Interventions involving a major dietary component improve cognitive function in cognitively healthy adults: a systematic review and meta-analysis.

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Abbreviations

CVD; Cardiovascular disease

CAIDE; (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) Dementia Risk Score

DASH; Dietary Approaches to Stop Hypertension

MedDiet; Mediterranean Diet

MMSE; Mini-Mental State Examination

3MS; Modified Mini-Mental Score

RCT; Randomized Controlled Trial

SMD; Standardized Mean Difference

Abstract

Accumulating evidence suggests a role for diet in promoting brain health. The purpose of this systematic review was to (i) quantitatively assess whether interventions with a major dietary component can enhance cognition in cognitively healthy adults, and, (ii) identify responsive domains of cognition to inform the design of future dietary trials. Electronic databases were systematically searched to find eligible randomized controlled trials that assessed the effect of interventions with a major dietary component on cognitive function or incident dementia, in adults without known cognitive impairment. Standardized mean differences (SMD) (95% confidence Interval [CI]) were combined using a random-effects meta-analysis and tests of homogeneity of variance were calculated. Two trials reported dementia outcomes and were qualitatively described. Fifteen trials encompassing 6,480 participants were eligible for meta-analysis. Compared to control, intervention improved performance on measures of global cognition (SMD=0.14; 95% CI 0.01 to 0.27, P=0.05; I^2 76%), executive function (SMD=0.11; 95% CI 0.04 to 0.18, P=0.003; I^2 0%) and processing speed (SMD=0.12; 95% CI 0.05 to 0.19, P=0.001; I^2 0%). There was no effect of intervention on delayed memory (SMD=0.04; 95% CI -0.02 to 0.09, P=0.18; I^2 4%). Significant heterogeneity and funnel plot asymmetry were detected for global cognition but removal of studies with high risk of bias did not change the pooled findings. Current evidence is limited but indicates that diverse interventions improve non-memory cognitive functions during normal cognitive aging. Measures of executive function and processing speed should be considered as feasible end-points in future dietary intervention trials.

Keywords: Randomized controlled trial; diet; cognitive function; dementia; meta-analysis

1. Introduction

Dementia is a global public health concern [1] due to increasing prevalence, high morbidity and rising socioeconomic burden [1,2]. Addressing modifiable risk factors is likely to be among the most promising way to reduce the number of future dementia cases [1-4] and considerable research efforts are being made to identify safe and effective interventions to protect against age-related neurodegeneration.

Accumulating evidence supports a role for diet on cognitive function and dementia risk. Epidemiological studies have shown a positive link between high quality dietary patterns (for example Mediterranean (MedDiet) and Dietary Approach to Stop Hypertension (DASH) diets) and better cognitive functioning [5-6], slower rate of cognitive decline [7-8] and reduced risk of dementia [8-10]. However, study findings have not been entirely consistent, largely because of heterogeneity in study populations, diet assessment and cognitive outcomes [11-12] and no firm dietary recommendations for brain health are available. Furthermore, causal relationships are difficult to discern from observational data.

Randomized controlled trials (RCTs) are considered the gold standard for evaluating causal associations. However, for prevention trials a major challenge is the identification of clinically relevant end-points that are responsive to modification of risk factors, particularly in individuals considered cognitively healthy or at early stages of neurodegeneration [13]. In the past few years, data from RCTs evaluating dietary interventions on cognitive outcomes have emerged. However, interventions have been extremely diverse and include diets such as the MedDiet, DASH, calorie-restricted and low carbohydrate, either alone, or delivered simultaneously with other

93 factors, such as physical activity and/or treatment of vascular risks. Due to the limited number of
94 studies conducted to date and the diverse nature of interventions, as well as differences in study
95 populations, length of follow-up and the range of cognitive outcomes assessed, it is difficult for
96 investigators to draw firm conclusions on the consistency of observed effects. Therefore, we
97 aimed to systematically review available RCT data to assess the effect of interventions with a
98 major dietary component, on domains of cognitive function and dementia risk in adults without
99 known cognitive impairment. A secondary aim was to identify cognitive domain end-points most
100 responsive to the interventions, as this will inform the design of future trials in this important
101 research field.
102
103 **2. Approach**
104 This review was conducted according to recommendations in the PRISMA statement [14] and
105 the protocol was registered with PROSPERO: CRD42017057070.
106
107 **2.1 Search strategy and selection criteria**
108 We conducted an electronic search using MEDLINE, Embase and PsycINFO databases for
109 studies published through to 1st March 2018. A combination of MeSH and search terms were
110 used to identify studies that included: 'diet*', 'dietary pattern', 'nutrition', 'food', 'nutrient',
111 'weight loss*', 'life style*', 'cognition*','cognitive function', 'cognitive decline', 'cognitive
112 impairment', 'dementia', 'Alzheimer's disease'. The primary search was limited to adults ≥ 18
113 years and English language publications. We also examined citation lists of retrieved articles for
114 potential studies not identified by the electronic search.
115

Two reviewers (CME, YL) independently assessed studies for eligibility for inclusion based on pre-defined criteria. We defined 'dietary intervention' as any intervention that targeted modification of diet as a major component. Studies were considered eligible if they: (i) were RCT design, (ii) evaluated the effect of dietary intervention in comparison to a control arm receiving an active intervention or no active intervention; (iii) were conducted in a population aged ≥ 18 years without known cognitive impairment; (iv) had an intervention period ≥ 3 months; (v) included a sample size ≥ 30; and (vi) reported outcomes of incident dementia (and subtypes) or cognitive function measured using valid neuropsychological tests.

