations between cerebral blood flow and cognitive function in humans [80]. Furthermore, increases in cerebrovascular blood flow induced by polyphenol consumption can also facilitate neurogenesis in the hippocampus [81], which offers an explanation for the observed memory benefits following polyphenol consumption.

4.2. Recommendations for future research

Habitual polyphenol consumption should be measured prior to the onset of the study and used as a covariate or exclusion criterion. The development of a comprehensive database detailing specific polyphenol content of everyday foods and drinks would vastly improve the accuracy and consistency of habitual polyphenol consumption estimates. Depending on the nature of the study and the anticipated mechanism, careful consideration should be given to level of polyphenol consumption for possible exclusion. Subsequently, other polyphenol consumption during the trial should be measured or restricted. However, restriction of habitual intake has implications for the potential mechanisms underlying the proposed study. Withdrawal of habitual polyphenol consumption may lead to a relative deficit in polyphenol consumption, and the proposed polyphenol intervention may therefore

only serve to replace the polyphenols removed from the diet. An alternative is to ensure that participants (possibly recruited on the basis of low polyphenol intake) maintain their habitual polyphenol consumption during the trial, which must be carefully monitored, using for example, a suitable FFQ or intake diary.

If previous human research with a specific polyphenol, nutrient or food is limited it can be useful and valid to employ a battery of cognitive tests assessing a wide range of cognitive functions and domains. However, wherever possible this 'scatter-gun' approach should be avoided. Cognitive test selection should be based on those tests which have previously detected effects or tests known to target brain areas associated with polyphenol localisation. In this case, the evidence suggests tests of immediate verbal and spatial memory, executive function, and psychomotor speed should be included. This also coincides with the animal literature showing that polyphenols can provide benefits for spatial memory (for a review see [11]). The absence of tests assessing delayed spatial memory should also be addressed. It is evident that a wide range of cognitive tests have been selected across relatively few studies. Unless a theoretical/mechanistic rationale can be provided, future studies should avoid selection of novel tests not previously applied in this field, as this practice hampers between study comparisons. Employing widely used, standardised tests with published norms is encouraged wherever possible. The specific timing and length of cognitive testing should be hypothesis driven. For example, if increased cerebral blood flow is anticipated to underlie cognitive effects of acute polyphenol consumption, the timing of cognitive testing should coincide with the hypothesised physiological effects. In addition, participants should be well-practised in the cognitive battery prior to the baseline testing session. At least one practice session should be administered and baseline performance could be included as a covariate in the analyses.

The exact procedures regarding cognitive testing and the environment in which testing occurs must be carefully documented to enable clear and valid comparisons within and between studies. This should include the time of day and location of testing, and the nature of any nutritional consumption prior to cognitive testing. Ideally, participants should be fasted upon arrival (or prior to polyphenol consumption in the case of acute studies) for a minimum of 8 hours, equivalent to an overnight fast, to reduced the potential acute effects of nutritional consumption on cognitive function. If fasting is not possible, the nature of the prior meal should be standardised across conditions and participants. Research has shown that the nature of an evening meal can affect cognitive performance the next morning, even after an overnight fast [82]. Cognitive testing in the morning is recommended to reduce time of day effects [83]. That said, investigations of the cognitive effects of lunch and evening meal manipulations are encouraged providing prior nutritional intake and physical/mental activity are carefully documented or controlled.

Measurement of the following potential confounds for cognitive performance should be reported or included as covariates: age, IQ, education, depression, gender, smoking, diabetes, and medication which can affect neurological function should be an exclusion criterion. Research also shows that presence of the apolipoprotein E4 (apoE4) genotype is associated with an increased risk of developing neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease [84, 85], and may potentially mediate the effect of polyphenol interventions on cognitive outcomes [86]. Future research would benefit from examining the effectiveness of polyphenol interventions in those with differing apoE genotypes. Finally, studies should be carefully designed to assess the cognitive effects of prolonged polyphenol supplementation *and* the acute cognitive effects of a polyphenol dose. The effect of polyphenols may be due to acute mechanisms (e.g. increased blood flow) or enduring changes/long term effects (e.g. increased neurogenesis and reduced concentration of pro-inflammatory agents). It is important that human studies of pure flavonoid and polyphenol consumption are undertaken concomitantly with clinical trials investigating the cognitive and physiological effects of polyphenol rich dietary interventions. The former are crucial for identifying underlying potential mechanisms, whilst the latter are essential for examining whether cognitive benefits can be consistently observed following consumption of flavonoids and polyphenols in the form of easily available foods at natural concentrations.

5. Conclusions

In conclusion this systematic review provides evidence that consumption of additional dietary polyphenols can lead to cognitive benefits. However,

any cognitive benefits are likely to be small and specific to certain cognitive domains. Declarative memory appears to be most sensitive to consumption of polyphenols from all sources, and there is evidence that specific cognitive effects differ depending on the polyphenol source. There is currently no evidence for an association between cognitive outcomes and polyphenol dose, duration of intervention, or population studied. This could be explained by methodological inconsistencies between studies. Further human studies are required with carefully designed methodology to elucidate the potential mechanisms underlying the relationship between polyphenol consumption and cognitive function.

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