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Impact of coffee-derived chlorogenic acid on cognition: a systematic review and meta-analysis

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Abstract

Coffee drinking has been associated with benefits for various health outcomes, with many attributed to the most prevalent family of polyphenols within coffee, chlorogenic acids (CGA). Whilst reviews of the association between coffee and cognition exist, evidence exploring effects of coffee-specific CGA on cognition has yet to be systematically synthesised. The purpose was to systematically review the current literature investigating the relationship between CGA from coffee and cognitive performance. A further objective was to undertake a meta-analysis of relevant randomised controlled trials (RCT). Observational and intervention studies were included if they considered coffee-based CGA consumption in human participants and applied a standardised measure of cognition. Furthermore, intervention studies were required to define the CGA content and include a control group/placebo. Studies were excluded if they examined CGA alone as an extract or supplement. A search of Scopus, PubMed, Web of Science, ScienceDirect and PsycINFO resulted in including twenty-three papers, six of which were interventions. The evidence from the broader systematic review suggests that CGA from coffee may need to be consumed chronically over a sustained period to produce cognitive benefits. However, the meta-analysis of RCT showed no benefits of coffee CGA intake on cognitive function ($d = 0.00$, 95% CI −0.05, 0.05). Overall, this review included a limited number of studies, the sample sizes were small, and a wide range of cognitive measures have been utilised. This indicates that further, good-quality interventions and RCT are required to systematically explore the conditions under which coffee CGA may provide benefits for cognitive outcomes.

Keywords: **chlorogenic acid: coffee: cognitive function**

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Introduction

Polyphenols are phytochemicals that derive from plant-based foods such as fruits, vegetables, whole grains, tea and coffee and have been shown to affect human health[1]. Previous studies have suggested that polyphenols can help prevent or be beneficial to chronic conditions including heart disease, neurodegenerative disorders, glycaemic disorders and obesity[2,3] through a variety of mechanisms such as activating genes related to stress response[2] and autophagy[3], as well as upregulating pathways that reduce inflammation[3,4]. Other actions include inhibiting enzymes related to carbohydrate digestion, thus affecting glucose absorption, modulation of hepatic glucose release and increased insulin sensitivity[5].

Coffee is a primary source of polyphenols for adults in many countries and has been associated with a positive impact on physical health[6,7]. Benefits associated with its consumption include reduced risk of diabetes and liver disease, as well as inverse associations with all-cause and cause-specific mortality[8–11]. The impact of coffee on human health has been attributed to its bioactive compounds, the most prevalent of which is a family of phenolic acids called chlorogenic acids (CGA)[12–14]. The biological activity of these compounds in coffee has been shown to be affected by a variety of factors including coffee bean species, roasting process and coffee brewing method[14–17]. The processes of decaffeination and production of instant coffee appear to have negligible effects on CGA content, while the degree of roasting seems to have the largest impact[18]. As coffee is roasted, CGA content decreases, but bioavailability increases until a certain point at which CGA content and activity both deteriorate[19]. Light- and medium-roasted coffees have been suggested to reach the highest antioxidant capacity[20–22]. Coffee's country of origin has also been found to affect its polyphenol content[23], and though studies on the polyphenol content from specific coffee-producing regions are limited, one available study found coffees originating in Ethiopia and India contained more polyphenols, yet coffee from Colombia was most resistant to polyphenol loss during roasting[21]. Moreover, coffees with good cup quality are associated with higher levels of CGA[22]. Cup quality is determined by a grading system standardised by the Specialty Coffee Association of America which has shown consistency through repeated use across countries. Using a standardised cupping form to ensure consistency, this grading system assesses taste, aroma and appearance of coffee beans before and after

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roasting, and after brewing[24]. The association between cup quality and CGA content is consistent with findings that higher-quality coffees are rated as such due to the higher concentration of bioactive compounds lending to the taste, flavour and mouthfeel[25,26]. Polyphenols are known to have high antioxidant activity, and so this has been used as a surrogate marker for polyphenol content[27]. Brewing coffee using a drip-filter method, which uses a cone lined with a paper or cloth filter and filled with ground coffee beans placed over a mug and then water poured over to extract brewed coffee, yielded the highest polyphenol content and antioxidant activity, while the convenient capsule-brewing method, which uses a pod filled with ground coffee inserted into a machine that then pushes hot water through the pod to extract brewed coffee, has the lowest antioxidant capacity[28,29]. These findings suggest that a filter-brewed, light- or medium-roasted coffee may be optimal for extracting bioactive compounds such as CGA.

CGA extract has been associated with beneficial physical health outcomes. These include improved blood pressure in people with normal blood pressure and mild hypertension, favourable changes in lipid and glucose metabolism in human participants and increased insulin sensitivity with doses ranging from 156 to 369 mg CGA[30,31]. Daily supplementation with a blend containing CGA was found to reduce basal blood glucose levels in adults with pre-existing type 2 diabetes[32,33]. Risk of diabetes was reduced by 30% in people drinking up to four cups of decaffeinated coffee[32], emphasising the role of non-caffeine constituents in coffee[34].

Cognitive benefits related to CGA have also been observed. One *in vitro* study found that a coffee polyphenol extract, which included CGA, prevented cognitive dysfunction in rodent models of Alzheimer's disease by degrading hippocampal amyloid β plaques, a hallmark of Alzheimer's disease[34]. Epidemiological studies have highlighted the reduced risk of neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease with three to five cups of coffee daily, which is considered to be a moderate level of coffee consumption[11,36,37]. This same moderate coffee consumption may reduce the risk of cognitive decline in healthy participants as well, and one trial found improvements in motor speed, psychomotor speed and executive function for the group administered CGA when compared with placebo[38]. CGA's neuroprotective effects may arise from its ability to pass the blood–brain barrier[39,40]. CGA has been implicated in a number of mechanisms that reduce oxidative stress in neuronal cells, including reducing nuclear condensation, which is associated with apoptosis, and suppression of cytokine TNF-α, an inflammatory biomarker which has been associated with insulin resistance and poor glucose control[38]. With respect to specific cognitive domains, rat models indicate that CGA may have the greatest effects on spatial learning, memory impairment and motor function[40], although it should be acknowledged that the range of cognitive domains which can be assessed in rodent models is limited.

