Special Article

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

Wolfgang Marx, Jaimon T. Kelly, Skye Marshall, Jennifer Cutajar, Brigitte Annois, Andrew Pipingas, Audrey Tierney, and Catherine Itsiopoulos

Context: *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.* ***Data Sources:*** *Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic literature review of randomized controlled trials was conducted.* ***Data Extraction:*** *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. Quality of the body of evidence was assessed by evidence for each outcome related to cognitive function for which data was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).* ***Results:*** *Ten studies were included. Three studies found resveratrol supplementation significantly improved some measures of cognitive performance, 2 reported mixed findings, and 5 found no effect. When data were pooled, resveratrol supplementation had a significant effect on delayed recognition (standardized mean difference [SMD], 0.39; 95% confidence interval [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 to −0.05; $I^2 = 0\%$; $P = 0.006$; $n = 3$ studies; $n = 163$ participants). Included studies generally had low risk of bias and were of moderate or high quality.* ***Conclusions:*** *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, characterized by reduced functioning in mental processes such as attention regulation, memory capacity, and processing speed,[1] can pose a substantial burden to the individual because 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 aging population, with a predicted doubling in the number of persons aged >60 years by 2050.[4] Although age-related cognitive decline is an inevitable part of

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aging, there are large interindividual 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 substantial morbidity, are projected to cost the Australian economy 1 trillion dollars over the next 40 years.[6] Therefore, due to the global aging population,[4] combined with the major 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 found 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 it 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 aging. Although the exact mechanism of action is unknown, reseveratrol may act on multiple pathways suggested to be involved in the prevention of age-related cognitive 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 has a positive effect on human cognitive performance, resveratrol supplementation could be a viable, low-cost treatment intervention for preserving cognitive performance in the aging 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 (Supplementary Appendix S1).[22] An initial systematic search of the following databases was conducted, without time limits, up to September 2016: Medline (via Scopus), Cumulative Index of Nursing and Allied Health Literature, 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).

Table 1 **PICOS criteria for inclusion and exclusion of studies**

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

Study selection

Eligible studies had to meet the following criteria: used a randomized controlled trial study design; recruited both healthy and clinical adult human participants (aged over 18 y); 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 because food items contain a vast array of bioactive compounds that 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, to reduce the number of search results while ensuring all relevant studies were captured, search terms relating to red wine and grapes were included whereas search terms related to other food sources were excluded. Cross-sectional studies, reviews, abstracts, study protocols, conference papers, or papers that did not report on any outcome of interest were excluded. Outcomes of interest for the study included any cognition measurements (eg, memory, processing speed), mood, and cognitive fatigue. Articles were first screened for eligibility based on titles and abstracts by 2 investigators. If considered potentially eligible, the full-text publication was retrieved and

independently reviewed by 2 review authors. Disagreements were managed by discussion to reach consensus.

Data extraction

Data extraction was done for 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, the following data was extracted: the mean change score, or end-of-study values when change scores were not available, along with their associated variance (standard deviation [SD], standard error [SE], or 95% confidence interval [CI]). For studies that included >1 resveratrol intervention arm, data was extracted for the arm of the highest dose or the resveratrol arm only in cases where the second resveratrol intervention had >2 active ingredients.

Risk of bias

All studies were independently assessed for bias by 3 authors 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 and assesses risk of bias as low, unclear, or high. Disagreements were managed by discussion to reach 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] The GRADE level of evidence was determined independently by 2 authors, with disagreements managed by discussion to reach consensus.

Data synthesis and analysis

Because of 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 framework's 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, Cochrane Collaboration 2014) for meta-analysis. To calculate the overall treatment effect, the difference between the change scores from baseline to the end of follow-up for the intervention group and the comparison group 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 standard deviation or calculated from the standard error of the mean or 95% confidence interval. 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 among 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 standardized mean differences (SMDs) because all studies used myriad outcome measures/scales. Standardized mean difference effect sizes of <0.4 were considered small, SMDs of 0.4–0.7 were considered moderate, and an SMD >0.7 was considered large.[30] We considered a statistically significant finding with $P < 0.05$. Meta-analyses with significant results are presented as a figure within the article, and meta-analyses with nonsignificant results are included as Appendix S2 in the Supporting Information online. Publication bias was assessed by visual inspection of funnel plots.

