

Effect of resveratrol supplementation on cognitive performance and mood in adults: A systematic literature review and meta-analysis of randomized controlled trials

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1 **The Effect of Resveratrol Supplementation on Cognitive**
2 **Performance and Mood in Adults: A Systematic Literature**
3 **Review and Meta-Analysis of Randomized Controlled Trials**

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17 review

18 *Abstract*

19 **Background/Aims:**

20 The aim of this systematic review was to evaluate clinical trial data regarding the effect of
21 resveratrol supplementation on cognitive performance and mood in populations that are
22 healthy and in the clinical setting.

23 **Methods:** Using the PRISMA guidelines, a systematic literature review of randomized
24 controlled trials was conducted. A meta-analysis was also conducted to determine treatment
25 effect on the following cognitive domains and mental processes: processing speed, number
26 facility, memory, and mood. Risk of bias was assessed using the Cochrane Collaboration
27 Risk of Bias tool; and quality of the body of evidence assessed by GRADE.

28 **Results/Discussion:** Ten studies were included. Three studies reported resveratrol
29 supplementation to significantly improve some measures of cognitive performance, two
30 reported mixed findings, and five reported no effect. When data was pooled, resveratrol
31 supplementation had a significant effect on delayed recognition (SMD 0.39 [95% CI 0.08,
32 0.70]; $I^2=0\%$; $p=0.01$; $n=3$ studies; $n=166$ participants) and negative mood (SMD -0.18 [95%
33 CI -0.31, -0.05]; $I^2=0\%$; $p=0.006$; $n=3$ studies; $n=163$ participants). Included studies
34 generally had low risk of bias and were moderate or high quality.

35 **Conclusion:** The results of this review indicate that resveratrol supplementation might
36 improve select measures of cognitive performance; however, the current literature is
37 inconsistent and limited.

38 *Introduction*

39 Age-related cognitive decline, characterised by reduced functioning in mental processes such
40 as attention regulation, memory capacity, and processing speed,¹ can pose a substantial
41 burden to the individual as it is associated with reduced functional independence and quality

42 of life.^{2,3} The societal impact of age-related cognitive decline is likely to be compounded by
43 the global ageing population, with a predicted doubling in the number of persons aged 60 or
44 older by 2050.⁴ While age-related cognitive decline is an inevitable part of ageing, there are
45 large inter-individual differences in the rate of decline that are attributed to modifiable
46 lifestyle factors such as exercise, body mass index, and dietary patterns.⁵ Moreover, a greater
47 number of these risk factors pose a heightened risk of dementia and Alzheimer's disease,
48 which, in addition to their significant morbidity, are projected to cost the Australian economy
49 one trillion dollars over the next forty years.⁶ Therefore, due to the global ageing population,⁴
50 combined with the significant health and cost burden associated with cognitive diseases,⁷ it is
51 imperative to investigate potential interventions that can ameliorate age-associated cognitive
52 decline and reduce the impact of later-life brain disease. Dietary polyphenols have been
53 investigated for their potentially beneficial effect on cognitive performance.⁸⁻¹¹ Observational
54 studies have reported polyphenol intake and adherence to polyphenol rich dietary patterns
55 such as the Mediterranean diet to be associated with improved measures of cognitive
56 performance.^{11,12} Several polyphenol-rich foods including various berries, green tea, and
57 cacao have also demonstrated improved measures of cognitive performance in clinical
58 trials.¹³

59 Resveratrol is a polyphenol found in foods such as red grapes, berries, peanuts and red wine,
60 and has been demonstrated in preclinical models to exhibit neuroprotective properties.^{14,15}
61 Resveratrol supplementation prevents streptozotocin-induced cognitive impairment and
62 protects against hippocampal neurodegeneration and against learning impairment in rodent
63 models.^{16,17} Additionally, resveratrol supplementation improved cognitive outcomes such as
64 spatial memory and memory acquisition in primate¹⁸ and rodent¹⁹ models of ageing. While
65 the exact mechanism of action is unknown, resveratrol may act on multiple pathways

66 suggested to be involved in age-related cognitive decline including enhanced endothelial
67 production of nitric oxide, oxidative stress reduction, inhibition of inflammation, and
68 modulation of sirtuin gene expression.^{20,21}

69 If resveratrol supplementation provides a positive effect on human cognitive performance,
70 resveratrol supplementation could be a viable, low-cost treatment intervention for preserving
71 cognitive performance in the ageing population. Therefore, this systematic review and meta-
72 analysis aimed to examine the potential effect of resveratrol supplementation on cognitive
73 performance and mood in adult humans.

74 ***Methodology***

75 **Literature search**

76 This review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
77 (PRISMA) guidelines as a methodological template.²² An initial systematic search of the
78 following databases was conducted, without time limits, up to September 2016: Medline (via
79 Scopus), CINAHL, Cochrane, Embase and Proquest. A further search was conducted in June
80 2017 before submission to ensure all relevant studies were identified. A snowball search was
81 conducted by searching for references published in relevant papers. Derived from the PICOS
82 criteria (Table 1), the search terms used were (Adult OR human) AND (Resveratrol OR
83 stilbenoid OR phytoalexin OR red wine OR red grape OR trans-resveratrol) AND (Cognitive
84 performance OR cognition OR mental capacity).

85 **Study selection**

86 Eligible studies required the following criteria: used a randomized controlled trial study
87 design; recruited both healthy and clinical adult human subjects (over 18); written in English,

88 and used an intervention of resveratrol supplementation (either standalone or in combination
89 with other compounds). We did not include studies that investigated resveratrol-containing
90 foods as food items contain a vast array of bioactive compounds which could influence
91 results and in contrast to supplements, are relatively low in concentrations of resveratrol, and
92 are unlikely to provide the therapeutic dose provided in previously reported supplementation
93 studies.^{23,24} However, red wine and grapes have been the primary focus of resveratrol-related
94 research and therefore, in order to reduce the number of search results while ensuring all
95 relevant studies were captured, search terms relating to red wine and grapes were included
96 while search terms relating to other food sources were excluded. Cross-sectional studies,
97 reviews, abstracts, study protocols, conference papers, or those that did not report on any
98 outcome of interest were excluded. Outcomes of interest for the study included any cognition
99 measurements (e.g. memory, processing speed), mood, and cognitive fatigue. Articles were
100 first screened for eligibility based on titles and abstracts by two investigators (JC and BA). If
101 considered potentially eligible, the full text publication was retrieved and independently
102 reviewed by two review authors (JC and BA). Disagreements were managed by discussion to
103 reach consensus.