Most coffee studies focus on the cognitive benefits of caffeine, but evidence is available that caffeine does not act alone in affecting cognitive function. An animal model of Alzheimer's disease demonstrated that non-caffeine compounds in coffee such as cafestol and kahweol may be responsible for neuroprotective activity[37] and may be acting in synergy with caffeine and other polyphenols[41]. A neuronal culture study by Kim *et al.*[42] found that exposing cells to 0.05 mg of caffeinated coffee and decaffeinated coffee, and 0.05 mg CGA as an extract, was neuroprotective against reactive oxygen species. Moreover, caffeinated and decaffeinated coffee showed similar efficacy, emphasising that non-caffeine bioactives may be driving these protective effects[42]. Cropley *et al.*[10] conducted a randomised controlled trial with older adults and manipulated CGA content in caffeinated and decaffeinated coffee to investigate effects on brain function using single dosages of 300–521 mg CGA. Cognitive function was tested 40 min after ingestion, with a 1-week washout period between dosages. This study found that decaffeinated coffee fortified with CGA positively impacted mood and behaviour more than regular caffeinated coffee[10], again suggesting the action of non-caffeine compounds in cognitive function.

There is a growing body of evidence examining the impact of CGA on cognitive function. However, evidence exploring the specific cognitive impact of CGA from coffee allowing for consideration of the food matrix, as opposed to an extract in which the bioactive properties of CGA may be different, has yet to be systematically synthesised[32,36,43,44]. Therefore, the aims of this systematic review and meta-analysis were (i) to explore whether changes in cognitive function could be attributed to CGA when consumed in coffee and (ii) to understand if certain cognitive domains are affected by CGA.

Method

Methods for conducting this review were pre-specified in a registered protocol on PROSPERO (registration number CRD42021242345). This systematic literature review was performed using the following search strategy. The Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used to guide this analysis, and the PRISMA flowchart is illustrated in Figure 1.

Search terms

Literature was searched using the search terms Coffee*, Chlorogenic acid* and Cognit* applying the Boolean operator 'and'. Truncations were used to ensure capture of all possible terms related to the search. Combinations of terms were as follows: coffee* and cognit*; chlorogenic acid* and cognit*; coffee* AND chlorogenic acid* and cognit*; coffee AND cognitive function NOT caffeine; coffee AND cognition NOT caffeine; chlorogenic acid AND cognition; chlorogenic acid AND cognition NOT caffeine; chlorogenic acid AND cognitive function; chlorogenic acid AND cognitive function NOT caffeine; coffee intake AND cognition NOT caffeine. The searches yielded 445 results from the databases below.

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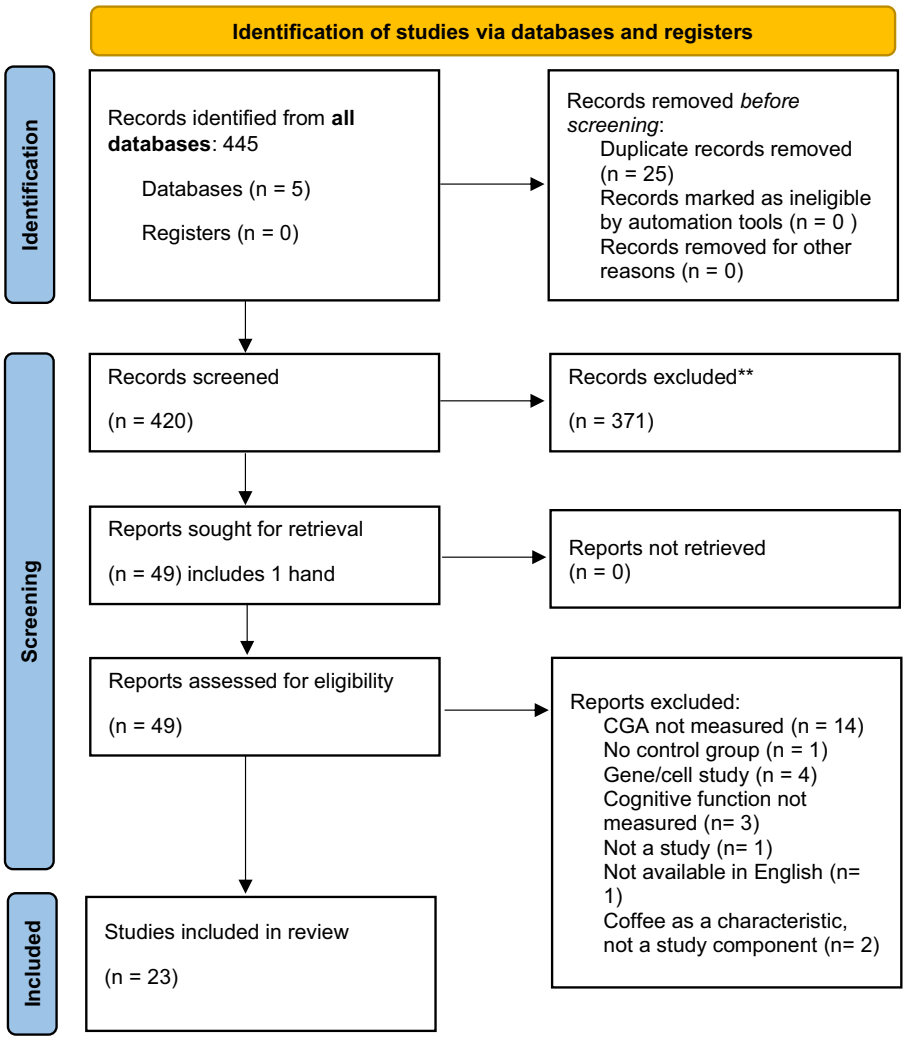

Fig. 1. PRISMA flow diagram for identifying studies for inclusion.