RESULTS

Three hundred 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. A total of 9 meta-analyses were conducted, with 8 studies being included in at least 1 meta-analysis (2 studies were 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 individuals, and individual study sample sizes ranged from 16 to 80 participants (Table 2)[32–41]. All studies were randomized double-blind controlled trials; 5 studies used cross-over designs. Nine studies used an inert placebo as the control, whereas Scholey et al.[32] compared a red wine supplemented with resveratrol with red wine not

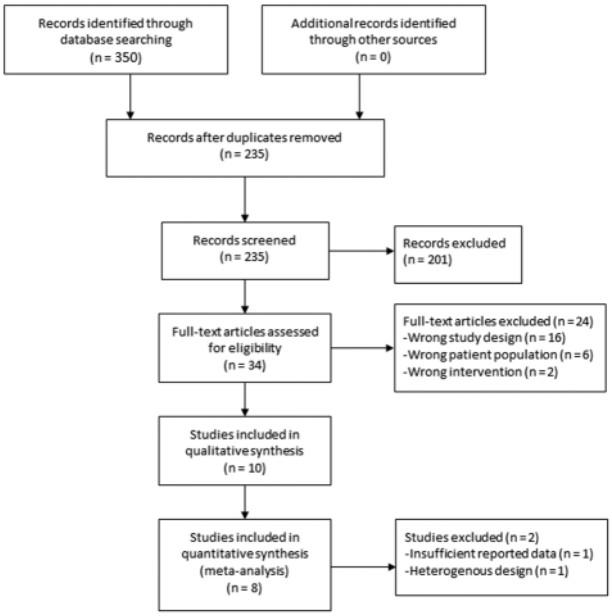

Figure 1 **PRISMA flow diagram of the literature search process.**

supplemented with resveratrol. Three studies included healthy young adults (aged 18–34 y),[35,37,38] 2 studies included healthy older adults (aged 65–78 y),[32,34] 2 included healthy overweight older adults,[39,40] 1 included schizophrenic adults,[41] 1 included older adults with mild cognitive decline,[36] and 1 included adults with type 2 diabetes mellitus.[33] The duration of the studies varied, with 6 studies using chronic daily doses up to 26 weeks.[34,36,37,39–41] The remaining 4 studies used single or multiple acute doses with 2–14 days of washout between doses.

Dosing regimen

Studies used a dose of resveratrol ranging from 75 mg to 500 mg, and participants were required to consume the resveratrol in capsule form, with the exception of participants in 1 study, which used wine enriched with 200 mg of resveratrol.[32] No adverse side effects from supplementation were reported. Four studies used a co-intervention of piperine or quercetin with the aim of increasing bioavailability of resveratrol supplementation.[36–39]

Outcome measures

Measures of cognition varied, with 4 studies using the Computerized Mental Performance Assessment System (COMPASS)[32,35,37,38] to conduct the serial subtractions (3 and 7) and the Rapid Visual Image Processing (RVIP) test. Two studies also used COMPASS to conduct serial 13 and serial 17 tests and either a 3-back or N-back test[37,38]; 3 studies used the Stroop Color Word Test[33,40,41]; 3 used variations of the Rey Auditory Verbal Learning Test (RAVLT)[34,36,39]; and 2 used the Trail Making Task.[33,34] Individual studies also included the following cognitive tests: the Computerized Multitasking 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 were mixed. Five studies found 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 7 s test ($P = 0.009$) in the intervention group (acute dose, 200 mg resveratrol-enriched red wine) but improvements only in the serial 3 s test ($P = 0.004$) in the control group (red wine only). Wightman et al.[37] also reported mixed results, with the intervention group reporting both lower and higher performance measures compared with placebo in the COMPASS serial 7 s test, serial 17 s test, 3-back test, and measures of fatigue. Wong et al.[33] reported improvements in performance index (accuracy/time) during a dual and multitasking test battery in 2 of the 3 intervention doses (75 mg and 300 mg) compared with placebo but no improvement in accuracy alone. The remaining 5 studies found 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 Color Word Test,[33,40,41] and the Trail Making Task.[33,34] Five studies with available data were entered into 2 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, numbers correct (SMD, −0.04; 95%CI, −0.38 to 0.31; $I^2 = 0\%$; $P = 0.84$; n = 3 studies; n = 86 participants) or time taken, although there was a near significant trend toward decreased time taken (SMD, −0.23; 95%CI, −0.48 to 0.01; $I^2 = 0\%$; $P = 0.06$; n = 5 studies; n = 211 participants).