104 **Data Extraction**

105 Data extraction (conducted by JC and BA, and cross-checked by WM) included the following
106 parameters: study design, sample size, total study period, population, timing of outcome
107 measures, type of intervention, dose and duration of resveratrol supplementation, outcomes
108 reported, results, study location and level of evidence. To perform the meta-analysis, we
109 extracted the mean change score, or end-of-study values when change scores were not
110 available, along with their associated variance (standard deviations [SD], standard error
111 [SE] or 95% confidence intervals [CI]). For studies reporting more than one resveratrol

112 intervention arm, we extracted the arm of the highest dose or the resveratrol arm only in cases
113 where the second resveratrol intervention had more than two active ingredients.

114 **Risk of Bias**

115 All studies were independently assessed for bias by three authors (JC and BA and WM) using
116 the Cochrane Handbook for Systematic Reviews of Interventions checklist.²⁵ This tool
117 includes criteria for assessing sequence generation, allocation concealment, blinding of
118 participants, blinding of personnel and outcome assessors, incomplete outcome data and
119 selective outcome reporting, which assesses risk of bias as low, unclear or high.

120 Disagreements were managed by consensus. All clinical studies were rated for evidence level
121 using the National Health and Medical Research Council Hierarchy of Evidence.²⁶ The
122 certainty in the body of evidence for each outcome related to cognitive function for which we
123 found data was assessed using the Grading of Recommendations, Assessment, Development
124 and Evaluation (GRADE) tool,²⁷ following steps and interpretation as specified in the
125 GRADE Handbook.²⁸ Determination of the GRADE level of evidence was determined
126 independently by two authors (SM and WM), with disagreements managed by consensus.

127 **Data Synthesis and Analysis**

128 Due to the range of cognitive function tests used in the included studies, the Cattall–Horn–
129 Carroll cognitive framework was used to group differing cognitive function tests based on the
130 frameworks proposed broad cognitive abilities and as used in previous nutraceutical trials.²⁹
131 When interventions and associated outcomes were assessed as sufficiently homogeneous, and
132 when sufficient information was available from the studies, quantitative data were pooled
133 into Review Manager (Version 5.3, The Cochrane Collaboration 2014) for meta-analysis. To
134 calculate the overall treatment effect, the difference between the intervention and comparison

135 groups' change scores from baseline to the end of follow-up was extracted. If change scores
136 were not available, end of intervention values were extracted, assuming baseline values were
137 similar.³⁰ The appropriate variance from each individual study was used, either as the SD or
138 calculated from the SEM or 95%CI. Meta-analysis of these values was performed using the
139 DerSimonian and Laird random-effects model³¹ and checked using the fixed-effect model to
140 ensure robustness and susceptibility to potential outliers. The I² statistic was used to assess
141 the inconsistencies between studies and describe the percentage of variability in effect.
142 Heterogeneity was considered substantial if the I² statistic was ≥50%. All effect sizes were
143 calculated using the standardised mean differences (SMD) as all studies used a myriad of
144 outcome measures/scales. Standardised mean difference effect sizes of <0.4 were considered
145 small, 0.4 – 0.7 moderate, and >0.7 large.³⁰ We considered a statistically significant finding
146 with p-values <0.05. Meta-analyses with significant results were presented as a figure within
147 the manuscript and meta-analyses with non-significant results were included as
148 supplementary material. Publication bias was assessed by visual inspection of funnel plots.

149 ***Results***

150 Three hundred and fifty articles were identified after the initial search with 115 of these
151 omitted as duplicates. A further 201 did not meet the inclusion criteria. Of the remaining 34
152 articles, 24 were excluded for reasons detailed in the PRISMA flow chart (Figure 1), leaving
153 10 articles for inclusion in the final review. We conducted nine meta-analyses with eight
154 studies being included in at least one meta-analysis (two studies excluded from meta-analyses
155 due to insufficient available data or heterogenous study design).^{32,33}

156 **Study Characteristics**

157 The total sample size of the studies included in this systematic review was 372 subjects and
158 individual study sample sizes ranged from 16 to 80 participants (Table 2³²⁻⁴¹). All studies
159 were randomized double-blind controlled trials with five studies using cross-over designs.
160 Nine studies used an inert placebo as the control group while Scholey et al.³² compared a red
161 wine supplemented with resveratrol to a red wine intervention that was not supplemented
162 with resveratrol. Three studies included healthy young adults (18-34 years old),^{35,37,38} two
163 studies included healthy older adults (65-78),^{32,34} two included healthy overweight older
164 adults,^{39,40} one included schizophrenic adults,⁴¹ one included older adults with mild cognitive
165 decline,³⁶ and one included adults with Type 2 Diabetes Mellitus (T2DM).³³ The duration of
166 the studies varied with six studies using chronic daily doses up to 26-weeks.^{34,36,37,39-41} The
167 remaining four studies used single or multiple acute doses with 2-14 days washout between
168 doses.

169 **Dosing regimen**

170 Studies used a dose of resveratrol ranging from 75 to 500mg and required subjects to
171 consume in capsule form, with the exception of one study that used wine enriched with
172 200mg resveratrol.³² No study reported any adverse side effects from supplementation. Four
173 studies used a co-intervention of piperine or quercetin with the aim to increase bioavailability
174 of resveratrol supplementation.³⁶⁻³⁹

175 **Outcome Measures**

176 Measures of cognition varied, with four studies using the Computerised Mental Performance
177 Assessment System (COMPASS)^{32,35,37,38} to conduct the serial subtraction 3 and 7, Rapid
178 Visual Image Processing (RVIP) test. Two studies also used the COMPASS to conduct serial

179 13 and 17's and either a 3-back or N-back test;^{37,38} three studies used the Stroop Colour-
180 Word Test;^{33,40,41} three used variations of the Rey Auditory Verbal Learning Test
181 (RAVLT);^{34,36,39} and two used the trail making task.^{33,34} Individual studies also included the
182 following cognitive tests: the Computerized Multi-Tasking Test Battery;³³ 15-minute word
183 recall;³⁹ the Cambridge Semantic Memory Battery and the Double Span Task;³⁴ and the
184 Hopkins Verbal Learning Test and the Weschler Adult Intelligence Scale.⁴¹

185 **Study Results**

186 The reported between-group differences in cognition was mixed. Five studies reported
187 significant improvements in some measures of cognitive performance. These included word
188 retention ($p=0.038$),³⁹ overall cognitive performance ($p=0.020$),³⁴ semantic and verbal
189 memory domains ($p=0.041$),³⁴ and anxiety ($p=0.025$).³⁴ Scholey et al.³² reported
190 improvements in the Serial 7s test ($p=0.009$) in the intervention group (acute dose, 200 mg
191 resveratrol enriched red wine) but that the control group (red wine only) reported
192 improvements in the Serial 3s test ($p=0.004$). Wightman et al.³⁷ also reported mixed results
193 with the intervention group reporting both lower and higher performance measures compared
194 to placebo in the COMPASS serial 7s, 17s and 3-back tests and measures of fatigue. Wong et
195 al.³³ reported improvements in performance index (accuracy/time) during a dual and multi-
196 tasking test battery in two of the three intervention doses (75mg and 300mg) compared to
197 placebo but no improvement in accuracy alone. The remaining five studies reported no
198 significant differences in cognitive measures.