Databases

The following databases were searched: Scopus (1823 to April 2023), PubMed (1948 to April 2023), Web of Science (1986 to April 2023), ScienceDirect (1995 to April 2023), PsycINFO (1866 to April 2023). A hand search of references from the included studies was also conducted, yielding one result. This review focused on formally published papers; thus, grey literature databases were not searched.

Searches were run through 'all fields' for all databases, and then filtered on the basis of the high number of results. In Scopus, only articles were included in the search, and studies using animal or disease models were excluded. In PubMed, only human trials were included; and books, documents, meta-analysis and reviews were excluded. In Web of Science, human studies and articles were included in the search, and for cases where results were ample, a search within the results using the keyword 'chlorogenic acid' was performed. In ScienceDirect, the following keywords were applied to the initial search results before being filtered to include only research articles: coffee, cognition, cognitive function, chlorogenic acid. In PsycINFO, search results were limited to peer-reviewed journals and journal articles, and human participants.

Inclusion and exclusion criteria

Studies were included if they examined the effect of coffee on cognitive function in both healthy and clinical adult human participants; this included caffeinated, decaffeinated and CGA-fortified coffee. Intervention studies, such as RCT, and observational cross-sectional or longitudinal studies were included. A further inclusion criterion was a standardised measure of cognition, meaning a (validated/reliable) measurement of cognitive function not a diagnostic tool, and therefore, studies with a clinical diagnosis of cognitive function only were excluded. The Mini Mental State Examination (MMSE) is often used as a diagnostic tool; however, it is a screening tool that measures cognitive impairment, and thus, studies using this questionnaire were retained[45]. Only papers available in English were included. For interventions, only studies stating the dosage

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of CGA were included; however, this criterion did not apply to cohort studies. Exclusion criteria were systematic reviews or meta-analyses and studies which examined CGA alone as an extract or supplement, or if they examined CGA from non-coffee food items. For intervention trials, absence of a control group or placebo was an exclusion criterion.

Data extraction

Study selection was initially performed by K.J. Papers were excluded on the basis of the title if it was evident that the research fell outside of the inclusion criteria specified, e.g. animal studies. Selected studies were then read in full to determine eligibility for inclusion.

Studies selected for inclusion were assessed for overall methodology quality and potential risk of bias using the Evidence Analysis Manual Quality Criteria Checklist (QCC) from the Academy of Nutrition and Dietetics (2016). Studies were assessed independently by K.J. and J.L. with disagreements resolved with a third party as needed.

Data were then extracted from the included studies independently by K.J. and J.L. Only data relevant to cognitive outcomes associated with CGA intake were extracted for analysis (for example, data relating to other measures such as physical, psychological and biochemical outcome measures were not extracted). The following data were collated from each study: the first author's last name, publication year, participants, CGA source and dose for RCT, study design, and standardised measures of cognition and their means and standard deviations.

Data synthesis

STATA (Version 17.0; StataCorp, College Station, TX) was used to perform the meta-analysis with the six RCT to explore the impact of CGA on cognitive function. Pre- and post-intervention means and standard deviations or standard errors were extracted for both control and treatment groups. One of the randomised, double-blind, placebo-controlled crossover trials, Ochiai *et al.*[7], had only baseline participant data for pre-intervention data, used an average of both groups to calculate a baseline mean and did not differentiate between control or intervention data until after the intervention.

Change-from-baseline scores were calculated for the control group and treatment group. The study by Camfield *et al.*[9] had multiple treatment arms, so data from two treatment groups were combined as they used the same dosage of CGA[46]. For another case[10] with multiple treatment arms using different dosages of CGA, one arm was selected on the basis of best practice to only combine relevant intervention groups or to otherwise choose one group to analyse[46]. This study used CGA in dosages of 224, 244 and 521 mg daily for 3 d; the 521 mg arm was chosen for analysis as the other included RCT used at least 300 mg of CGA[46]. These cases were discussed and agreed upon by all authors. For change-from-baseline means, the end score was subtracted from the baseline score. Change from baseline standard deviations were imputed using the following formula:

$$SD_{Echange} = \sqrt{[SD^2_{Ebaseline} + SD^2_{Efinal} - (2 \times \text{Correlation Coefficient} \times SD_{Ebaseline} \times SD_{Efinal})]}$$

A correlation coefficient of 0.5 was assumed as recommended by Cochrane and others since this value was not provided and could not be calculated from the given data (e.g. Refs. 46–49).

Once change scores had been calculated, the data were imported into STATA, allowing the forest plots to be generated using a random effects model and Cohen's *d*. Heterogeneity was evaluated using the I^2 statistic (%), with ≤30%, between 30% and 50%, between 50% and 75%, and ≥75% indicating low, moderate, substantial and considerable heterogeneity, respectively[44]. Risk of bias was assessed with the AND's QCC.

Two subgroup meta-analyses were performed to understand the effect of CGA on cognitive function by study and then the effect by cognitive domain. For the former, tests were grouped by study and analysed by STATA; effect sizes were reversed for individual tests where lower scores reflected better performance (e.g. reaction time) to account for directionality.

