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

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

3

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24 **Abbreviations**

25 CVD; Cardiovascular disease

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

27 DASH; Dietary Approaches to Stop Hypertension

28 MedDiet; Mediterranean Diet

29 MMSE; Mini-Mental State Examination

30 3MS; Modified Mini-Mental Score

31 RCT; Randomized Controlled Trial

32 SMD; Standardized Mean Difference

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47 **Abstract**

48 Accumulating evidence suggests a role for diet in promoting brain health. The purpose of this  
49 systematic review was to (i) quantitatively assess whether interventions with a major dietary  
50 component can enhance cognition in cognitively healthy adults, and, (ii) identify responsive  
51 domains of cognition to inform the design of future dietary trials. Electronic databases were  
52 systematically searched to find eligible randomized controlled trials that assessed the effect of  
53 interventions with a major dietary component on cognitive function or incident dementia, in  
54 adults without known cognitive impairment. Standardized mean differences (SMD) (95%  
55 confidence Interval [CI]) were combined using a random-effects meta-analysis and tests of  
56 homogeneity of variance were calculated. Two trials reported dementia outcomes and were  
57 qualitatively described. Fifteen trials encompassing 6,480 participants were eligible for meta-  
58 analysis. Compared to control, intervention improved performance on measures of global  
59 cognition (SMD=0.14; 95% CI 0.01 to 0.27, P=0.05;  $I^2$  76%), executive function (SMD=0.11;  
60 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,  
61 P=0.001;  $I^2$  0%). There was no effect of intervention on delayed memory (SMD=0.04; 95% CI -  
62 0.02 to 0.09, P=0.18;  $I^2$  4%). Significant heterogeneity and funnel plot asymmetry were detected  
63 for global cognition but removal of studies with high risk of bias did not change the pooled  
64 findings. Current evidence is limited but indicates that diverse interventions improve non-  
65 memory cognitive functions during normal cognitive aging. Measures of executive function and  
66 processing speed should be considered as feasible end-points in future dietary intervention trials.

67

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

69

70 **1. Introduction**

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

76

77 Accumulating evidence supports a role for diet on cognitive function and dementia risk.

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

85

86 Randomized controlled trials (RCTs) are considered the gold standard for evaluating causal  
87 associations. However, for prevention trials a major challenge is the identification of clinically  
88 relevant end-points that are responsive to modification of risk factors, particularly in individuals  
89 considered cognitively healthy or at early stages of neurodegeneration [13]. In the past few years,  
90 data from RCTs evaluating dietary interventions on cognitive outcomes have emerged. However,  
91 interventions have been extremely diverse and include diets such as the MedDiet, DASH,  
92 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 1<sup>st</sup> 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  $\geq 18$   
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

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

124

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

132

## 133 **2.2 Data extraction**

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

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

142

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

156

### 157 **2.3 Assessment of study quality**

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



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

163

## 164 **2.4 Statistical Analyses**

165 Incident dementia was reported in two trials [16,17] therefore, findings were qualitatively

166 described. To quantify the effect of diet interventions on cognitive function in cognitively

167 healthy adults, we calculated between-group standardized mean difference (SMD) and 95%

168 confidence intervals (95% CI) at follow-up for each of the cognitive domains and then pooled

169 results using a random-effects meta-analysis [18] to take account of heterogeneity between and

170 within included trials. SMDs of  $\leq 0.2$ ,  $>0.5$  and  $<0.8$ , and  $>0.8$  were considered small, moderate,

171 and large effects, respectively [19]. Where necessary, we used standard formulae to convert the

172 reported effect estimates from individual studies into SMD (95% CI). For studies with more than

173 one active treatment group, we included the most intensive intervention in the meta-analysis or

174 where similarly intensive interventions were evaluated (e.g. MedDiet supplemented with olive

175 oil or nuts) we considered the alternate intervention in sensitivity analyses. Where multivariate

176 analyses were presented by the authors, we calculated SMD adjusted for confounders in the final

177 reported model.

178

179 Study heterogeneity was assessed using both Cochran's Q-statistic ( $P < 0.05$ ) and the *I*-squared

180 ( $I^2$ ) statistic. We considered an  $I^2$  value greater than 50% indicative of high heterogeneity [20].