Table 2 **Summary table of included studies**

Reference	Study design	Country	Level of evidence	Sample size	Total study period	Population details[a]	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 × 1 d, 7 d washout	Healthy adults Age: 20.17 y (18–25) BMI: not reported	Baseline, 45 min after consumption	250 mg of trans-resveratrol OR 500 mg of 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 × 1 d, minimum 48-h washout	Healthy older adults Age: 70.44 ± 4.37 y BMI: not reported	Baseline and 60 min after consumption	100 mL of red wine OR 100 mL of red wine enriched with 200 mg of 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 × 1 d visits to clinic (conducted 2–14 days apart)	Healthy adults Age: 21 ± 3.2 y BMI (mean ± SD): 24.2 ± 2.38 kg/m^2	Baseline and 40 min after consumption	250 mg of trans-resveratrol OR 250 mg of trans-resveratrol and 20 mg 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 × 1 d, 7 d wash out	T2DM adults Age: 46.40 ± 11.18 y (resveratrol group), 41.00 ± 7.87 y (control group) BMI (mean): 30.3 kg/m^2	75 min after consumption	75, 150, 300 mg of trans-resveratrol OR placebo	Computerized multi-tasking test battery comprising, Stroop Color Word Test, N-back task, visual warning, and high number tap, Trail Making Task and serial subtraction 3		Performance index (accuracy/time) was improved in 75 mg and 300 mg doses compared with 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 × 6 wk	Healthy obese adults Age: 61 ± 1.3 y BMI (mean ± SD): 33.3 ± 0.6 kg/m^2	Baseline, weeks 6 and 12	75 mg of trans-resveratrol OR placebo	Stroop Color Word Test		No significant improvement in cognition

(continued)

Table 2 **Continued**

Reference	Study design	Country	Level of evidence	Sample size	Total study period	Population details[a]	Outcomes measured at:	Intervention	Cognitive outcomes	Mood outcomes	Results
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 64.8 ± 6.8 y (resveratrol group), 63.7 ± 5.3 y (control group) BMI (range): 25–30 kg/m^2	Baseline and 26 weeks	200 mg of resveratrol and 320 mg of quercetin OR placebo	RAVLT (German version) and 15-min word recall		Significant improvement in word retention (memory function) from baseline to 26 weeks in resveratrol group compared with placebo ($P = 0.038$)
Wightman et al. (2015)[37]	Randomized, double-blind, placebo-controlled, parallel-groups trial	United Kingdom	II	60	28 d	Healthy adults Age: 20.52 y (18–29) BMI: Not reported	Day 1, baseline and 45 min after consumption. Day 28, prior to consumption and 45 min afte consumption	500 mg of trans-resveratrol and 10 mg of 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 7s test ($P = 0.016$), fewer correct responses in the serial 17s 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 d	Schizophrenic men Age: 46.40 ± 11.18 y (resveratrol group), 41.00 ± 7.87 y (control group) BMI: Not reported	Baseline and 30 d	200 mg of trans-resveratrol OR placebo	Hopkins Verbal Learning Test, Stroop Color Word Test, and Weschler Adult Intelligence Scale		No significant between-group differences reported

(continued)

Table 2 **Continued**

Reference	Study design	Country	Level of evidence	Sample size	Total study period	Population details[a]	Outcomes measured at:	Intervention	Cognitive outcomes	Mood outcomes	Results
Evans et al. (2017)[34]	Randomized, double-blind, placebo-controlled, parallel-groups trial	Australia	II	80	14 wk	Postmenopausal women Age: 61.5 ± 1.1 y (resveratrol group), 61.5 ± 1.2 y (control group) BMI (mean ± SD): 26.8 ± 0.8 kg/m^2 (resveratrol group), 26.6 ± 0.8 kg/m^2 (control group)	Baseline and 14 wk	150 mg of 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 with 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 the Profile of Mood States) was significantly reduced ($P = 0.025$) in the intervention group compared with 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 wk	Mild cognitive impairment Age: 65 ± 9 y (resveratrol group), 69 ± 7 y (control group) BMI (mean ± SD: 26 ± 3 kg/m^2 (resveratrol group), 26 ± 3 kg/m^2 (control group)	Baseline and 26 wk	200 mg or resveratrol and 350 mg of quercetin OR placebo	RAVLT (German version)		No significant difference in cognitive outcomes

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; 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; SD, standard deviation.