For the cognitive domain analysis, each cognitive test used in each of the six RCT studies for the meta-analysis was classified into cognitive domains according to the Cattell–Horn–Carrol (CHC) model of cognition. The CHC model is a factor analysis-based taxonomy of cognitive abilities that attempts to create a common structure and vocabulary for communicating cognitive research by bringing together multiple theories of cognition[50,51]. It has been supported for cognitive assessment in healthy and clinical populations. The CHC model categorises cognitive function into broad abilities, narrow abilities and specific abilities. Specific abilities can be measured directly with tasks, and these are clustered by correlation into narrow abilities, and highly correlated narrow abilities are then clustered into broad abilities[51]. Broad abilities were used to categorise tasks into cognitive domains and include visuospatial ability, working memory, long-term memory encoding and retrieval, acquired knowledge, processing speed and fluid reasoning[52]. One major area of critique is the lack of executive function in this model. However, the argument has been made that executive function is poorly defined and generally refers to a range of other cognitive functions. The CHC model has been tested and shown to capture these functions embedded within other domains[52]. This categorisation allowed composite scores to be calculated for each cognitive domain represented in each study, allowing for each cognitive domain to be represented in the meta-analysis. Composite scores were calculated by combining change from baseline means and standard deviations for treatment and control groups in each study.

Results

Initial searches yielded 445 studies, 25 of which were duplicates, leaving 445 studies. After screening and checking for inclusions/

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exclusion criteria, twenty-three studies remained. Additional hand-searching yielded one further RCT.

Study characteristics

In total, twenty-three studies were obtained, six of which were clinical trial interventions[6, 7, 8, 9, 10, 53] and seventeen of which were observational; of the latter, nine were longitudinal studies[11,13,14,16,43,54–57] and eight were cross-sectional studies[12, 15, 17, 58–62] (Tables 1 and 2).

RCT. Five RCT were crossover trials[6,7,9,10,53], and one was a parallel-groups trial[8], all of which lasted between 4 and 48 weeks. Papers were published between the years 2012 and 2020. Five RCT included healthy adults[6,8–10,53], and one included participants with mild cognitive impairment[7]. Four RCT included aging adults, aged 50 or older[7–10], and two included younger participants aged 18–35 years[6,53]. Three trials investigated the immediate (acute) effects of CGA ingestion and measured outcomes at intervals up to 3 h[6,9,10]. These were all crossover trials and had each condition separated by a washout period[6,9,10]. The remaining two studies were long-term (chronic) trials with regular CGA ingestion over the course of 4–16 weeks; these studies measured outcomes at baseline, midway and end point[7,8,53].

The dosage of CGA ranged from 224 to 553 mg. CGA was administered as a beverage in all trials, with one trial using coffee flavour[10] and the remaining trials using another flavour[6–9,53].

Twenty-one different cognitive tests were used including two distinct global batteries, and data were reported across nine cognitive domains, as defined by the CHC model[52].

Observational studies. From the seventeen observational studies selected, nine were longitudinal cohort studies[11,13,14,16,43,54–57] and eight were cross-sectional studies[12,15,17,58–62]. The studies were published between 2002 and 2021. These observational studies took place over 1–20 years.

It was understood that quantifying CGA content would be difficult in cohort studies, and indeed no cohort study was found that measured CGA content and instead coffee intake was measured using self-reports and food frequency questionnaires (FFQ). Most observational studies considered older adults[11–17,43,53,55,57,60,61], while one had a lower mean age of 38.5 years[62]. Three observational studies looked at clinical populations including older adults with cardiovascular risks[58], participants recently diagnosed with Parkinson's disease[54] and adults with HIV[59].

Effects on cognitive domain

Cognitive domains were explored with the aforementioned CHC model of cognition. Nine studies looked at memory: four RCT[6,8,10,53] and five observational[55,56,58,59,61]. The four RCT found limited effects of coffee on cognition. However, four of the five observational studies found positive effects of coffee intake on memory[56,58,59,61]. These observational studies looked at populations over periods ranging from 1 to 16 years. The absence of effects for the RCT with contrasting benefits observed in studies of greater than 1 year duration may indicate that long-term coffee CGA intake is needed to see beneficial effects on memory.

Six studies explored working memory, three of which were observational studies[56,58,59] and three of which were RCT[6,9,53]. All three observational studies found positive correlations between working memory and coffee intake, with two of those studies finding that women who drank coffee regularly performed especially well on memory tasks[56,58]. One RCT[53] found a beneficial impact on working memory; however, the remaining two RCT found no difference between the control group or the CGA[6] or in fact a negative impact of CGA on memory[9]. This latter study tested working memory using the serial 3's and 7's task[9], while Jackson *et al.*[53] worked with a younger population with a mean age of 23 years and measured memory with a word recall. Two observational studies which did find an association used a digit-based recall task[58,59], whilst cross-sectional assessment with a word-based task[56] showed weaker benefits. The difference in cognitive measures could potentially explain these varying outcomes for memory, with some tests such as digit-based tasks being more sensitive than others, although there is not currently enough evidence here to systematically examine this. As mentioned, one possible emerging pattern is that consumption over a longer duration is required for observable benefits to memory.

Processing speed was explored in twelve studies, six of which found associations with coffee drinking[6,8,55–57,59,61]. Two of the six RCT in this group found significant effects of coffee-derived CGA on processing speed[8,53] Five of six observational studies found positive associations between coffee intake and processing speed[55–57,59,61]. Dong *et al.*[61] found that processing speed, measured by performance on the digit symbol substitution test, was better preserved in people who regularly consumed caffeinated coffee, but not decaffeinated, while Johnson-Kozlow *et al.*[56] found that decaffeinated coffee drinking was associated with better processing speed as measured with the trail making test part B. These contrasting findings on the effects of decaffeinated coffee may warrant further investigation and lend support to the suggestion that there are effects of coffee which are independent of any caffeine effects. Furthermore, these findings may indicate that long-term intake is needed to observe effects, and that coffee CGA may act synergistically with other compounds such as caffeine to influence processing speed.

