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The 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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Abstract

Background/Aims:

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

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

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

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

Introduction

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

of life.[2,3] The societal impact of age-related cognitive decline is likely to be compounded by the global ageing population, with a predicted doubling in the number of persons aged 60 or older by 2050.[4] While age-related cognitive decline is an inevitable part of ageing, there are large inter-individual differences in the rate of decline that are attributed to modifiable lifestyle factors such as exercise, body mass index, and dietary patterns.[5] Moreover, a greater number of these risk factors pose a heightened risk of dementia and Alzheimer's disease, which, in addition to their significant morbidity, are projected to cost the Australian economy one trillion dollars over the next forty years.[6] Therefore, due to the global ageing population,[4] combined with the significant health and cost burden associated with cognitive diseases,[7] it is imperative to investigate potential interventions that can ameliorate age-associated cognitive decline and reduce the impact of later-life brain disease. Dietary polyphenols have been investigated for their potentially beneficial effect on cognitive performance.[8-11] Observational studies have reported polyphenol intake and adherence to polyphenol rich dietary patterns such as the Mediterranean diet to be associated with improved measures of cognitive performance.[11,12] Several polyphenol-rich foods including various berries, green tea, and cacao have also demonstrated improved measures of cognitive performance in clinical trials.[13]

Resveratrol is a polyphenol found in foods such as red grapes, berries, peanuts and red wine, and has been demonstrated in preclinical models to exhibit neuroprotective properties.[14,15] Resveratrol supplementation prevents streptozotocin-induced cognitive impairment and protects against hippocampal neurodegeneration and against learning impairment in rodent models.[16,17] Additionally, resveratrol supplementation improved cognitive outcomes such as spatial memory and memory acquisition in primate[18] and rodent[19] models of ageing. While the exact mechanism of action is unknown, reseveratrol may act on multiple pathways

suggested to be involved in age-related cogntive decline including enhanced endothelial production of nitric oxide, oxidative stress reduction, inhibition of inflammation, and modulation of sirtuin gene expression.[20,21]

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

Methodology

Literature search

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

Study selection

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

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

Data Extraction

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

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

Risk of Bias

All studies were independently assessed for bias by three authors (JC and BA and WM) using the Cochrane Handbook for Systematic Reviews of Interventions checklist.[25] This tool includes criteria for assessing sequence generation, allocation concealment, blinding of participants, blinding of personnel and outcome assessors, incomplete outcome data and selective outcome reporting, which assesses risk of bias as low, unclear or high. Disagreements were managed by consensus. All clinical studies were rated for evidence level using the National Health and Medical Research Council Hierarchy of Evidence.[26] The certainty in the body of evidence for each outcome related to cognitive function for which we found data was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool,[27] following steps and interpretation as specified in the GRADE Handbook.[28] Determination of the GRADE level of evidence was determined independently by two authors (SM and WM), with disagreements managed by consensus.

Data Synthesis and Analysis

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

groups' change scores from baseline to the end of follow-up was extracted. If change scores were not available, end of intervention values were extracted, assuming baseline values were similar.[30] The appropriate variance from each individual study was used, either as the SD or calculated from the SEM or 95%CI. Meta-analysis of these values was performed using the DerSimonian and Laird random-effects model[31] and checked using the fixed-effect model to ensure robustness and susceptibility to potential outliers. The I^2 statistic was used to assess the inconsistencies between studies and describe the percentage of variability in effect. Heterogeneity was considered substantial if the I^2 statistic was $\geq$50%. All effect sizes were calculated using the standardised mean differences (SMD) as all studies used a myriad of outcome measures/scales. Standardised mean difference effect sizes of <0.4 were considered small, 0.4 – 0.7 moderate, and >0.7 large.[30] We considered a statistically significant finding with p-values <0.05. Meta-analyses with significant results were presented as a figure within the manuscript and meta-analyses with non-significant results were included as supplementary material. Publication bias was assessed by visual inspection of funnel plots.

Results

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

Study Characteristics

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

Dosing regimen

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

Outcome Measures

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

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

Study Results

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

Processing speed

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

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

Number facility

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

Memory

Memory was measured by RAVLT[34,36,39], N-back accuracy,[37,38] and the Hopkins Verbal Learning Test[41] by a total of six studies encompassing 244 participants. There was sufficient information provided by three studies to perform meta-analyses on the RAVLT subset scores; delayed recall, delayed recognition, and learning ability. Resveratrol supplementation had a significant effect but low effect size on delayed recognition (SMD 0.39 [95% CI 0.08, 0.70]; I^2=0%; p=0.01; n=3 studies; n=166 participants; Figure 2)[34,36,39]; however, no significant effect on delayed recall (SMD 0.23 [95% CI -0.16, 0.63]; I^2=38%; p=0.25; n=3 studies;