199 ***Processing speed***

200 A total of 8 studies involving a total of 267 participants measured visual processing speed
201 outcomes,^{32-35,37,38,40,41} including RVIP reaction time,^{32,35,37,38} Stroop colour word test,^{33,40,41}

202 and the Trail Making Test.^{33,34} Five studies with available data were entered into two separate
203 meta-analyses which assessed differences in number of correct answers or the time taken to
204 complete the task. Resveratrol supplementation did not significantly influence either measure
205 of processing speed, in numbers correct (SMD -0.04 [95% CI -0.38, 0.31]; $I^2=0\%$; $p=0.84$;
206 $n=3$ studies; $n=86$ participants), or time taken, although there was a near significant trend
207 towards decreased time taken (SMD -0.23 [95% CI -0.48, 0.01]; $I^2=0\%$; $p=0.06$; $n=5$ studies;
208 $n=211$ participants).

209 ***Number facility***

210 Number facility was reported in 4 studies including 123 participants.^{32,35,37,38} Reported
211 number facility outcomes included serial 3's,^{32,35} serial 7's,^{32,35,37,38} serial 13's,^{37,38} and serial
212 17's.^{37,38} Meta-analysis of three studies^{35,37,38} with available data was conducted, which
213 included serial number facility outcomes reported as serials correct and serials incorrect.
214 Meta-analysis showed no significant effect of resveratrol supplementation on serials correct
215 (SMD -0.17 [95% CI -0.38, 0.05]; $I^2=0\%$; $p=0.12$; $n=3$ studies; $n=86$ participants) or serials
216 incorrect (SMD 0.04 [95% CI -0.21, 0.28]; $I^2=25\%$; $p=0.78$; $n=3$ studies; $n=86$ participants).

217 ***Memory***

218 Memory was measured by RAVLT^{34,36,39}, N-back accuracy,^{37,38} and the Hopkins Verbal
219 Learning Test⁴¹ by a total of six studies encompassing 244 participants. There was sufficient
220 information provided by three studies to perform meta-analyses on the RAVLT subset scores;
221 delayed recall, delayed recognition, and learning ability. Resveratrol supplementation had a
222 significant effect but low effect size on delayed recognition (SMD 0.39 [95% CI 0.08, 0.70];
223 $I^2=0\%$; $p=0.01$; $n=3$ studies; $n=166$ participants; Figure 2)^{34,36,39}; however, no significant
224 effect on delayed recall (SMD 0.23 [95% CI -0.16, 0.63]; $I^2=38\%$; $p=0.25$; $n=3$ studies;

225 n=166 participants) or learning ability (SMD 0.28 [95% CI -0.26, 0.81]; $I^2=65%$; $p=0.31$; $n=3$
226 studies; $n=166$ participants).

227 ***Mood***

228 A total of five studies involving a total of 203 participants reported a variety of mood-related
229 outcomes following resveratrol supplementation.^{32,34,35,37,38} Mood was measured using the
230 following questionnaires: Profile of Mood States (POMS) questionnaire,^{34,37} the Bond-Lader
231 Visual Analogue Mood scales,³² the Centre for Epidemiologic Studies Depression scale,³⁴
232 and visual analogue scales.^{35,38} The results of two meta-analysis report a non-significant
233 change in ratings of positive mood (SMD -0.02 [95% CI -0.28, 0.24]; $I^2=0%$; $p=0.88$; $n=3$
234 studies; $n=163$ participants) and a significant improvement in negative mood (SMD -0.18
235 [95% CI -0.31, -0.05]; $I^2=0%$; $p=0.006$; $n=3$ studies; $n=163$ participants; Figure 3)^{34,37,38} with
236 a low effect size.

237 **Risk of Bias assessment and certainty of evidence-base**

238 Figure 4 shows the risk of bias across the included studies. Overall, the assessment of bias
239 reported generally low risk of bias across all domains, particularly for reporting bias and
240 performance bias for all studies. Five studies were rated as high risk of other bias due to the
241 inclusion of additional bioactive compounds to the intervention which may have influenced
242 the results.^{32,34,36-38} Visual inspection of funnel plots provided no evidence of publication
243 bias. Using the GRADE tool, all outcomes were rated at high or moderate quality except for
244 learning ability which was rated as low quality due to imprecision and significant
245 heterogeneity (I^2 of 65%) (Table 3). Imprecision due to small sample sizes of individual
246 meta-analyses was the most common reason for downgrading the quality rating.

247 *Discussion*

248 The aim of this review was to systematically evaluate the strength of current research
249 regarding the efficacy of resveratrol supplementation in cognitive performance. Although
250 there is promising preclinical research to suggest resveratrol supplementation influences
251 cognition,^{16,17,20} the published clinical research currently provides mixed results, with 5 of 10
252 studies reporting no significant effect on cognitive performance. Furthermore, the results of
253 our meta-analysis and GRADE assessment reported moderate to high confidence that
254 resveratrol supplementation has no significant effect on most outcomes in the general
255 population, excepting a small effect in improving delayed recognition and negative mood.

256 Delayed recognition appears to decline in older adults and mood disorders are prevalent
257 within all age groups.^{42,43} Resveratrol is a relatively low-cost, widely-available, and well-
258 tolerated intervention which may be an effective intervention for these outcomes. However,
259 given the small effect size and limited sample sizes of included studies, the results of our
260 meta-analysis should be interpreted with caution and clinical judgment should be used when
261 using resveratrol supplementation in a clinical setting.

262 The length of the trial periods varied greatly from one day to six months with trials using a
263 shorter duration generally finding no significant results compared to longer term trials. Due to
264 the small number of studies, a sensitivity analysis was unable to be conducted for each meta-
265 analysis to assess this. However, of the studies that reported significant effects from
266 resveratrol supplementation, two of three longest running trials reported significant
267 improvements in some measures of cognitive performance.^{34,39} Therefore, these results
268 suggest that long-term resveratrol supplementation may be required to achieve improvements
269 in cognitive measures. However, these results contrast with Kobe et al.³⁶ which also
270 conducted a 26-week study but reported no significant differences in cognitive performance.