The majority of observational studies looked at global cognitive function. Eleven of twelve observational studies found positive associations between coffee drinking and global cognitive function. Two studies found positive associations specifically for women[43,56], and one found positive effects only for caffeinated coffee[61]. Kim *et al.*[60] found negative effects from coffee intake but explored coffee as part of a food pattern rather than exploring coffee on its own. This study created food patterns based on regular intake of participants; the authors found that people who regularly drank coffee also ate refined grains more often and, thus, investigated coffee as part of a 'white rice–noodles–coffee' food pattern, which was the dietary pattern associated with poorer cognitive function[60]. This diet pattern can be considered as similar to a Western diet which is high in refined grains, which has previously been associated

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Table 1. Characteristics of randomised controlled trials (RCT)

Citation	Design	Participants			Intervention		CGA Source	Cognitive Measures	Significant cognitive outcomes
		No.	Age (mean)	Sex	Length	CGA Dose			
Jackson et al. 2020	randomized, double-blind, placebo-controlled crossover	32	m = 22.3 ± 4.3	6M/26F	4 weeks	440 mg	Coffee cherry	CDB[1]	Coffeeberry extract was associated with no signifcant cognitive effects.
Ochiai et al. 2019	randomized, double-blind, placebo-controlled crossover	28	m = 73.5 ± 6.0	14M/14F	48 weeks	1106 mg	Green coffee beans	MMSE[2], ADAS-cog[3], TMT-A[4], TMT-B[5]	Continuous CGA beverage intake significantly reduced errors in TMT-B
Saitou et al. 2018	randomized, double-blind, parallel-group, placebo-controlled trial. Conditions lasted 16 weeks	38	m (placebo) = 58.5 ± 6.3; m (treatment) = 59.3 ± 5.0	21M/17F	16 weeks	300 mg	Green coffee beans	Cognitrax[6]	CGA intake may improve motor activity and attention control.
Camfield et al. 2013	randomized, double blind, acute-dose cross-over, placebo-controlled, single centre, clinical	60	m = 64.5 ± 5.9	26M/34F	6 weeks	532 mg	Green coffee beans, decaffeinated	RVIP[7], N-back, inspection time, Jensen Box, Serial 3's and 7's	Green coffee blend condition showed improvements in sustained attention, decision time, reaction time, alertness, and reduce sypmtoms of headache, jitteriness, and mood.
Cropley et al. 2012	double-blind, placebo-controlled crossover	39	m = 62.5 ± 6.0	20M/19F	6 weeks	521 mg	Roasted and green coffee beans	RVIP[7], Mismatch negativity, VVLT[8] verbal delayed recall, VVLT[8] delayed recognition, inspection time, Stroop color-word test	Short-term intake of decaffeinated coffee with high total CGA impacts positive mood and mood-related behavioral effects
Jackson et al. 2021	acute, randomized (counterbalanced), double-blind, placebo-controlled, crossover	46	m = 23.0 ± 5.8	16M/30F	28 days	440 mg	Coffee cherry	CDB[1], serial 3's and 7's	Coffee berry had limited effects on cognitive function, but did increase accuracy on RVIP after 3rd and 4th repetition

Table 2. Characteristics of observational studies

Citation	Caffeine Controlled	Design	Duration	Participants			Coffee Intake Measures	Cognitive Measures	Significant cognitive outcomes
				No.	Age	Sex			
Eskelinen, et al. 2009	No	Cohort - CAIDE	1972-1998	1409	65-70	53M4/875F	Quantitatively assessed by three categories: low (0-2 cups daily), moderate (3-5 cups daily), and high (5 or more cups daily)	MMSE	Moderate coffee consumption in midlife decreased dementia and AD risk in late life, with results more pronounced among men.
Huang et al. 2021	No	Cross-sectional - NAHSIT	2014-2016	1,115	65 & older	526M/589F	Simplified food frequency questionnaire and 24 hour recall	MMSE	Higher intake of coffee was associated with lower rates of cognitive frailty
Zupo et al. 2021	No	Cohort - MICOL3 and 4	2003-2005 and 2013-2015	584	64 & older	346M/238F	FFQ	MMSE	Lower coffee intake was seen in those with more cognitive impairment
Ng et al. 2020	No	Cross-sectional - SLAS-2	2008-2013	2844	55 & older	1,064M/ 1,780F	FFQ	MMSE	Coffee consumption was insignificantly related to better biological aging, which included cognitive function
Chuang et al. 2019	No	Cross-sectional - NAHSIT	2014-2016 and 1999-2000	2681	65 & older	N/A	FFQ	MMSE	Higher MMSE scores associated with higher consumption of coffee
Fischer et al. 2018	No	Cohort -AGECoDe	2003-2015	2622	75 & older	910M/1,712F	FFQ	SIDAM	Higher coffee intake was not associated with memory decline or incidence of AD
Kim et al. 2015	No	Cross-sectional - KMRCCS	2009-2010	765	60 & older	331M/434F	106 item FFQ	MMSE (Korean version)	The WNC (White rice, Noodles, Coffee) diet pattern was associated with more cognitive impairment when compared to MFDF (Multigrain rice, Fish, Dairy products, Fruits and fruit juices) diet pattern.
Valls-Pedret, et al. 2012	No	Cross-sectional - PREDIMED	2004-2009	447	60-80	214M/233F	137-item FFQ	MMSE, RAVLT, Wechsler Memory Scale, digit span test of the Wechsler Adult Intelligence Scale, Color Trail Test	Coffee intake was associated with better memory function and global cognition.
Cho et al. 2018	No	Cohort	2011-2015	196	ages not specified	101M/95F	Semi-structured interview	MMSE	Coffee drinkers had significantly lower non-motor sypmtoms of PD and higher MMSE scores
Noguchi-Shinohara et al. 2014	No	Cohort -Nakajima Project	2007-2008 and 2011-2013	490	60 & older	162M/328F	Self-adminstered questionnaire	MMSE and Clinical Dementia Rating	Coffee consumption was associated with younger age and higher MMSE scores at follow-up