181 Evidence of publication bias was assessed by examining funnel plot asymmetry and by Begg and

182 Egger tests [21]. In cases of high heterogeneity, we repeated the pooled analysis after removing

183 studies assessed as high risk of bias. All statistical analyses were performed using Review

184 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 ( $\geq$   
202 60 years) [16,17,22,27,29,30,31,33], one in adults  $\geq$  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  $\geq$  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].

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

211  
212 Each trial was assessed for risk of bias. Two trials were considered low [16,31], seven were  
213 considered moderate [17,22,26-28,30,32,33] and five were considered high [23-25,29,34] risk of  
214 bias as shown in Figure 6.

215

### 216 **3.2 Effect of intervention on incident dementia**

217 Dementia incidence was reported in two RCTs [16,17]. The PreDIVA trial [16] involving 3,526  
218 older adults, assessed the effectiveness of a multi-domain intervention to optimize diet, physical  
219 activity, smoking, weight and blood pressure, compared to usual primary care, on dementia  
220 incidence. After 6.7 years, dementia occurred in 121 (7%) of the intervention group and 112  
221 (7%) of the control group, with no significant intervention effect on all-cause dementia (HR  
222 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 =  
223 0.74). Secondary analyses indicated significant beneficial effects on all-cause dementia for  
224 participants with hypertension (HR 0.54, 95% CI 0.32-0.92; P = 0.02) and those without pre-  
225 existing CVD (HR 0.64, 95% CI 0.44-0.94; P = 0.02), who adhered more strictly to the  
226 intervention. The PREDIMED-Navarra trial [17], reported fewer cases of dementia in the  
227 MedDiet supplemented with olive oil (n = 12, 3%) or nuts (n = 6, 2%) intervention groups,  
228 compared with a low-fat control group (n = 17, 5%) after 6.5 years of follow-up. However, risk  
229 estimates were not reported given the small number of dementia cases observed in this study.

230

231 **3.3 Effect of intervention on cognitive function**

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

234

235 **3.3.1 Global cognition**

236 Ten RCTs involving 6,057 participants (3,188 intervention and 2,869 control) reported global  
237 cognitive function on a composite score [22,31, 32], MMSE [16,17,27,29,33] or the Modified  
238 Mini-Mental score (3MS) [25,30]. Figure 2 shows the pooled analysis of all ten trials that  
239 indicated a significant beneficial effect of intervention on global cognitive function (SMD =  
240 0.14; 95% CI 0.01, 0.27, P = 0.03) compared to control with high between study heterogeneity  
241 ( $I^2$  76%). A funnel plot showed potential asymmetry (not shown) with evidence of publication  
242 bias (Begg's P = 0.03 and Egger's P = 0.02).

243

244 **3.3.2 Executive function**

245 Nine RCTs involving 2,830 participants (1,445 intervention and 1,385 control) reported  
246 executive function on the Stroop interference [22-25,32], Trail Making Test B [28,30] or Color  
247 Trail 2 [33]. One trial reported a composite executive function score that incorporated Stroop  
248 interference and Trail B-A tests [31]. The combined analysis showed a small positive effect of  
249 intervention versus control on executive function (SMD = 0.11; 95% CI 0.04, 0.18, P = 0.003;  $I^2$   
250 0%) shown in Figure 3.

251

252 **3.3.3 Processing speed**

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

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

258

#### 259 **3.3.4 Delayed memory**

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

265

#### 266 **3.4 Sensitivity analysis**

267 For studies with two active treatment groups, the less intensive treatment was examined in the  
268 sensitivity analysis. None of the less intensive treatments were more effective on the outcomes.  
269 We performed a sensitivity analysis for global cognition by removing trials with high risk of bias  
270 [23-25,29,34]. This attenuated the combined effect (SMD = 0.13 [95% CI, 0.04, 0.30], P = 0.13)  
271 but heterogeneity remained high ( $I^2$  79%, P < 0.001). We also removed two trials with the  
272 shortest (3-4-month) follow-up time [32, 34] and this attenuated the effect for global cognition  
273 (SMD 0.11 [95% CI, -0.02, 0.24], P=0.09) but had little effect on the pooled estimates for  
274 executive function (SMD 0.10 [95% CI, -0.03, 0.18], P<0.01) or processing speed (SMD 0.12  
275 [95% CI, 0.05, 0.20], P<0.001).