271 Furthermore, there was clinical heterogeneity in the cohorts investigated with some including
272 young healthy adults while others included older adults and those with diabetes, mild
273 cognitive impairment or schizophrenia. Two studies suggest that resveratrol supplementation
274 may have more pronounced effects in certain populations with worse cognitive performance,
275 that being older individuals or populations with chronic diseases.^{32,33} It may be that
276 populations with cognitive impairment will have more distinguished performance differences
277 than high performing populations. However, included studies that recruited older participants
278 or participants with chronic diseases did not report consistently positive improvements in
279 cognition.

280 The dose of resveratrol used in the included studies ranged from 75 to 500mg with no clear
281 trend related to the efficacy of the intervention, suggesting that the differences in results
282 between studies may not be due to the dosage used. The poor bioavailability of resveratrol,
283 however, may account for the variation of results.²⁵ Some studies included additional
284 nutrients such as piperine and quercetin to improve the bioavailability of resveratrol. In
285 animal studies, piperine significantly enhances maximum serum resveratrol levels and area
286 under the curve when compared to resveratrol alone⁴⁴ and thus, was used by Whitman et
287 al.^{37,38} in two separate studies. However, results from their acute trial³⁸ reported no significant
288 improvements in cognition and their chronic-dosing trial³⁷ reported inconsistent changes in
289 some measures of cognitive testing. Two of the included studies supplemented 320-350 mg
290 of quercetin in addition to resveratrol,^{36,39} which is believed to inhibit the sulphation of
291 resveratrol in the body and increase its bioavailability.⁴⁵ While the addition of these nutrients
292 may improve bioavailability of resveratrol, it may also confound the results as it is unclear if
293 a treatment effect (or lack of effect) is due to resveratrol or from the additional bioactive
294 nutrients, which may have interacted with the effect of resveratrol or acted independently.
295 Furthermore, Whitman et al.³⁷ demonstrated that plasma resveratrol metabolites can

296 accumulate with chronic dosing which suggests chronic administration of resveratrol may be
297 an alternative strategy to improving plasma concentrations.

298 There are multiple food sources that are rich in a variety of polyphenols. These include, but
299 are not limited to, green tea,⁸ cacao,¹⁰ and berries,⁹; which have all been demonstrated to
300 affect cognitive performance. The total polyphenol intake of participant habitual diet and
301 consumption of polyphenol-rich foods prior to measurement was, to varying degrees,
302 controlled for in many of the included studies. Strategies included asking participants to
303 maintain their usual diet,^{34,39,41} abstain from resveratrol or polyphenol rich foods,^{40,41}
304 monitoring dietary records for gross changes in diet,^{34,37,40} and providing detailed lists of
305 polyphenol rich foods to limit.⁴⁰ However, while many of these strategies could reduce
306 polyphenol variation during the intervention period, they are less likely to control for group
307 differences in polyphenol intake. Therefore, measures to control for group differences in total
308 polyphenol intake such as dietetic education and food monitoring may be beneficial for future
309 clinical studies.

310 Finally, due to the small sample sizes and few reported details on power calculations in many
311 of the included studies, it is possible that many require additional statistical power to detect a
312 significant difference in cognitive scores. For example, Wong et al.⁴⁰ stated being sufficiently
313 powered to detect changes in flow mediated dilation, but attributed the lack of effect size in
314 cognitive outcomes to a lack of statistical power. However, our meta-analyses of pooled
315 results determined resveratrol supplementation to improve only in one of the seven outcomes
316 we analysed.

317 A limitation of our meta-analysis was that despite the wide-range of similar cognitive tests
318 used in the included studies, there was a lack of homogeneity in how the tests were reported
319 which limited the number of studies that could be included for analysis. Future trials are

320 encouraged to provide standardized results or supplementary material and/or datasets to assist
321 with future meta-analyses in this area.

322 **Conclusion**

323 The current literature does not provide consistent support for the use of resveratrol
324 supplementation on improving cognitive performance. In some instances, resveratrol has
325 been shown to enhance some cognitive performance measures; however, there is limited
326 consistency between studies. Future trials that are sufficiently powered, utilise longer
327 intervention periods, and address confounding issues including background polyphenol intake
328 and bioavailability are required

329 **Author Contributions**

330 JTK was involved in the meta-analysis, SM was involved in the GRADE analysis, JC and BA
331 were involved for search and screening of included studies, AP, CI, and AT provided content
332 expertise, WM was responsible for all stages of the manuscript and analysis. All authors were
333 involved in the production of the manuscript.

334 **Funding and conflict of interest declaration**

335 No authors declare a conflict of interest for this study. No funding was provided for this
336 review.

337 **Supporting Information**

338 Appendix S1. PRISMA checklist

339 Appendix S2. Additional forest plots for non-significant meta-analyses

References

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1. Harada CN, Natelson Love MC, Triebel K. Normal Cognitive Aging. *Clinics in geriatric medicine*. 2013;29(4):737-752.
2. Millan-Calenti JC, Tubio J, Pita-Fernandez S, Rochette S, Lorenzo T, Maseda A. Cognitive impairment as predictor of functional dependence in an elderly sample. *Archives of gerontology and geriatrics*. 2012;54(1):197-201.
3. Pan C-W, Wang X, Ma Q, Sun H-P, Xu Y, Wang P. Cognitive dysfunction and health-related quality of life among older Chinese. *Scientific Reports*. 2015;5:17301.
4. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Prospects: The 2017 Revision, Key Findings and Advance Tables*. 2017.
5. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2015;11(9):1015-1022.
6. Solfrizzi V, Panza F, Frisardi V, et al. Diet and Alzheimer's disease risk factors or prevention: the current evidence. *Expert review of neurotherapeutics*. 2011;11(5):677-708.
7. Alzheimer's Australia. Economic cost of dementia. 2017.
8. Ide K, Yamada H, Takuma N, et al. Green tea consumption affects cognitive dysfunction in the elderly: a pilot study. *Nutrients*. 2014;6(10):4032-4042.
9. Krikorian R, Shidler MD, Nash TA, et al. Blueberry Supplementation Improves Memory in Older Adults. *Journal of agricultural and food chemistry*. 2010;58(7):3996-4000.
10. Mastroiacovo D, Kwik-Urbe C, Grassi D, et al. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study—a randomized controlled trial. *The American journal of clinical nutrition*. 2015;101(3):538-548.
11. Valls-Pedret C, Lamuela-Raventos RM, Medina-Remon A, et al. Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *Journal of Alzheimer's disease : JAD*. 2012;29(4):773-782.
12. Kesse-Guyot E, Fezeu L, Andreeva VA, et al. Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later. *The Journal of nutrition*. 2012;142(1):76-83.
13. Bell L, Lamport DJ, Butler LT, Williams CM. A Review of the Cognitive Effects Observed in Humans Following Acute Supplementation with Flavonoids, and Their Associated Mechanisms of Action. *Nutrients*. 2015;7(12):10290-10306.
14. Burns J, Yokota T, Ashihara H, Lean ME, Crozier A. Plant foods and herbal sources of resveratrol. *Journal of agricultural and food chemistry*. 2002;50(11):3337-3340.
15. Albani D, Polito L, Signorini A, Forloni G. Neuroprotective properties of resveratrol in different neurodegenerative disorders. *BioFactors (Oxford, England)*. 2010;36(5):370-376.
16. Sharma M, Gupta YK. Chronic treatment with trans resveratrol prevents intracerebroventricular streptozotocin induced cognitive impairment and oxidative stress in rats. *Life sciences*. 2002;71(21):2489-2498.