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

Mood

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

Risk of Bias assessment and certainty of evidence-base

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

Discussion

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

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

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

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

The dose of resveratrol used in the included studies ranged from 75 to 500mg with no clear trend related to the efficacy of the intervention, suggesting that the differences in results between studies may not be due to the dosage used. The poor bioavailability of resveratrol, however, may account for the variation of results.[25] Some studies included additional nutrients such as piperine and quercetin to improve the bioavailability of resveratrol. In animal studies, piperine significantly enhances maximum serum resveratrol levels and area under the curve when compared to resveratrol alone[44] and thus, was used by Whitman et al.[37,38] in two separate studies. However, results from their acute trial[38] reported no significant improvements in cognition and their chronic-dosing trial[37] reported inconsistent changes in some measures of cognitive testing. Two of the included studies supplemented 320-350 mg of quercetin in addition to resveratrol,[36,39] which is believed to inhibit the sulphation of resveratrol in the body and increase its bioavailability.[45] While the addition of these nutrients may improve bioavailability of resveratrol, it may also confound the results as it is unclear if a treatment effect (or lack of effect) is due to resveratrol or from the additional bioactive nutrients, which may have interacted with the effect of resveratrol or acted independently. Furthermore, Whiteman et al.[37] demonstrated that plasma resveratrol metabolites can

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

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

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

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

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

Conclusion

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

Author Contributions

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

Funding and conflict of interest declaration

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

Supporting Information

Appendix S1. PRISMA checklist

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

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499 Figure 1. PRISMA Flow Diagram

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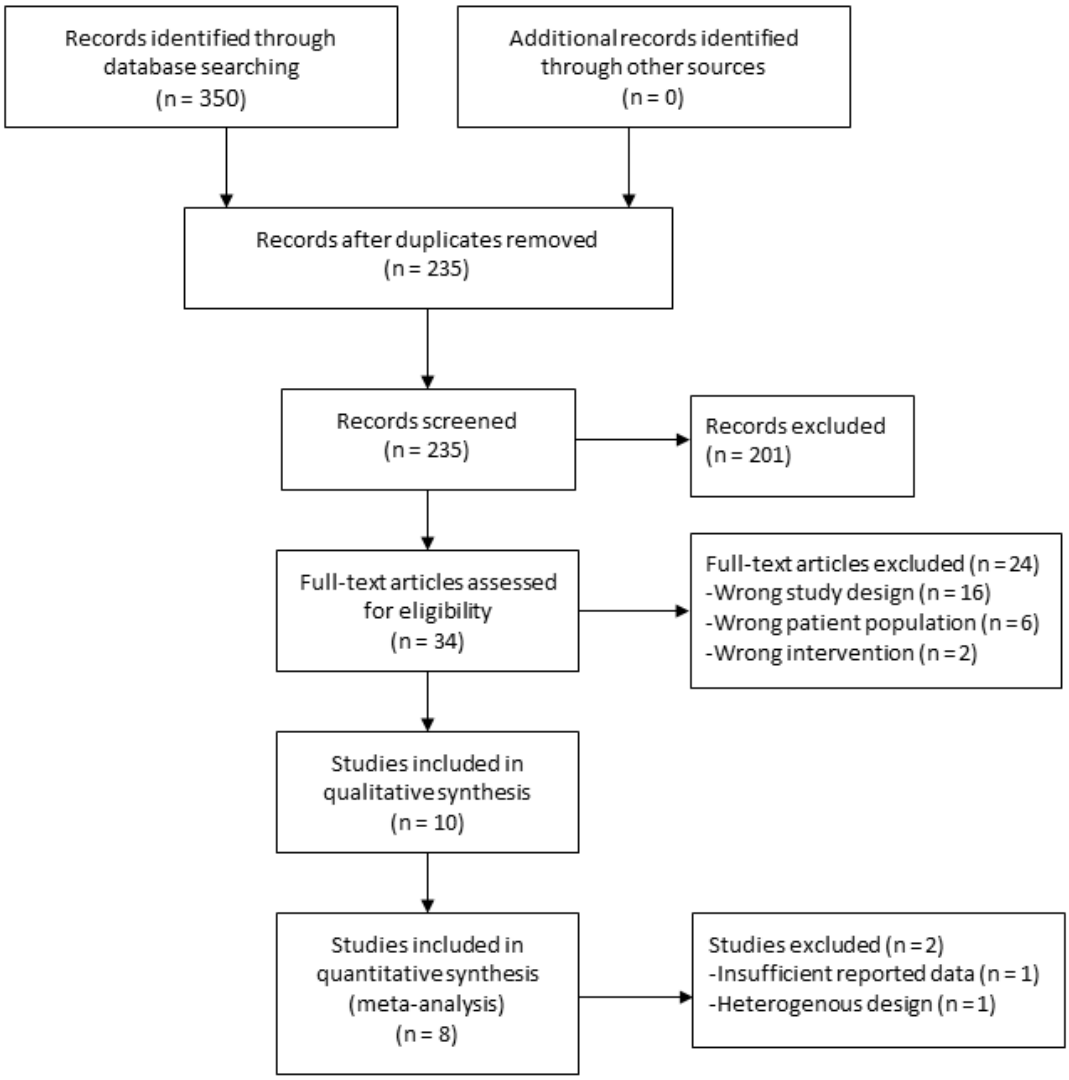