276

277 **4. Discussion**

278 This is one of the first meta-analysis examining the effect of interventions with a major diet  
279 component on cognitive outcomes in adults without known cognitive impairment. Results from  
280 one large trial [16], showed no overall effect of a multicomponent intervention on dementia after  
281 6.7 years, but a significantly lower risk for those with greatest adherence to the intervention. In  
282 terms of cognitive function, the pooled analysis of available data showed positive effects of  
283 intervention on global cognition, executive function and processing speed but no effect on  
284 delayed memory. In all cases, pooled effect sizes were small (SMD 0.1 to 0.2).

285  
286 Cognitive function declines progressively during normal aging with high variability in the rate of  
287 decline, particularly in older age [35]. Processing speed and executive function appear to decline  
288 earlier and, to a greater extent, than other cognitive domains [36] and impairment in these  
289 abilities can interfere with other complex processes, such as memory and behavior and adversely  
290 affect the ability to perform everyday tasks [37-39]. Therefore, interventions to improve  
291 processing speed and executive function may be an effective means to counter the  
292 pathophysiological brain changes leading to cognitive decline during aging. Our pooled results  
293 show that interventions with a major dietary component improve these cognitive abilities in non-  
294 demented adults and are particularly public health relevant, given the longer life expectancy of  
295 populations worldwide, and the anticipated rapid increase in the number of people affected by  
296 cognitive impairment.

297  
298 We did not observe a pooled effect of intervention on delayed memory. This may be partly  
299 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



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

350

## 351 **5. Conclusions**

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

358

## 359 **6. Future research to advance this area**

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

367

368

369

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375  
376

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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