Table 2. (*Continued*)

Citation	Caffeine Controlled	Design	Duration	Participants			Coffee Intake Measures	Cognitive Measures	Significant cognitive outcomes
				No.	Age	Sex			
Braganca et al. 2016	No	Cross-sectional	Baselie data	130	18-50	82M/48F	Self-report	HIV Neurobehavioral Research Center (HNRC) Battery	A statistically significant, positive correlation existed between daily espresso consumption and attention/working memory, executive functioning, and Global Deficit Score
Arab et al., 2011	Yes	Cohort - CHS	1989-1999	4799	65 & older	2,077M/ 2,722F	FFQ	3MS	Women showed slower rates of cognitive decline with some level of coffee consumption which was nonlineraly related to consumption frequency. This effect was not seen in men.
Araújo et al. 2016	No	Cohort - Rotterdam Study	1990-2009	2914	55 & older	1,306M/ 1,608F	Semi-quantitative FFQ	LDST, Stroop test, WFT, 15-WLT, and PPB (both hands)	Coffee consumption was associated with better performance on executive function tests, but worse on memory tests. Drinking 3 or more cups of coffee per day (vs 1 cup daily) was associated with a better score on the LDST, WFT, Stroop colour naming subtask and the stroop inference subtask; and with worse performance on 15 WLT delayed recall.
Dong et al. 2020	Yes	Cross-sectional - NHANES	2011-2012 and 2013-2014	2513	60 & older	1,214M/ 1,299F	24 hour diet recalls and FFQ	CERAD, animal fluency test, and Digit Symbol Substitution Test (DSST)	Significant associations between total coffee, caffeinated coffee, caffeine intake with DSST score and CERAD, but no significant associations between decaffeinated coffee and cognitive performance
Johnson-Kozlow et al. 2002	No	Cohort - Rancho Bernardo Study	1972-1992	1528	50-98	638M/890F	Willett Semiquantitative FFQ	The BSRT, Heaton Visual Reproduction Test, MMSE, information-memory-concentration test of Blessed et al., TMT-B, Category fluency	For women there was associations between lifetime coffee consumption and better scores on the Buschke-Fuld Selective Reminding Total Recall, Long Term Recall, and Short-Term Recall tests, the Heaton Visual Reproduction Delayed Recall Test, the MMSE, and the Category Fluency Test. In men higher current caffeinated coffee intake was associated with poorer scores on "World" Backwards task. Overall, TMT-B performance was positively associated with current decaffeinated coffee intake.

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Table 2. (*Continued*)

Citation	Caffeine Controlled	Design	Duration	Participants			Coffee Intake Measures	Cognitive Measures	Significant cognitive outcomes
				No.	Age	Sex			
Gardener, et al., 2021	No	Cohort - Australian Imaging, Biomarkers, and Lifestyle (AIBL) study	2006-2019	227	60 & older	92M/135F	CSIRO FFQ	battery assessed six cognitive domains — episodic recall memory, recognition memory, executive function, language, attention and processing speed	Higher coffee consumption at baselin was associated with slower decline for executive function, attention, and the AIBL Preclinical AD Cognitive Composite (PACC), and lower risk of succumbing to mild cognitive impairment or Alzhemier's Disease
Heggy, et al., 2021	No	Cross-sectional - Qatar Biobank Study (QBB)	Baseline data	1000	20 & older	500M/500F	EPIC FFQ	Mean Reaction Time (MRT) assessed with touch screen, computer-based self-administered 60-task test	Regular coffee consumption was positively associated with cognitive function as higher intake of coffee showed lower MRT

with poorer cognitive functioning[63]. Furthermore, this study did not investigate if coffee was consumed with or without additions, such as milk and sugar, which could be important as a typical Western diet tends to be higher in sugar-sweetened beverages which can negatively impact cognitive function[63,64]. Moreover, only one observational study in this review assessed additions to coffee, such as milk and sugar, but did not analyse this data as a covariate[61] despite findings that adding dairy to coffee decreases urinary output of CGA and its metabolites, implying poorer absorption of these bioactive compounds[66]. Additions to coffee may also affect the volume of coffee being consumed, which itself could decrease exposure and absorption of polyphenols. A recent review concluded that adding cow's milk to coffee may have a negative effect on the functionality of polyphenols, but outcomes of consuming milk and coffee together may be dose dependent[67]. However, there is limited evidence available at present to understand the optimal ratio of coffee to milk[67]. This finding may indicate that the neuroprotective effects of coffee are helped or hindered by other dietary factors[68,69]. In support, Jackson *et al.*[53] reported that a combination of 440 mg CGA and 275 mg of apple polyphenols significantly improved performance on the peg and ball task. Investigating how foods commonly added to and consumed along with coffee impact cognition may be worthwhile in understanding how to maximise the potential cognitive benefits of CGA-rich coffee.

Some cognitive domains had limited data. Motor function was explored by only two observational studies with no associations found. Reaction time was explored by only two RCT[9,10], which presented similar findings in terms of improvement with intake of coffee-based CGA, and one observational study[62], which found an inverse relationship between coffee intake and mean reaction time. Visual processing was explored by one RCT and found to be positively impacted by CGA derived from coffee[8,70]. These may be worthwhile domains to explore as they all are important in retaining quality of life, and visual processing and reaction time have been shown to be affected by age and chronic disease[71].