- 386 17. Kim D, Nguyen MD, Dobbin MM, et al. SIRT1 deacetylase protects against
387 neurodegeneration in models for Alzheimer's disease and amyotrophic lateral
388 sclerosis. *The EMBO journal*. 2007;26(13):3169-3179.
- 389 18. Dal-Pan A, Pifferi F, Marchal J, Picq J-L, Aujard F, on behalf of RC. Cognitive
390 Performances Are Selectively Enhanced during Chronic Caloric Restriction or
391 Resveratrol Supplementation in a Primate. *PLOS ONE*. 2011;6(1):e16581.
- 392 19. Oomen CA, Farkas E, Roman V, van der Beek EM, Luiten PGM, Meerlo P. Resveratrol
393 Preserves Cerebrovascular Density and Cognitive Function in Aging Mice. *Frontiers in*
394 *Aging Neuroscience*. 2009;1:4.
- 395 20. Singh N, Agrawal M, Doré S. Neuroprotective Properties and Mechanisms of
396 Resveratrol in in Vitro and in Vivo Experimental Cerebral Stroke Models. *ACS*
397 *Chemical Neuroscience*. 2013;4(8):1151-1162.
- 398 21. Li H, Xia N, Forstermann U. Cardiovascular effects and molecular targets of
399 resveratrol. *Nitric oxide : biology and chemistry*. 2012;26(2):102-110.
- 400 22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting
401 systematic reviews and meta-analyses of studies that evaluate healthcare
402 interventions: explanation and elaboration. *BMJ*. 2009;339.
- 403 23. Brasnyo P, Molnar GA, Mohas M, et al. Resveratrol improves insulin sensitivity,
404 reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients.
405 *The British journal of nutrition*. 2011;106(3):383-389.
- 406 24. Timmers S, Konings E, Bilet L, et al. Calorie restriction-like effects of 30 days of
407 resveratrol supplementation on energy metabolism and metabolic profile in obese
408 humans. *Cell metabolism*. 2011;14(5):612-622.
- 409 25. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version
410 5.0.2
- 411 26. National Health and Medical Research Council. NHMRC additional levels of evidence
412 and grades for recommendations for developers of guidelines. *Commonwealth of*
413 *Australia: National Health and Medical Research Council* 2009.
- 414 27. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines:
415 a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*.
416 2011;64(4):380-382.
- 417 28. *Handbook for grading the quality of evidence and the strength of recommendations*
418 *using the GRADE approach. Updated October 2013.*
419 <http://gdt.guidelinedevelopment.org2013>.
- 420 29. Pase MP, Stough C. An evidence-based method for examining and reporting
421 cognitive processes in nutrition research. *Nutrition research reviews*. 2014;27(2):232-
422 241.
- 423 30. Higgins, Julian, Green. 17.8.2 Study summaries using more than one patient-
424 reported outcome. In: *Cochrane handbook for systematic reviews of*
425 *interventions*. 2011.
- 426 31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*.
427 1986;7(3):177-188.
- 428 32. Scholey A, Benson, S., Stough, C., Stockley, C. Effects of resveratrol and alcohol on
429 mood and cognitive function in older individuals. *Nutrition and Aging*. 2014;2(133-
430 138.).

- 431 33. Wong RH, Raederstorff D, Howe PR. Acute Resveratrol Consumption Improves
432 Neurovascular Coupling Capacity in Adults with Type 2 Diabetes Mellitus. *Nutrients*.
433 2016;8(7).
- 434 34. Evans HM, Howe PRC, Wong RHX. Effects of Resveratrol on Cognitive Performance,
435 Mood and Cerebrovascular Function in Post-Menopausal Women; A 14-Week
436 Randomised Placebo-Controlled Intervention Trial. *Nutrients*. 2017;9(1):27.
- 437 35. Kennedy DO, Wightman EL, Reay JL, et al. Effects of resveratrol on cerebral blood
438 flow variables and cognitive performance in humans: a double-blind, placebo-
439 controlled, crossover investigation. *The American journal of clinical nutrition*.
440 2010;91(6):1590-1597.
- 441 36. Kobe T, Witte AV, Schnelle A, et al. Impact of Resveratrol on Glucose Control,
442 Hippocampal Structure and Connectivity, and Memory Performance in Patients with
443 Mild Cognitive Impairment. *Frontiers in neuroscience*. 2017;11:105.
- 444 37. Wightman EL, Haskell-Ramsay CF, Reay JL, et al. The effects of chronic trans-
445 resveratrol supplementation on aspects of cognitive function, mood, sleep, health
446 and cerebral blood flow in healthy, young humans. *The British journal of nutrition*.
447 2015;114(9):1427-1437.
- 448 38. Wightman EL, Reay JL, Haskell CF, Williamson G, Dew TP, Kennedy DO. Effects of
449 resveratrol alone or in combination with piperine on cerebral blood flow parameters
450 and cognitive performance in human subjects: a randomised, double-blind, placebo-
451 controlled, cross-over investigation. *The British journal of nutrition*. 2014;112(2):203-
452 213.
- 453 39. Witte AV, Kerti L, Margulies DS, Floel A. Effects of resveratrol on memory
454 performance, hippocampal functional connectivity, and glucose metabolism in
455 healthy older adults. *The Journal of neuroscience : the official journal of the Society*
456 *for Neuroscience*. 2014;34(23):7862-7870.
- 457 40. Wong RH, Berry NM, Coates AM, et al. Chronic resveratrol consumption improves
458 brachial flow-mediated dilatation in healthy obese adults. *Journal of hypertension*.
459 2013;31(9):1819-1827.
- 460 41. Zortea K, Franco VC, Guimaraes P, Belmonte-de-Abreu PS. Resveratrol
461 Supplementation Did Not Improve Cognition in Patients with Schizophrenia: Results
462 from a Randomized Clinical Trial. *Frontiers in psychiatry*. 2016;7:159.
- 463 42. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High Occurrence of Mood
464 and Anxiety Disorders among Older Adults: The National Comorbidity Survey
465 Replication. *Archives of general psychiatry*. 2010;67(5):489-496.
- 466 43. Whiting WL, Smith AD. Differential age-related processing limitations in recall and
467 recognition tasks. *Psychology and aging*. 1997;12(2):216-224.
- 468 44. Johnson JJ, Nihal M, Siddiqui IA, et al. Enhancing the bioavailability of resveratrol by
469 combining it with piperine. *Molecular nutrition & food research*. 2011;55(8):1169-
470 1176.
- 471 45. De Santi C, Pietrabissa A, Spisni R, Mosca F, Pacifici GM. Sulphation of resveratrol, a
472 natural compound present in wine, and its inhibition by natural flavonoids.
473 *Xenobiotica; the fate of foreign compounds in biological systems*. 2000;30(9):857-
474 866.