[a]Age is reported as mean (range) or mean ± standard deviation.

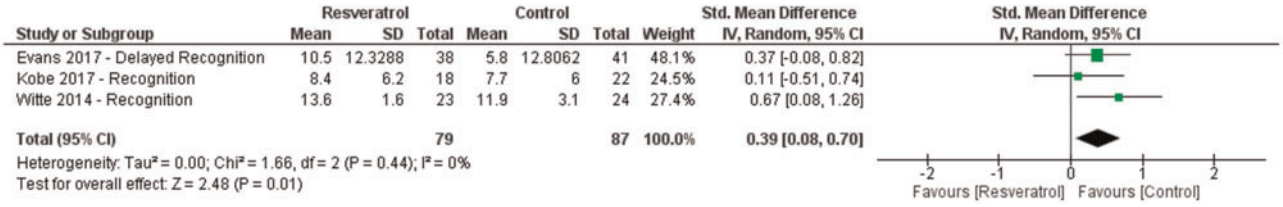

Figure 2 **Meta-analysis on the effect of resveratrol supplementation on delayed recognition.**

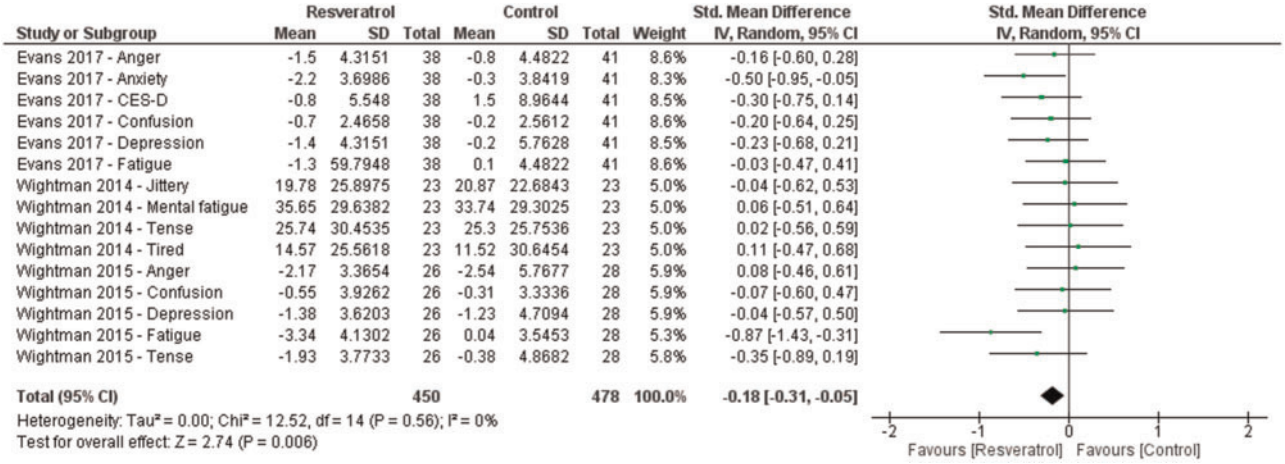

Figure 3 **Meta-analysis on the effect of resveratrol supplementation on negative mood.**

Number facility

Number facility was measured in 4 studies that included a total of 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 was conducted using 3 studies[35,37,38] with available data, 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 to 0.05; I^2=0%; $P = 0.12$; n = 3 studies; n = 86 participants) or serials incorrect (SMD, 0.04; 95%CI, −0.21 to 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] in a total of 6 studies that included a total of 244 participants. There was sufficient information provided by 3 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 to 0.63; I^2 = 38%; $P = 0.25$; n = 3 studies; n = 166 participants) or learning ability (SMD, 0.28; 95%CI, −0.26 to 0.81; I^2 = 65%; $P = 0.31$; n = 3 studies; n = 166 participants).