Sex differences

Differences between males and females were observed in three[11,43,56] of the five studies looking at sex differences[11,17,43,56,58], and indeed previous studies have reported declines in the majority of cognitive domains for both sexes over the lifespan[72]. One observational study suggested the protective effects of midlife coffee drinking were more evident in males[11]. Gurvich *et al.*[72] reported that healthy males showed greater decline in specific domains such as motor speed and visuospatial processing while females showed resistance to steep declines in cognitive function. This susceptibility to age-related changes may allow for greater observable differences. Another study found that current male coffee drinkers, mean age 73 years, scored poorer than females on backwards spelling tests[56], suggesting that the time of life that coffee is consumed may also be a factor in coffee's protective effects. Two observational studies both looking at older adults suggested more favourable associations of lifetime

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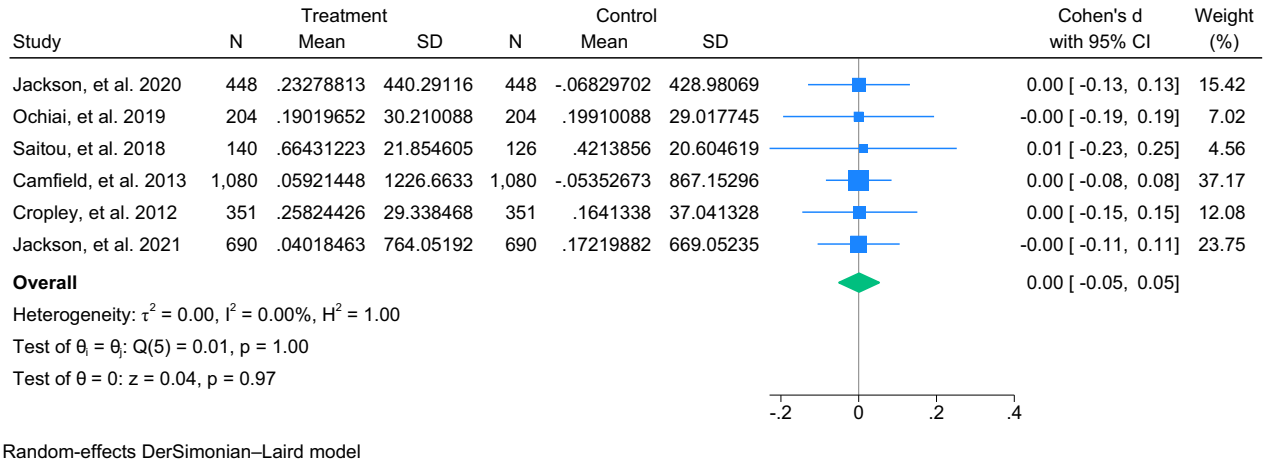

Fig. 2. Random-effects DerSimonian–Laird model.

coffee drinking in females than males on global cognitive measures and memory tasks[43,56]. Physiological differences exist between males and females that have been found to interact with the activity of polyphenols. For example, the polyphenols in red wine relaxed aortic rings in female rodents, and this was attributed to the polyphenols increasing the expression of endothelial nitric oxide synthase (eNOS), an important factor regulating the cardiovascular system, which was higher in female rats[73]. Another example is the antihypertensive effects soy was found to have in men and postmenopausal women[74]. Even oxidative damage may differ between sexes, as one rodent study found that levels of reactive oxygen species scavengers such as superoxide dismutase was lower in male rodents and higher in females while levels of hydrogen peroxide were higher in males and lower in females, which implies an unequal baseline[74]. Further exploration into cognitive differences and changes over the lifespan based on sex and health status could reveal specific domains that could be bolstered by CGA-rich coffee.

Meta-analysis

The meta-analyses looking at changes in cognitive function from CGA-based interventions from the six RCT included in this review[6–10,53] showed no significant effects of coffee CGA on cognition ($d = 0.00$, 95% CI −0.05, 0.05; Figure 2). All studies included in the meta-analysis used standardised measures of cognition to evaluate differences in cognitive function before and after the CGA intervention, and specified the dosage of CGA used in that intervention.

Some important differences amongst these RCT exist, such as the population studied. The study by Saitou *et al.*[8] enrolled participants complaining of memory changes, while Cropley *et al.*[10] included participants on the basis of MMSE scores above 24. Moreover, Saitou *et al.*[8] provided 300 mg of CGA as opposed to 521 mg of CGA in Cropley *et al.*'s study[10]. Therefore, the absence of benefits in Saitou *et al.*'s[8] study could be explained by the cognitively impaired population and a relatively low dose. Furthermore, the negative outcome for CGA may be accounted for by general poorer functioning in the CGA group compared with the placebo group in this parallel-groups design. In this meta-analysis, the analyses by cognitive domain showed no significant effects of CGA (Supplemental Tables 24–29).

Risk of bias

All papers were assessed using the QCC and deemed 'positive' or 'neutral' (Supplemental Tables 1–23). Overall, the risk of bias from participant selection and blinding was low, but potential areas for higher risk of bias included funding and withdrawal management. Implications are explored in the discussion below.

Discussion

Overall, the evidence from the meta-analysis with the six, good-quality RCT does not support an effect of coffee-based CGA on cognition, nor was there evidence from the meta-analysis showing effects on specific cognitive domains. Inconsistencies between studies and methodological factors may have contributed to the null findings in the meta-analysis, particularly given that there was some supportive evidence from the wider systematic review. Findings from the broader systematic review include positive effects of coffee-derived CGA and coffee consumption on memory, attention, executive function, alertness and motor activity, and a lower risk of cognitive impairment, dementia and Alzheimer's disease, after chronic coffee intake.