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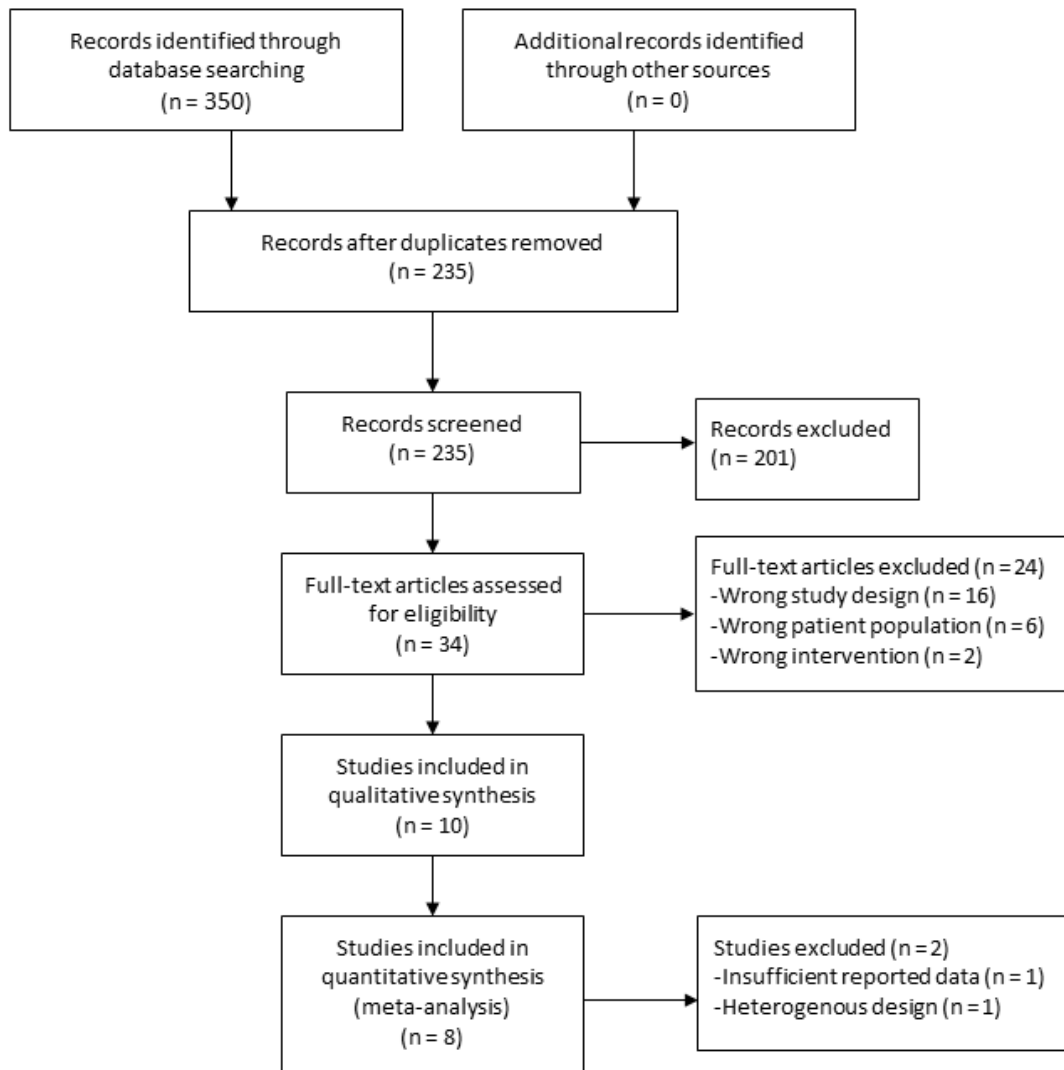
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499 Figure 1. PRISMA Flow Diagram

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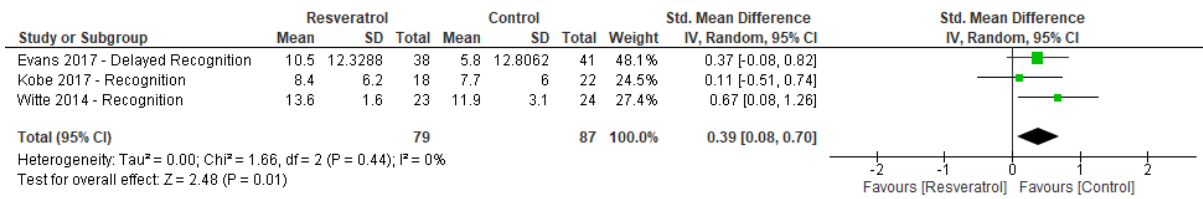
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506 Figure 2. Meta-analysis on the effect of resveratrol supplementation on delayed recognition