We excluded non-randomized trials, cohort studies, or interventions that assessed the effect of nutrition supplements rather than dietary behavior, for example, macronutrient, vitamin or mineral supplements. We excluded trials conducted in populations with neurological conditions that could affect cognitive function such as Parkinson's disease, mild cognitive impairment, traumatic brain injury, depression or stroke. Duplicate articles from the same study examining similar end-points were also excluded. Disagreements between reviewers regarding study eligibility were resolved by discussion with a third reviewer (KY).

2.2 Data extraction

Two reviewers (CME, YL) extracted data from full text articles using a standard template to summarize: sample size, population characteristics, intervention description, control/comparator description, duration of follow-up, cognitive tests, study outcome(s) and post-intervention effect estimates for intervention and control groups that included risk estimates for dementia outcome (for example, Hazard Ratio [HR]) and means for cognitive outcomes, along with corresponding

measures of dispersion, for example SDs, or 95% CIs. For studies that examined composite cognitive outcomes, the effect sizes for composite measure(s) were extracted as well as individual neuropsychological test results where possible.

The primary outcomes were dementia incidence and cognitive function. To allow cognitive function outcomes to be combined in a meta-analysis, the validated neuropsychological tests reported in individual studies were examined by an expert neuropsychologist (ARK) who classified them into cognitive domains according to standard theory as shown in Table A.1. This process resulted in four cognitive domain categories that were utilized for meta-analysis. These were; g*lobal cognitive function* [which included tests to assess multiple aspects of cognition including orientation, language and memory as well as cognitive composites that summarized performance across a battery of neuropsychological measures], *executive function* [which included tests of mental flexibility and problem solving], *processing speed* [which included tests of ability to perform cognitive tasks quickly] and *delayed memory* [retention, recall and recognition of previously presented information]. For each domain, validated cognitive test scores or composite test scores that were reported consistently across studies were examined in the meta-analysis as shown in Table 1.

2.3 Assessment of study quality

The internal validity of eligible trials was assessed by two independent reviewers (YL, GP) using the Cochrane risk of bias tool [15]. Reviewers graded risk of bias across six potential sources: selection, performance, detection, attrition, reporting, and other sources. For each study, overall risk of bias was assessed as low (low graded bias across at least five categories), moderate (low

graded bias across at least four categories) or high (low graded bias in less than four categories).

2.4 Statistical Analyses

Incident dementia was reported in two trials [16,17] therefore, findings were qualitatively described. To quantify the effect of diet interventions on cognitive function in cognitively healthy adults, we calculated between-group standardized mean difference (SMD) and 95% confidence intervals (95% CI) at follow-up for each of the cognitive domains and then pooled results using a random-effects meta-analysis [18] to take account of heterogeneity between and within included trials. SMDs of ≤0.2, >0.5 and <0.8, and >0.8 were considered small, moderate, and large effects, respectively [19]. Where necessary, we used standard formulae to convert the reported effect estimates from individual studies into SMD (95% CI). For studies with more than one active treatment group, we included the most intensive intervention in the meta-analysis or where similarly intensive interventions were evaluated (e.g. MedDiet supplemented with olive oil or nuts) we considered the alternate intervention in sensitivity analyses. Where multivariate analyses were presented by the authors, we calculated SMD adjusted for confounders in the final reported model.

Study heterogeneity was assessed using both Cochran's Q-statistic ($P < 0.05$) and the *I*-squared (I^2) statistic. We considered an I^2 value greater than 50% indicative of high heterogeneity [20]. Evidence of publication bias was assessed by examining funnel plot asymmetry and by Begg and Egger tests [21]. In cases of high heterogeneity, we repeated the pooled analysis after removing studies assessed as high risk of bias. All statistical analyses were performed using Review Manager Software (Review Manager, Version 5.3, Copenhagen: The Nordic Cochrane Centre,

185 The Cochrane Collaboration, Denmark).

186

187 **3. Results**

188 **3.1 Study characteristics**

189 The PRISMA flowchart for eligible studies is shown in Figure 1. The primary search yielded
190 1,615 original titles of which 1,589 were excluded after title and abstract screen. One additional
191 article [22] was identified from a citation search within identified articles. Full texts of 27 studies
192 were independently assessed by two reviewers and 12 were excluded (Figure 1). Fifteen RCTs
193 met the inclusion criteria [16, 17, 22-34] as shown in Table 1.