Mood

A total of 5 studies that involved a total of 203 participants found 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] Two meta-analyses found a nonsignificant change in ratings of positive mood (SMD, −0.02; 95%CI, −0.28 to 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 to −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

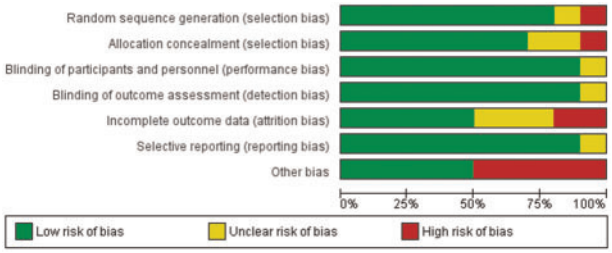

Figure 4 **Risk of bias: judgments of review authors on each risk of bias item presented as percentages across all included studies (n = 10).**

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 in 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 for affecting 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 finding no significant effect on cognitive performance. Furthermore, the present meta-analyses and GRADE assessment found 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 effective for these outcomes. However, given the small effect size and limited sample sizes of included studies, the results of the present meta-analyses 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 1 day to 6 months, with trials that had a shorter duration generally finding no significant results compared with longer term trials. Due to the small number of studies, it was not possible to conduct a sensitivity analysis for each meta-analysis to assess this. However, of the studies that found significant effects from resveratrol supplementation, 2 of the 3 longest-running trials found 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 those of Kobe et al.,[36] who also conducted a 26-week study but found no significant differences in cognitive performance.

Furthermore, there was clinical heterogeneity in the cohorts investigated, with some including young healthy adults, whereas 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, such as 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 find consistently positive improvements in cognition.

The dose of resveratrol used in the included studies ranged from 75 mg to 500 mg 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 with resveratrol alone[44] and thus was used by Wightman et al.[37,38] in 2 separate studies. However, results from their acute trial[38] indicated no significant improvements in cognition, and their chronic-dosing trial[37] found inconsistent changes in some measures of cognitive testing. Two of the included studies supplemented resveratrol with 320–350 mg of quercetin,[36,39] which is believed to inhibit the sulphation of resveratrol in the body and increase its bioavailability.[45] Although the addition of these nutrients may improve the bioavailability of resveratrol, it may also confound the results because it is unclear whether a treatment effect (or lack of effect) is due to resveratrol or the additional bioactive nutrients, which may have interacted with the effect of resveratrol

Table 3 **Grading of Recommendations, Assessment, Development, and Evaluation assessment of resveratrol supplementation compared with control for enhancing cognitive performance**

Quality assessment							No. of patients		Effect	Quality[a]
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resveratrol supplementation	Placebo	Absolute (95%CI)	
Processing speed: no. of correct answers										
3	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	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	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	110	110	SMD 0.23 SD lower (0.48 lower to 0.01 higher)	⊕⊕⊕◯ Moderate
Number facility: serials correct										
8 outcomes included from 3 studies	Randomized 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	Randomized 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										
3 outcomes included from 3 studies	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	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	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	79	87	SMD 0.23 SD higher (0.16 lower to 0.63 higher)	⊕⊕⊕◯ Moderate
Memory: learning ability										
3 outcomes included from 3 studies	Randomized trials	Not serious	Serious[c]	Not serious	Serious[b]	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	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	110	115	SMD 0.17 SD lower (0.43 lower to 0.09 higher)	⊕⊕⊕◯ Moderate
Mood: negative mood										
15 outcomes included from 3 studies	Randomized trials	Not serious	Not serious	Serious[d]	Not serious	None	450	478	SMD 0.18 SD lower (0.31 lower to 0.05 lower)	⊕⊕⊕◯ Moderate

Abbreviations: CI, confidence interval; SD, standard deivation; SMD, standardized mean difference.

[a]⊕ = very low, ⊕⊕ = low, ⊕⊕⊕ = moderate, ⊕⊕⊕⊕ = high.

[b]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.

[c]Heterogeneity was significant with an I^2 of 65%.

[d]The pooled analysis for negative mood used negative mood items from multiple mood questionnaires rather than the total score from 1 validated tool; therefore, we have some uncertainty about how the results directly reflect negative mood.

or acted independently. Furthermore, Wightman 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.

Multiple food sources 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] or 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, although 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, because of 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, the present meta-analyses of pooled results determined resveratrol supplementation to improve only 1 of the 7 outcomes we analyzed.

A limitation of the meta-analyses 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 in each analysis. Future trials are encouraged to provide standardized results or supplementary information 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 to improve cognitive performance. In some instances, resveratrol has been shown to enhance some cognitive performance measures; however, there is limited consistency among studies. Future trials that are sufficiently powered, have longer intervention periods, and address confounding issues, including background polyphenol intake and bioavailability, are required.

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Supporting Information

The following Supporting Information is available in the online version of this article available at the publisher's website.

Appendix S1 **PRISMA checklist**

Appendix S2 **Additional forest plots for nonsignificant meta-analyses**

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