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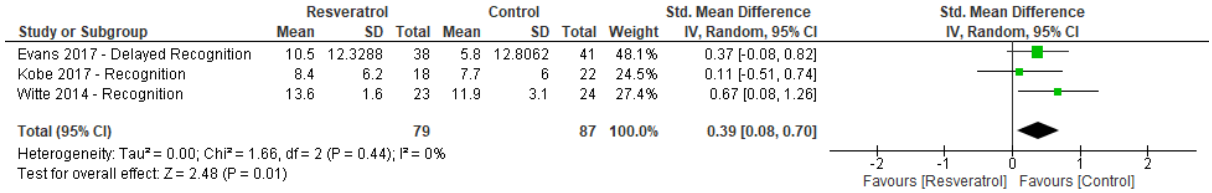
Figure 2. Meta-analysis on the effect of resveratrol supplementation on delayed recognition



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

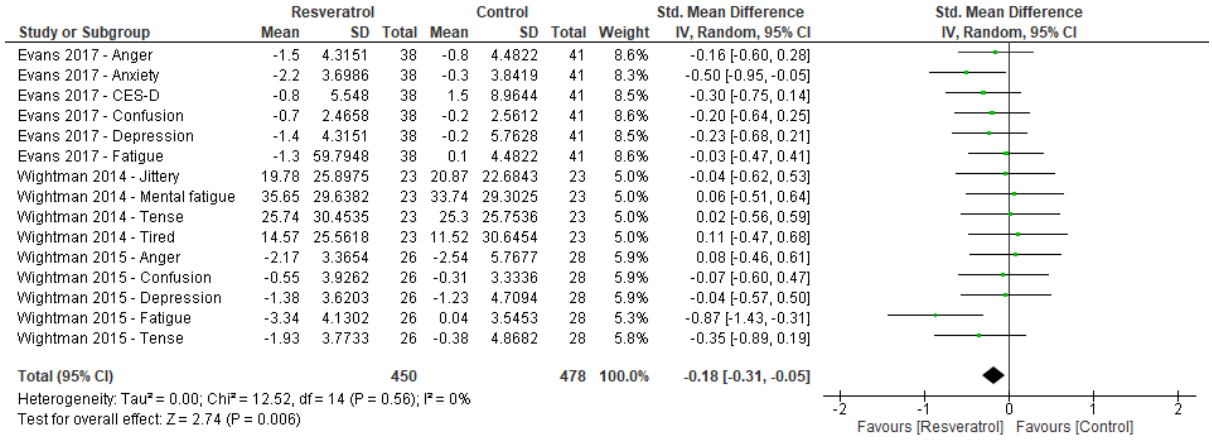


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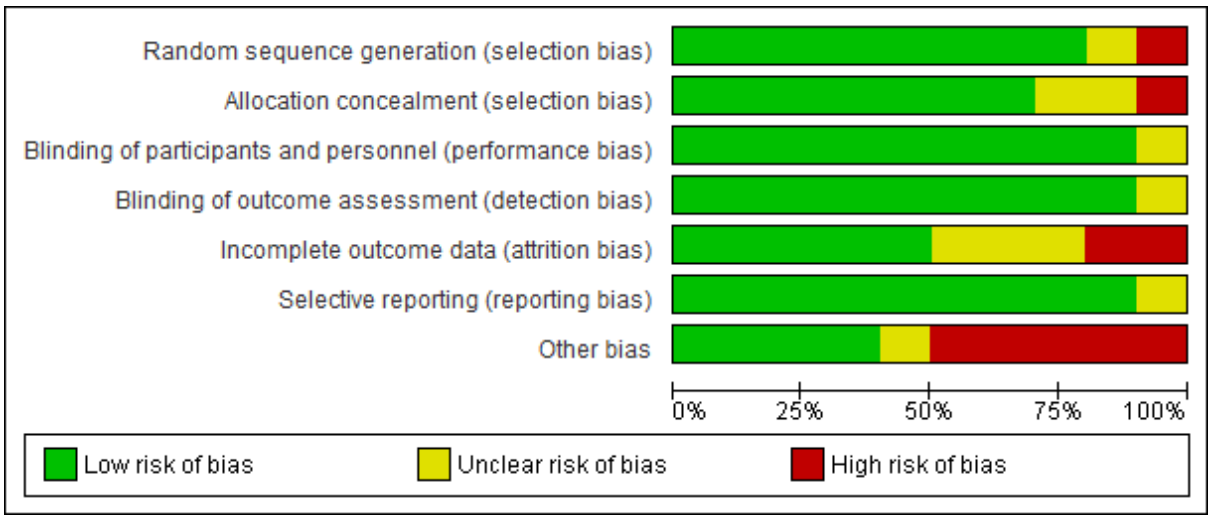
Figure 4. Risk of bias: review authors' judgments' on each risk of bias item presented as percentages across all included studies (n=10).



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 Evidence	Sample size (n)	Total Study period	Population details	Outcomes measured at:	Intervention	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/m2	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/m2	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/m2	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/m2					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

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;											

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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

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

Explanations

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.

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

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 some uncertainty about how the results directly reflect negative mood.