194

195 Most trials (n = 7) were conducted in Europe (Spain, Netherlands, Germany, Italy and Finland),
196 followed by Australia (n = 3), USA (n = 3), Canada (n = 1) and Korea (n = 1). Two studies
197 involved participants from different PREDIMED study centers (Barcelona [33] and Navarra [17,
198 28]) and were considered as separate studies. Furthermore, authors from the PREDIMED-
199 Navarra center reported independent end-points of interest in two articles [17, 28] and to avoid
200 duplication, we included only the cognitive outcomes shown in Table 1 for each of these articles.
201 All studies involved both males and females, eight were conducted exclusively in older adults (≥
202 60 years) [16,17,22,27,29,30,31,33], one in adults ≥ 50 years [34]. Two trials were conducted in
203 individuals at high Cardiovascular disease (CVD) risk [17,33] one in individuals at increased
204 dementia risk (CAIDE ≥ 6) [31], two in people with type 2 diabetes [25,26], two in obese adults
205 [23,30] and one in hypertensive adults [32]. The length of follow-up ranged from 3 months to 8
206 years. Five trials were nested in larger RCTs [17,25,26,28,32,33] and three of these did not
207 include a baseline cognitive function measurement [25,26,28].

Cognitive outcomes from 15 RCTs were pooled in meta-analyses; ten trials reported outcome measures of global cognitive function and processing speed and nine trials reported measures of executive function and delayed memory.

Each trial was assessed for risk of bias. Two trials were considered low [16,31], seven were considered moderate [17,22,26-28,30,32,33] and five were considered high [23-25,29,34] risk of bias as shown in Figure 6.

3.2 Effect of intervention on incident dementia

Dementia incidence was reported in two RCTs [16,17]. The PreDIVA trial [16] involving 3,526 older adults, assessed the effectiveness of a multi-domain intervention to optimize diet, physical activity, smoking, weight and blood pressure, compared to usual primary care, on dementia incidence. After 6.7 years, dementia occurred in 121 (7%) of the intervention group and 112 (7%) of the control group, with no significant intervention effect on all-cause dementia (HR 0.92, 95% CI 0.71-1.19; P = 0.54) or Alzheimer's disease (HR 1.05, 95% CI 0.78-1.41; P = 0.74). Secondary analyses indicated significant beneficial effects on all-cause dementia for participants with hypertension (HR 0.54, 95% CI 0.32-0.92; P = 0.02) and those without pre-existing CVD (HR 0.64, 95% CI 0.44-0.94; P = 0.02), who adhered more strictly to the intervention. The PREDIMED-Navarra trial [17], reported fewer cases of dementia in the MedDiet supplemented with olive oil (n = 12, 3%) or nuts (n = 6, 2%) intervention groups, compared with a low-fat control group (n = 17, 5%) after 6.5 years of follow-up. However, risk estimates were not reported given the small number of dementia cases observed in this study.

3.3 Effect of intervention on cognitive function

The pooled effect of interventions with a major diet component on cognitive domains is shown in Figures 2-5 and described in more detail below.

3.3.1 Global cognition

Ten RCTs involving 6,057 participants (3,188 intervention and 2,869 control) reported global cognitive function on a composite score [22,31, 32], MMSE [16,17,27,29,33] or the Modified Mini-Mental score (3MS) [25,30]. Figure 2 shows the pooled analysis of all ten trials that indicated a significant beneficial effect of intervention on global cognitive function (SMD = 0.14; 95% CI 0.01, 0.27, P = 0.03) compared to control with high between study heterogeneity (I^2 76%). A funnel plot showed potential asymmetry (not shown) with evidence of publication bias (Begg's P = 0.03 and Egger's P = 0.02).

3.3.2 Executive function

Nine RCTs involving 2,830 participants (1,445 intervention and 1,385 control) reported executive function on the Stroop interference [22-25,32], Trail Making Test B [28,30] or Color Trail 2 [33]. One trial reported a composite executive function score that incorporated Stroop interference and Trail B-A tests [31]. The combined analysis showed a small positive effect of intervention versus control on executive function (SMD = 0.11; 95% CI 0.04, 0.18, P = 0.003; I^2 0%) shown in Figure 3.

3.3.3 Processing speed

Ten RCTs involving 3,037 participants (1,548 intervention and 1,489 control) reported

processing speed on the Trail Making Test A [17,25,26,30], Inspection time [23,24], Digit Symbol Substitution [32], Color Trail 1 [33] or a composite processing speed score [22,31]. The pooled analysis showed faster processing speed in response to intervention compared to control (SMD = 0.12; 95% CI 0.05, 0.19, P = 0.001; I^2 0%) shown in Figure 4.

3.3.4 Delayed memory

Nine RCTs involving 5,690 participants (2,958 intervention and 2,732 control) reported delayed memory on the Rey Auditory Verbal Learning Test [22,24-26,28,33], Visual Association [16], Visual Paired Associates [32] or a composite memory score [31]. Figure 5 shows the pooled analysis of the nine trials, which indicated no significant effect of intervention on delayed memory (SMD = 0.04; 95% CI -0.02, 0.09, P = 0.18; I^2 4%).