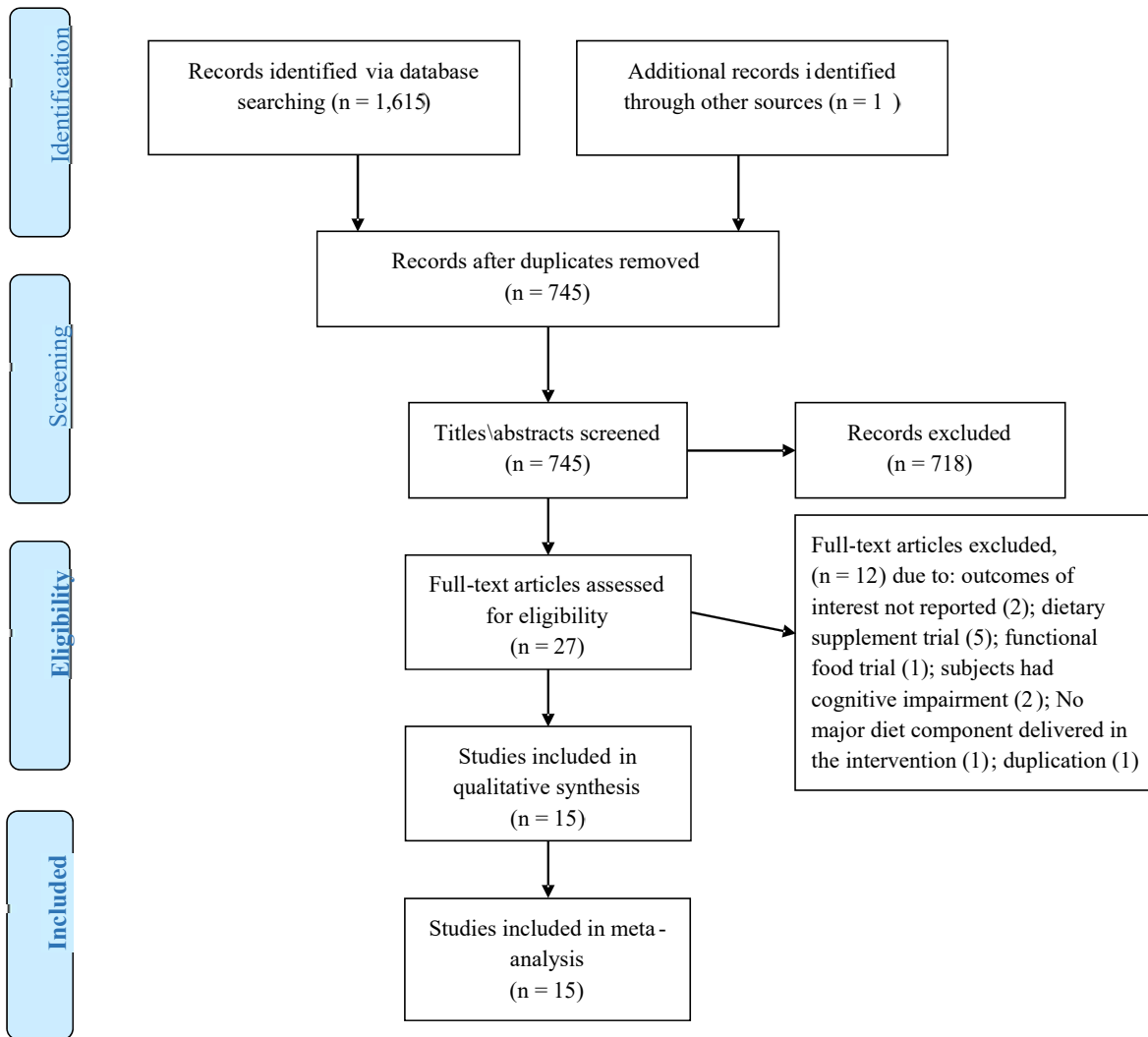


Figure 2. Forest plot showing the effect of intervention versus control on global function (n = 10)

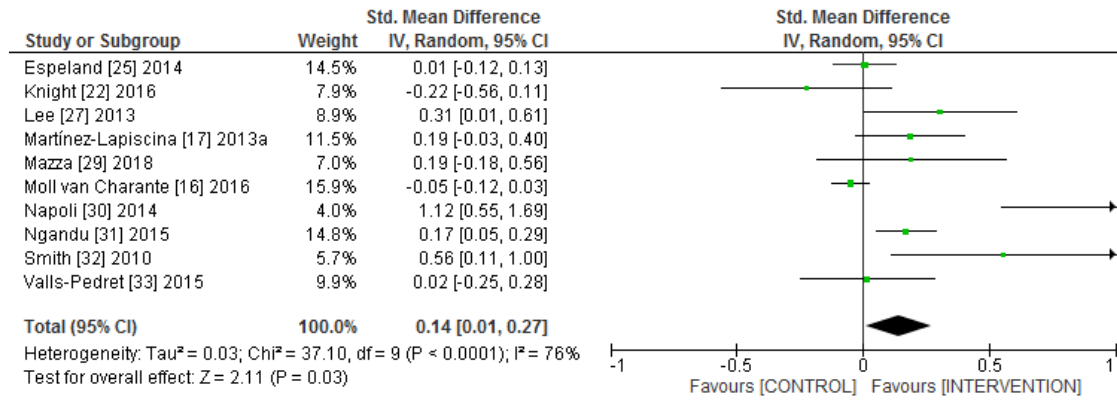


Figure 3. Forest plot showing the effect of intervention versus control on executive function (n = 9)

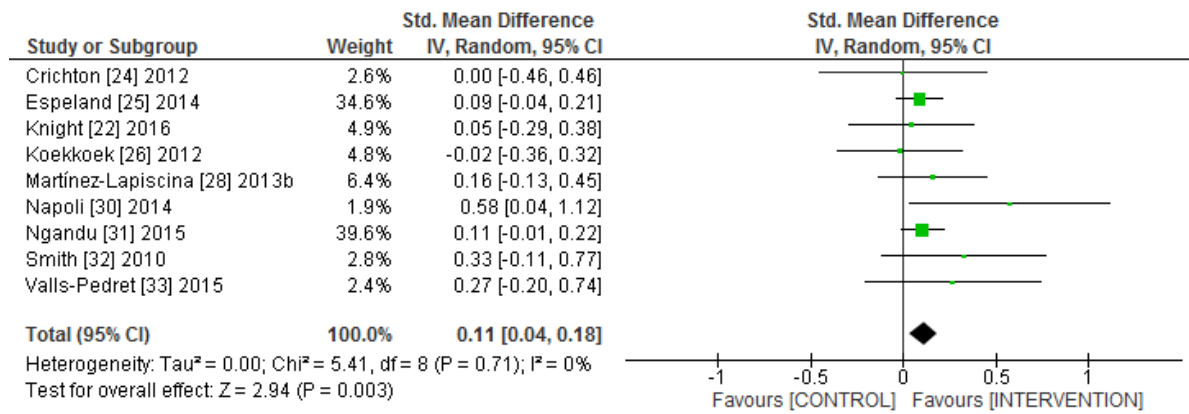


Figure 4. Forest plot showing the effect of intervention versus control on processing speed (n = 10)