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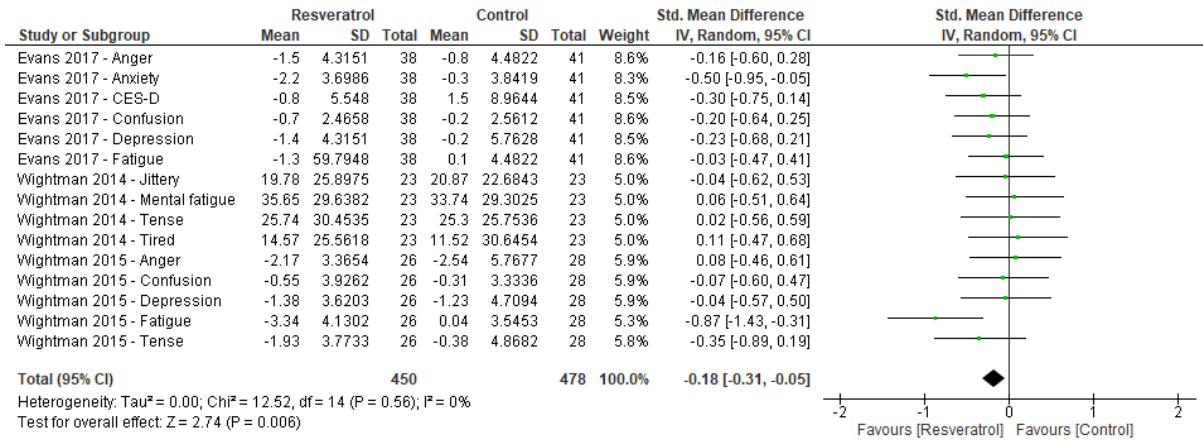
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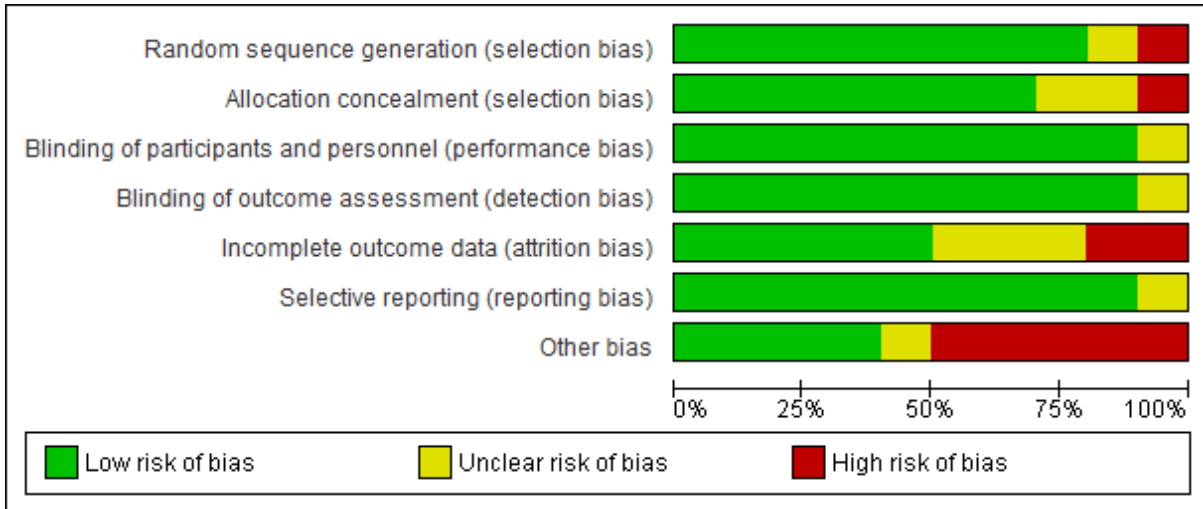
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542 Figure 3. Meta-analysis on the effect of resveratrol supplementation on negative mood



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544 Figure 4. Risk of bias: review authors' judgments' on each risk of bias item presented as
545 percentages across all included studies (n=10).



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547 Table 1. PICOS criteria for research question

Population	Adult humans (healthy or chronic disease populations)
Intervention	Resveratrol supplementation
Comparator	Placebo or control intervention
Outcome	Cognitive function domains or mood
Setting	Any

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550 Table 2. Summary table of included studies

Author/ Date	Study design	Country	Level of Evidenc e	Sampl e size (n)	Total Study period	Population details	Outcomes measured at:	Interventio n	Cognitive outcomes	Mood outcomes	Results
Acute consumption studies											
Kennedy et al. 2010 ³⁵	Randomized , double blind placebo controlled, cross-over trial	United Kingdom	II	24	3 x 1 day, 7 day wash out	Healthy adults Age (years, mean (range)): 20.17 (18-25) BMI: Not reported	Baseline, 45 minutes post- consumption	250mg trans- resveratrol OR 500mg trans- resveratrol OR placebo	COMPASS cognitive assessment system tests (Serial subtractions 3 and 7, RVIP).	Mental fatigue using a visual analogue scale	No significant, treatment- related differences on cognitive task performance and mental fatigue
Scholey et al. 2014 ³²	Randomized , double blind, cross- over trial	Australia	II	16	2 x 1 day, minimum 48-hour washout	Healthy older adults Age (years, mean±std): 70.44±4.37 BMI: Not reported	Baseline and 60 minutes post- consumption	100ml red wine OR 100ml red wine enriched with 200 mg resveratrol	COMPASS cognitive assessment system tests (serial subtractions 3 and 7, RVIP),	Mood using the Bond- Lader Visual Analogue Mood scales	Red wine group made more responses with Serial 3s (p=0.004), Resveratrol group made more responses with Serial 7s (p=0.009). No other significant effects
Wightman et al. 2014 ³⁸	Randomized , double blind, placebo controlled, cross-over trial	United Kingdom	II	23	3 x 1 day visits to clinic (conducted 2-14 days apart)	Healthy adults Age (years, mean±std): 21±3.2 BMI (mean±std): 24.2±2.38 kg/m ²	Baseline and 40 minutes post- consumption	250mg trans- resveratrol OR 250mg trans- resveratrol and 20mg of piperine OR placebo	COMPASS cognitive assessment system tests (Serial subtractions 7, 13 and 17, RVIP and N- back),	Mood using a visual analogue scale	No significant treatment- related differences in cognitive or mood measures

Wong et al. 2016 ³³	Randomized, double-blind placebo controlled, cross-over trial	Australia	II	36	4 x 1 day, 7 day wash out	T2DM adults Age (years, mean±std): 46.40±11.18 (Resveratrol group), 41.00±7.87 (Control group) BMI (mean): 30.3 kg/m ²	75 min post consumption	75, 150, 300mg trans-resveratrol OR placebo	Computerized Multi-Tasking Test Battery comprising, Stroop Color-Word test, N-back task, Visual Warning and High Number Tap, Trial Making Task and Serial Subtraction 3	Performance index (accuracy/time) was improved in 75mg and 300mg doses compared to placebo (P<0.001 for both doses). No other significant between group differences reported
Chronic consumption studies										
Wong et al. 2013 ⁴⁰	Randomized, double blind, placebo controlled, cross-over trial	Australia	II	28	2 x 6 weeks	Healthy obese adults Age (years, mean±std): 61±1.3 BMI (mean±std): 33.3±0.6 kg/m ²	Baseline, week 6 and week 12	75mg trans-resveratrol OR placebo	Stroop Color-Word Test	No significant improvement in cognition.
Witte et al. 2014 ³⁹	Pair-wise matched, double blind, placebo controlled, parallel-groups trial.	Germany	II	46	26 weeks	Healthy overweight older adults Age (years, mean±std): 64.8±6.8 (Resveratrol group), 63.7±5.3 (Control group)	Baseline and 26 weeks	200mg resveratrol and 320mg of quercetin OR placebo	RAVLT (German version) and 15-minute word recall	Significant improvement in word retention (memory function) from baseline to 26 weeks in resveratrol group, compared to