3.4 Sensitivity analysis

For studies with two active treatment groups, the less intensive treatment was examined in the sensitivity analysis. None of the less intensive treatments were more effective on the outcomes. We performed a sensitivity analysis for global cognition by removing trials with high risk of bias [23-25,29,34]. This attenuated the combined effect (SMD = 0.13 [95% CI, 0.04, 0.30], P = 0.13) but heterogeneity remained high (I^2 79%, P < 0.001). We also removed two trials with the shortest (3-4-month) follow-up time [32, 34] and this attenuated the effect for global cognition (SMD 0.11 [95% CI, -0.02, 0.24], P=0.09) but had little effect on the pooled estimates for executive function (SMD 0.10 [95% CI, -0.03, 0.18], P<0.01) or processing speed (SMD 0.12 [95% CI, 0.05, 0.20], P<0.001).

4. Discussion

This is one of the first meta-analysis examining the effect of interventions with a major diet component on cognitive outcomes in adults without known cognitive impairment. Results from one large trial [16], showed no overall effect of a multicomponent intervention on dementia after 6.7 years, but a significantly lower risk for those with greatest adherence to the intervention. In terms of cognitive function, the pooled analysis of available data showed positive effects of intervention on global cognition, executive function and processing speed but no effect on delayed memory. In all cases, pooled effect sizes were small (SMD 0.1 to 0.2).

Cognitive function declines progressively during normal aging with high variability in the rate of decline, particularly in older age [35]. Processing speed and executive function appear to decline earlier and, to a greater extent, than other cognitive domains [36] and impairment in these abilities can interfere with other complex processes, such as memory and behavior and adversely affect the ability to perform everyday tasks [37-39]. Therefore, interventions to improve processing speed and executive function may be an effective means to counter the pathophysiological brain changes leading to cognitive decline during aging. Our pooled results show that interventions with a major dietary component improve these cognitive abilities in non-demented adults and are particularly public health relevant, given the longer life expectancy of populations worldwide, and the anticipated rapid increase in the number of people affected by cognitive impairment.

We did not observe a pooled effect of intervention on delayed memory. This may be partly explained by a "ceiling effect" for detection of diet-induced improvement in memory among

300 cognitively healthy adults. In experimental studies, reduction in energy and fat appear to improve
301 long-term memory function in obese adults [40] and recent clinical data has shown improved
302 memory function in response to diet-induced weight loss in obese patients with cognitive
303 impairment [41]. Therefore, those at high risk of memory impairment may benefit most from
304 dietary modification and further clinical trials in vulnerable populations are warranted. It also
305 remains possible that diet has protective effects on other aspects of memory such as visuospatial
306 memory that were not fully investigated in this meta-analysis.
307
308 Several plausible biologic pathways support a role for diet in optimizing brain health. Diet has
309 important anti-oxidant and anti-inflammatory properties that can reduce both oxidative stress and
310 inflammation implicated in the pathogenesis of cognitive decline and dementia.
311 Experimental studies have shown direct effects of diet on neuronal cell signaling [42], neuronal
312 membrane integrity [43] and inflammation [44] and diet can have an indirect impact on brain
313 health by modulating cardio-metabolic risk. Compelling evidence from several clinical trials
314 have demonstrated significant reductions in cardiometabolic risk in response to diet intervention,
315 even in the absence of weight loss [45,46]. Processing speed and executive function are
316 adversely affected by hypertension, atherosclerosis and cardiovascular disease [47,48].
317 Therefore, it is possible that the observed benefit of dietary intervention on these cognitive
318 abilities is mediated by improved cardiometabolic health. However, further mechanistic evidence
319 is needed to explain how diet influences cognition and dementia. Incorporation of neuroimaging
320 biomarkers in future studies could provide greater insight into potential mechanisms of diet on
321 brain health. Preclinical changes in brain structure precede cognitive decline and can predict
322 dementia risk [49]. Evidence supporting a protective role for high quality diets on MRI-measured

323 brain structure in middle-age [50] and older adults [51] is beginning to emerge but require
324 prospective confirmation in larger populations.
325
326 Several limitations should be considered in interpreting findings from this meta-analysis. First,
327 included trials were highly diverse in the nature (composition, dose, delivery and duration) of
328 intervention evaluated. For example, interventions ranged from single food group to whole diet
329 interventions to multicomponent interventions that targeted diet as well as other lifestyle
330 behaviors and cognitive training. Hence, it is not possible to determine the effects attributable to
331 diet on cognitive performance. There were too few dietary interventions to allow meaningful
332 meta-analysis across cognitive domains, however, the effects observed were generally stronger
333 for the multicomponent trials. For the dietary trials, follow-up ranged from 3 months to 6 years
334 and most of these studies were considered poor quality. Therefore, from the data currently
335 available, it is not possible to define optimal dietary strategies to enhance cognitive function, nor
336 the optimal duration of intervention. Additional high-quality trials that are well designed and
337 focus solely on diet intervention for cognitive health are required. Second, while heterogeneity
338 was substantial across interventions, we attempted to minimize this for cognitive outcomes by
339 pooling results across standardized cognitive domains. Publication bias was not detected in most
340 pooled analyzes but substantial heterogeneity and publication bias was evident for global
341 cognition. In this case, removal of trials with high risk of bias did not improve overall
342 heterogeneity. Other potential differences between the studies include the global cognition
343 measures and populations studied, such as age, genetic risk and educational status, which may
344 account for some of the individual variation in response to intervention. Despite limitations, our
345 results are the most comprehensive effort to quantitatively synthesize the effectiveness of

interventions with a major dietary component for cognitive functioning in non-demented adults and our findings have relevance for informing end-point measures for future dietary intervention studies. We adhered to recommendations for conducting systematic reviews and performed an objective assessment of the internal validity for included trials.