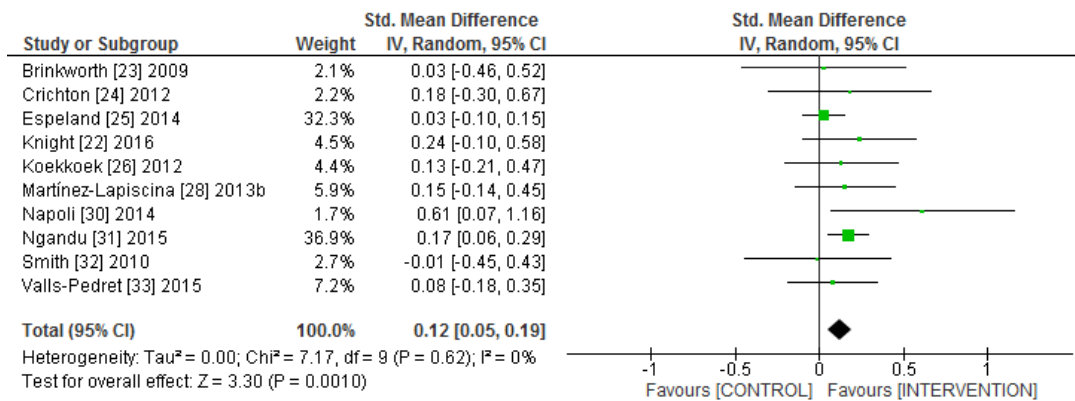


Figure 5. Forest plot showing the effect of intervention versus control on delayed memory (n = 9)

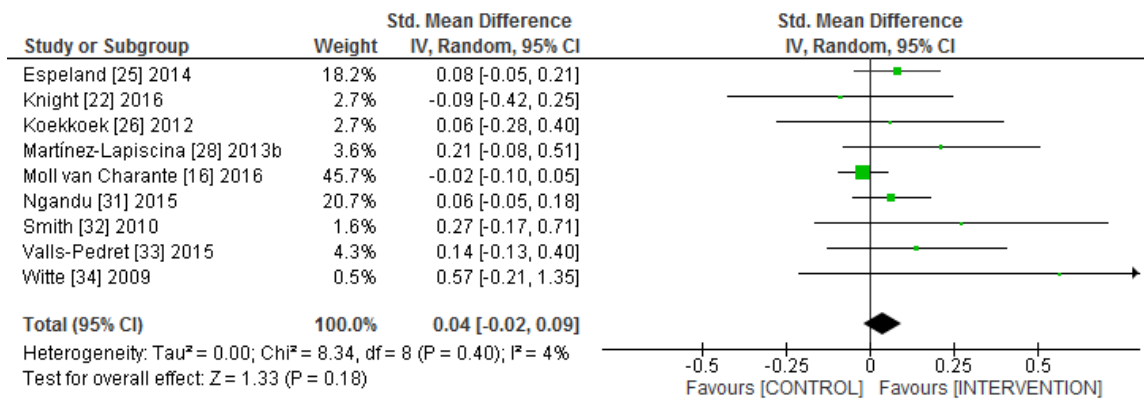


Figure 6: Summary of the risk of bias across six categories for the included studies in this systematic review and meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brinkworth [23] 2009	?	?	?	+	+	?	+
Crichton [24] 2012	?	?	?	?	-	+	-
Espeland [25] 2014	?	?	?	+	+	-	+
Knight [22] 2016	+	+	+	+	?	?	+
Koekkoek [26] 2012	+	+	-	?	+	-	+
Lee [27] 2013	+	+	-	+	?	+	-
Martínez-Lapiscina [17] 2013a	+	+	+	+	-	-	+
Martínez-Lapiscina [28] 2013b	+	+	?	+	+	?	+
Mazza [29] 2018	?	?	?	?	-	+	+
Moll van Charante [16] 2016	+	+	?	+	+	+	+
Napoli [30] 2014	?	+	?	+	?	+	+
Ngandu [31] 2015	+	+	+	+	?	+	+
Smith [32] 2010	+	?	+	+	?	-	+
Valls-Pedret [33] 2015	+	+	-	+	-	+	-
Witte [34] 2009	-	?	?	?	?	+	+

**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 $\geq 25$	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	$\geq 65$	166	MedDiet	Habitual diet	6 mon	-	Mean z-score for 11 Modified Stroop cognitive tests		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	$\geq 60$	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 $> 20$	$\geq 65$ yr	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