						BMI (range): 25–30 kg/m ²					placebo (p=0.038)
Wightman et al. 2015 ³⁷	Randomized, double blind, placebo controlled, parallel-groups trial.	United Kingdom	II	60	28 days	Healthy adults Age (years, mean (range)): 20.52 (18-29) BMI: Not reported	Day 1, Baseline and 45 minutes post-consumption . Day 28, prior to consumption and 45 min post-consumption	500mg trans-resveratrol and 10 mg piperine OR placebo	COMPASS cognitive assessment system tests (Serial subtractions 7, 13 and 17, RVIP and 3-back)	Mental illness using the General Health Questionnaire, Mood using the Profile of Mood States,	At Day 28 timepoint, prior to consumption, resveratrol group reported improved accuracy in 3-back test (p=0.006). In an ANOVA analysis (treatment × repetition × day), the resveratrol group had fewer incorrect responses in the serial 7's test (P=0.016), fewer correct responses in the serial 17's test (P=0.019), and fewer

											incorrect responses in the 3-back test (P=0.021). Resveratrol significantly improved fatigue (P = 0.003)
Zortea et al. 2016 ⁴¹	Randomized, double blind, placebo controlled, parallel-groups trial.	Brazil	II	19	30 days	Schizophrenic men Age (years, mean±std): 46.40±11.18 (Resveratrol group), 41.00±7.87 (Control group) BMI: Not reported	Baseline and 30 days	200mg trans-resveratrol OR placebo	Hopkins Verbal Learning Test, Stroop Color and Word Test, and Weschler Adult Intelligence Scale		No significant between-group differences reported.
Evans et al. 2017 ³⁴	Randomized, double blind, placebo controlled, parallel-groups trial.	Australia	II	80	14 weeks	Post-menopausal women Age (years, mean±std): 61.5±1.1 (Resveratrol group), 61.5±1.2 (Control group) BMI: 26.8±0.8 (Resveratrol group), 26.6±0.8 (Control group)	Baseline and 14 weeks	150mg trans-resveratrol OR placebo	RAVLT, the Cambridge Semantic Memory Battery, the Double Span Task, and the Trail Making Task	Mood using the Profile of Mood States questionnaire, Depression using the Centre for Epidemiologic Studies Depression scale	Compared to placebo, the intervention significantly improved overall cognitive performance (p=0.003), semantic memory (p=0.043) and verbal memory (p=0.043). Adjusting for depressive symptoms, verbal memory

										(p=0.037) and overall cognitive performance (p=0.023) remained significantly improved by resveratrol. Anxiety (as measured by POMS) was significantly reduced (p = 0.025) in the intervention group compared to placebo. No significant changes were observed in other components of cognitive performance or mood
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Kobe et al. 2017 ³⁶	Randomized, double blind, placebo controlled, parallel-groups trial.	Germany	II	40	26 weeks	Mild cognitive impairment Age (years, mean±std): 65±9 (Resveratrol group), 69±7 (Control group) BMI: 26±3 (Resveratrol group), 26±3 (Control group)	Baseline and 26 weeks	200mg resveratrol and 350mg quercetin OR placebo	RAVLT (German version)	No significant difference in cognitive outcomes
Abbreviations: CBF, cerebral blood flow; COMPASS, Computerized Mental Performance Assessment System; FMD, flow mediated dilation; POMS, Profile of Mood States; RAVLT, Rey Auditory Verbal Learning Test; RVIP, Rapid Visual Information Processing;										

552 Table 3: GRADE assessment of resveratrol supplementation compared to control for enhancing cognitive performance

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resveratrol	Placebo	Absolute (95% CI)	
Processing speed: number of correct answers										
3	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	67	64	SMD 0.04 SD lower (0.38 lower to 0.31 higher)	⊕⊕⊕○ MODERATE
Processing speed: time taken to complete the task										
4	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	110	110	SMD 0.23 SD lower (0.48 lower to 0.01 higher)	⊕⊕⊕○ MODERATE
Number facility: serials correct										

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resveratrol	Placebo	Absolute (95% CI)	
8 outcomes included from 3 studies	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	179	170	SMD 0.17 SD lower (0.38 lower to 0.05 higher)	⊕⊕⊕⊕ HIGH
Number facility: serials incorrect										
8 outcomes included from 3 studies	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	179	170	SMD 0.04 SD higher (0.21 lower to 0.28 higher)	⊕⊕⊕⊕ HIGH
Memory: delayed recognition										

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resveratrol	Placebo	Absolute (95% CI)	
3 outcomes included from 3 studies	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	79	87	SMD 0.39 SD higher (0.08 higher to 0.7 higher)	⊕⊕⊕○ MODERATE
Memory: delayed recall										
3 outcomes included from 3 studies	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	79	87	SMD 0.23 SD higher (0.16 lower to 0.63 higher)	⊕⊕⊕○ MODERATE
Memory: learning ability										

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resveratrol	Placebo	Absolute (95% CI)	
3 outcomes included from 3 studies	Randomised trials	Not serious	Serious ^b	Not serious	Serious ^a	None	79	87	SMD 0.28 SD higher (0.26 lower to 0.81 higher)	⊕⊕○○ Low
Mood: positive mood										
4 outcomes included from 3 studies	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	110	115	SMD 0.17 SD lower (0.43 lower to 0.09 higher)	⊕⊕⊕○ MODERATE
Mood: negative mood										

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resveratrol	Placebo	Absolute (95% CI)	
15 outcomes included from 3 studies	Randomised trials	Not serious	Not serious	Serious ^c	Not serious	None	450	478	SMD 0.18 SD lower (0.31 lower to 0.05 lower)	⊕⊕⊕○ MODERATE

553 **CI:** Confidence interval; **SMD:** Standardised mean difference

554 **Explanations**

555 a. Although the confidence intervals were narrow, the total sample size of all included studies was very low leading to lack of confidence in the precision estimate.

556 b. Heterogeneity was significant with an I-squared of 65%

557 c. The pooled analysis for negative mood used negative mood items from multiple mood questionnaires rather than the total score from one validated tool; therefore, we have

558 some uncertainty about how the results directly reflect negative mood.