5. Conclusions

In summary, this review demonstrates small beneficial effects of interventions that include a major dietary component on non-memory cognitive domains in adults without known cognitive impairment. These small effects could potentially translate to a substantial improvement in cognitive health if implemented at a population level. Our results indicate that change in processing speed and executive function are feasible end-point measures in future diet intervention trials.

6. Future research to advance this area

Further research is required to determine the precise nature of dietary modification to enhance cognition in different populations and the duration of intervention needed for optimal effect. Incorporation of neuro-imaging outcome measures could help to elucidate mechanisms of action and identify subtle neurological diet-induced changes that may not be possible to detect with standard cognitive tests. In addition, few diet intervention studies have incorporated clinical dementia end-points therefore further well-designed RCTs are needed to comprehensively investigate the effect of diet on dementia and subtypes of dementia.

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Figure 1: PRISMA flow chart of the process used to select trials for inclusion in this systematic review and meta-analysis

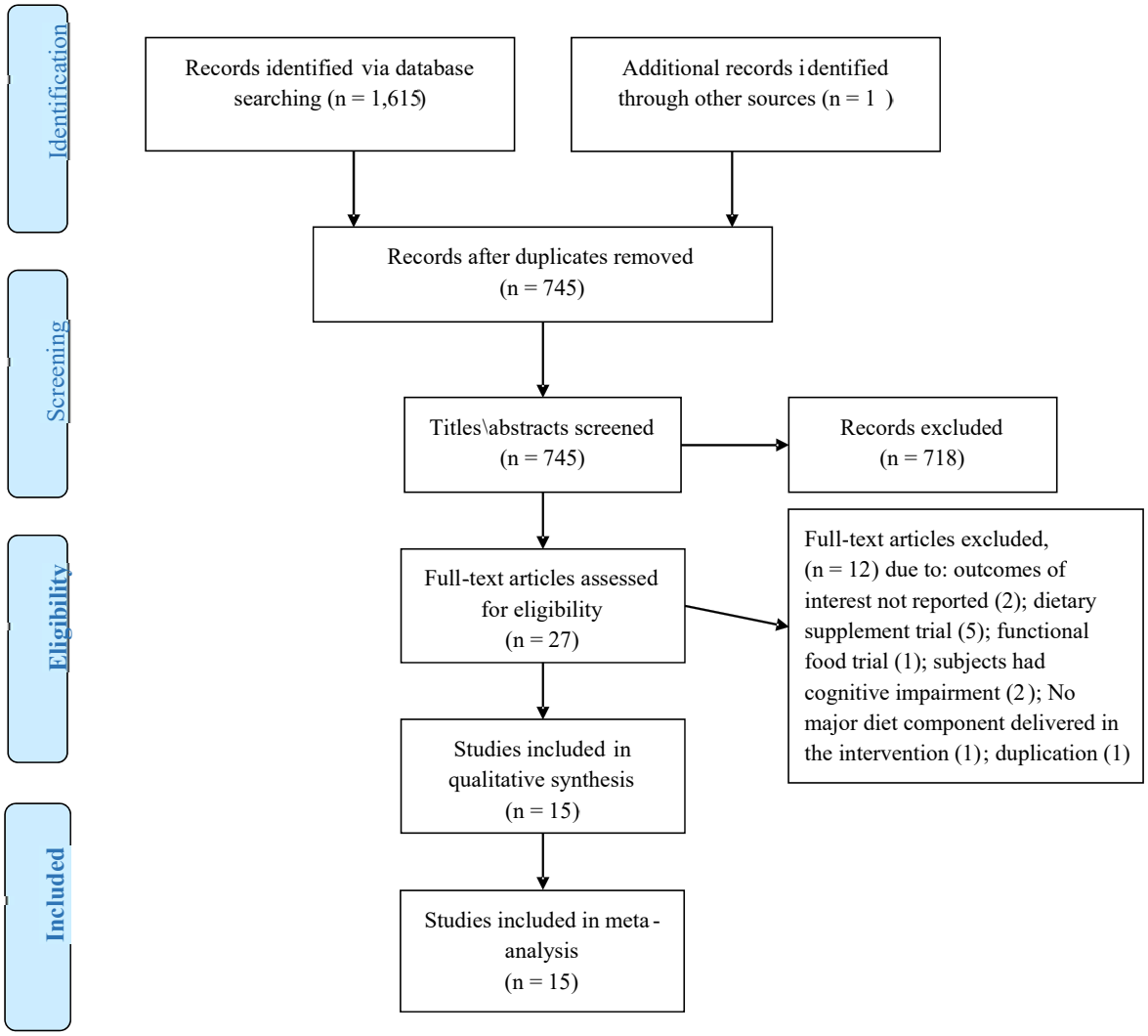

Figure 2. Forest plot showing the effect of intervention versus control on global function (n = 10)

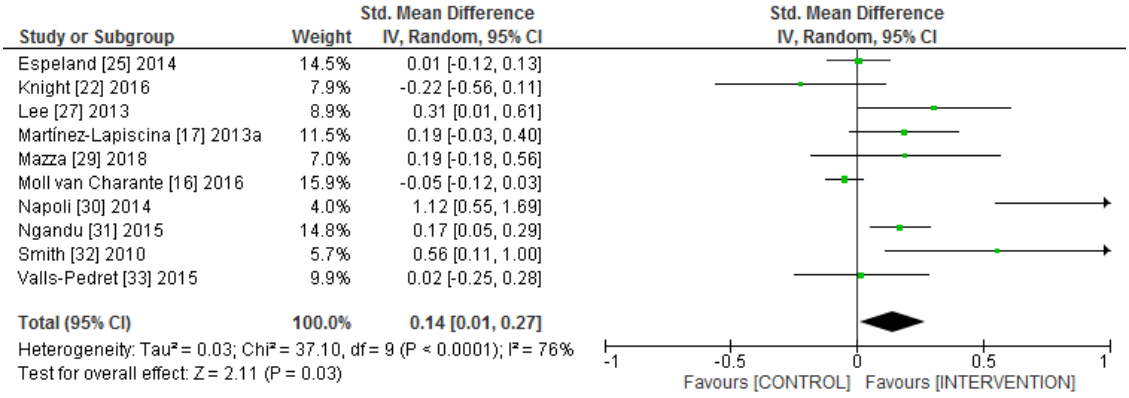

Figure 3. Forest plot showing the effect of intervention versus control on executive function (n = 9)

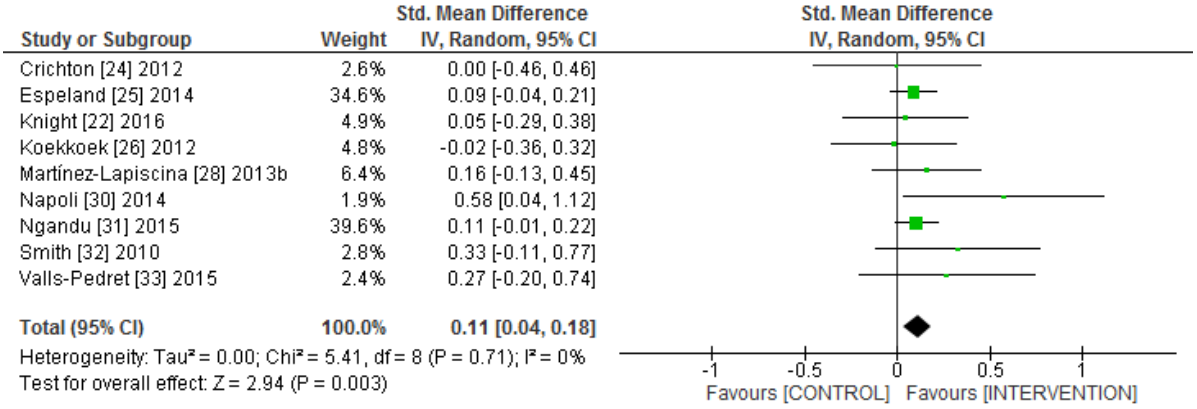

Figure 4. Forest plot showing the effectffect of intervention versus control on processing speed (n = 10)

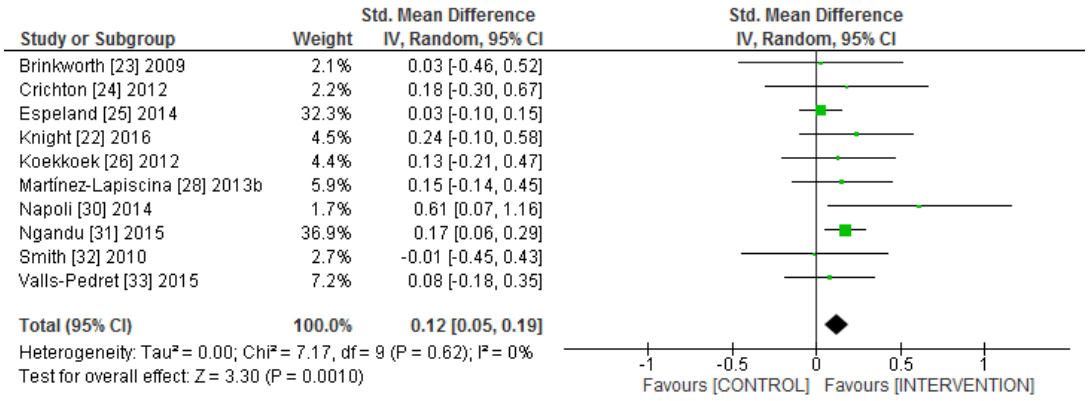

Figure 5. Forest plot showing the effect of intervention versus control on delayed memory (n = 9)

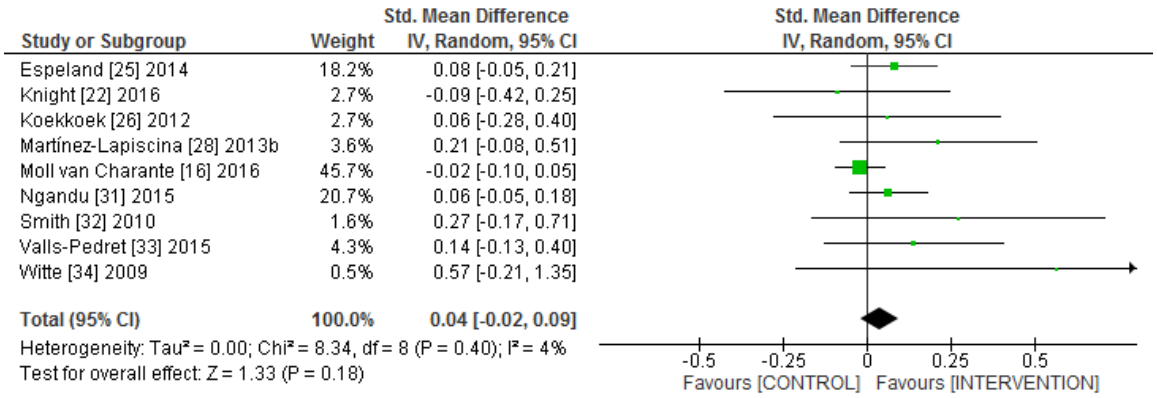

Figure 6: Summary of the risk of bias across six categories for the included studies in this systematic review and meta-analysis

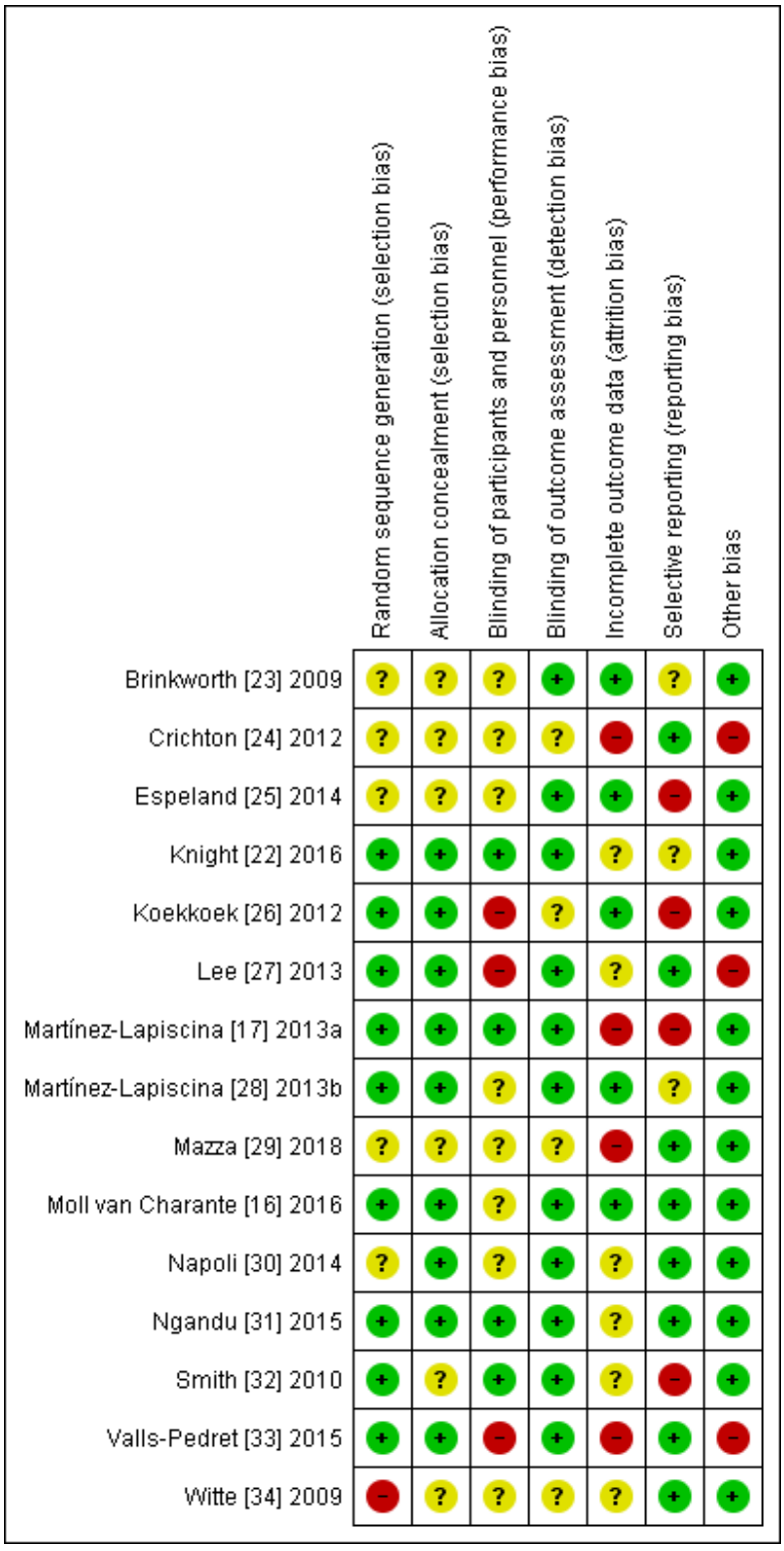

Table 1: Characteristics of trials examining the effect of diet-based intervention on cognitive function or dementia incidence (n = 15)

Ref	County	Population	Age (years)	Sample size	Intervention	Control	Follow-up	Cognitive outcomes of interest				
								Dementia	Global function	Executive function	Processing speed	Delayed memory
23	Australia	Abdominally obese adults	24-64	118	Low Carbohydrate diet	Low Fat diet	12 mon	-	-	-	Inspection Time	-
24	Canada Australia	Healthy adults with BMI ≥25	18–75	59	High dairy diet	Low dairy diet	12 mon	-	-	Stroop	Inspection Time	RAVLT
25	USA	Type 2 diabetics	45–76	978	Diet and physical activity	Diabetes Structured Education	8 yr.	-	3MS	Stroop	TMT-A	RAVLT
22	Australia	Older adults	≥65	166	MedDiet	Habitual diet	6 mon	-	Mean z-score for 11 cognitive tests	Modified Stroop	Mean z-score for symbol search and coding test	RAVLT
26	Netherlands	Type 2 Diabetics		258	Intensive lifestyle advice	Standard care	~3.2 yr.	-	-	Stroop	TMT-A	RAVLT
27	Korea	Older adults	≥ 60	460	Increased fruit and vegetable intake; 2 servings fish/wk.; physical activity 30min x 3/wk.	Standard care	18 mon	-	MMSE	-	-	-
17	Spain	Adults at high CVD risk	55–80	1055 max	1) MedDiet + Olive Oil 2) MedDiet + nuts	Low fat diet	6.5 yr.	Cases per group	MMSE	-	-	-
28	Spain	Adults at high CVD risk	55–80	271	1) MedDiet + Olive Oil 2) MedDiet + nuts	Low fat diet	6.5 yr.	-	-	TMT-B	TMT-A	RAVLT
29	Italy	Older adults with MMSE >20	≥65yr	110	MedDiet + Olive Oil	MedDiet	12 mon	-	MMSE			
16	Netherlands	Older adults	70-78	3526	Diet, physical activity, smoking cessation, weight and blood pressure management	Standard care	6.7 yr.	Dementia incidence	MMSE	-	-	VAT

Ref	County	Population	Age (years)	Sample size	Intervention	Control	Follow-up	Cognitive outcomes of interest				
								Dementia	Global function	Executive function	Processing speed	Delayed memory
30	USA	Obese older adults	≥ 65	107	1) Diet weight-management program 2) Exercise 3) Diet and exercise	General healthy diet information	12 mon	-	3MS	TMT-B	TMT-A	RAVLT
31	Finland	Older adults with CAIDE ≥6	60-77	1260	Intensive diet, exercise, cognitive training, vascular risk monitoring	Standard care - general health advice	2 yr.	-	Mean z-score for all 14 cognitive tests	Mean z- score for 5 cognitive tests	Mean z-score for 3 cognitive tests	Mean z- score for 4 cognitive tests
32	USA	Hypertensive overweight adults	52.3±9.6	124	1) DASH-diet alone (DASH-A), 2) DASH-weight management 3) DASH-weight management and exercise	Standard care	4 mon	-	Mean z-score for 5 cognitive tests	Stroop	DSST	VPA
33	Spain	Adults at high CVD risk	55–80	447	1) MedDiet + Olive Oil 2) MedDiet + nuts	Low fat diet	4.1 yr.	-	MMSE	Color Trail 2	Color Trail 1	RAVLT
34	Germany	Adults with MMSE ≥26	50-80	50	Calorie restricted diet	Habitual diet	3 mon	-	-	-	-	RAVLT

BMI= Body Mass Index; RAVLT = Rey Auditory Verbal Learning Test; HbA1c = Glycated haemoglobin; TMT-A = Trail Making Test A; MMSE = Mini-Mental State Examination; CVD = Cardiovascular disease; MedDiet = Mediterranean diet; TMT-B = Trail Making Test B; VAT – Visual Association Test; 3MS = Modified Mini-Mental State; CAIDE = Cardiovascular Risk Factors, Aging, and Incidence of Dementia; DASH = Dietary Approaches to Stop Hypertension; DSST = Digit Symbol Substitution Test