All studies included in this review had a strong design; however, there were differences in the population selection criteria. Cropley *et al.*[10] found significant results in their population who scored 24 and above on the MMSE at screening, whereas Camfield *et al.*[9] included participants scoring 27 and higher on the MMSE at screening and found no significant results. Moreover, Ochiai *et al.*[7] found significant effects in a population with mild cognitive impairment. This may indicate that the effects of CGA could be more important for those already experiencing some cognitive impairment, whereas effects in cognitively healthy populations may be more difficult to observe. The length of the intervention may also have an impact. For example, positive effects of CGA were found in two

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RCT of 12 and 16 weeks duration[7,8] whereas two RCT with an acute design assessing cognition after a single dose of CGA found no effects[6,9]. Interestingly, Jackson *et al.*[6] used 440 mg and tested participants up to 3 h after ingestion and found no effect; however, benefits were found when participants were tested up to 6 h after ingestion with the same CGA dosage. Multiple studies have found that the majority of CGA is metabolised in the colon by microflora after being hydrolysed by esterases, and that the metabolites resulting from hydrolysis vary depending on an individual's unique microflora and other compounds or foods consumed with CGA[75,76]. Once absorbed, CGA can cross the blood–brain barrier[76]. It is known that digestion through the colon can take up to 36 h; thus, it is possible that effects will not be observed in the 0–5 h postprandial period that the aforementioned acute studies tested within[75]. This may warrant further exploration into the time-related effects of CGA, as well as the effects of microflora on the bioavailability of CGA. Additionally, the QCC was helpful in highlighting potential bias based on funding, but there were no apparent differences in outcomes based on a positive or neutral rating.

This review had some limitations. Firstly, it contained a limited number of studies each with small sample sizes, a wide range of cognitive measures and an overall small magnitude of effect (Cohen's $d = 0.00$). The small degree of variability between studies ($I^2 = 0.00\%$) will likely be biased in this meta-analysis as there are a small number of studies[77]. One RCT chose to take a group average at baseline prior to randomisation, which can be considered a significant limitation as this approach would prevent researchers from assessing any differences between the intervention and control groups[7]. Moreover, the small number of studies included in the meta-analysis explored a wide range of CGA dosages, from 300 to 1106 mg, with some of these studies sourcing the CGA from unroasted, green coffee beans and others sourcing from roasted coffee beans. Despite green coffee beans having higher concentrations of CGA, roasted coffee has shown increased bioactivity of CGA[78,79]. Beneficial effects were found by one RCT looking at coffee with regular CGA content (224 mg) versus coffee with high CGA content (521 mg), with the higher-CGA coffee participants reporting improvements in mood[10]. Unfortunately, there is a lack of data on dose–response effects of CGA on cognitive function. This would be a worthwhile area to explore based on past studies that have demonstrated a dose–response relationship of coffee-derived CGA on plasma content of CGA and blood pressure[80,81]. More studies are needed to explore dose–response effects of CGA derived from unroasted and roasted coffee to better understand how degree of roasting may be affecting cognitive outcomes and human health more widely.

Another limitation to consider is that the positive effects from the observational studies may have been impacted by confounding factors such as dietary choices and lifestyle behaviours. Moreover, the lack of data on CGA dosages available from observational studies prevented the narrative portion of the review from exploring the effects of coffee-derived CGA, allowing only an exploration of coffee drinking on cognitive function. This brings forth the limitation of the non-standardised measure of coffee intake. The observational studies employed different food frequency questionnaires administered at various intervals that captured coffee as daily, weekly or monthly intake. Other studies opted for 24-h diet recalls, or even used an interview schedule to simply categorise participants as coffee drinkers or not, regardless of intake frequency. This may have led to overestimations or underestimations of coffee intake and an inability to capture nuances of coffee drinking as daily differences may arise. These non-standardised measures create an overall lack of accuracy when trying to associate coffee intake to outcomes. Future studies should endeavour to use the same measure to capture coffee intake and perhaps develop a coffee intake questionnaire that captures multiple aspects of coffee intake such as daily and weekly volume, additions, caffeination and brew type. One observational study explored food patterns and associated dietary patterns higher in coffee with poorer cognitive function; however, coffee was not investigated on its own[60]. As mentioned earlier in this review, coffee's neuro-protective effects may be influenced by other dietary factors and thus would be worthwhile to explore individually and in combination with other foods or additions. Moreover, other coffee compounds such as trigonelline, cafestol, theobromine and kahweol will also be important factors to consider as these have been found to exert effects including decreasing inflammation and influencing lipid metabolism[82,83]. Theobromine in particular has been associated with protective cognitive effects in older adults, possibly by inhibiting amyloid-β production pathway[83,84]. Only two observational studies and two RCT differentiated between caffeinated and decaffeinated coffee intake, which is an important point for future studies to consider in order to better understand the effects of non-caffeine components in coffee[9,10,43,61]. Differentiating caffeination status in coffees can be especially helpful for large-scale studies where testing for CGA content may be impractical.

A strength of this review is the use of random-effects models to include a range of studies. Moreover, this review used high-quality studies with human participants and standardised measures of cognition. This is one of the first systematic reviews and meta-analyses to explore the cognitive impacts of CGA derived specifically from coffee. The findings of this review indicate that more research is needed to explore the relationship between CGA from coffee and cognitive function. Future studies could explore coffee as a whole food to consider the synergistic effects of the food matrix as only one RCT compared coffees with varying levels of CGA[10]. As mentioned at the start of this review, considering a coffee's country of origin may also help predict CGA content, and should be a point for future studies to consider. Recent studies exploring the effects of origin have found country of origin to be an important factor affecting coffee's polyphenol content, with some studies even finding differences based on different regions of a single country[85–87]. Future studies should also control for caffeine. Only one RCT[10] and two observational studies[44,61] considered caffeine, and as discussed earlier, the effects of CGA may be influenced by other compounds in coffee. Currently, no good-quality studies exist that control for caffeine. Only two RCT used CGA sourced from decaffeinated coffee beans[7,8], but this was not studied against CGA sources from caffeinated coffee beans. Only one RCT

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compared caffeinated versus decaffeinated coffees with varying levels of CGA in their intervention[10]. Exploring the effects of caffeinated and decaffeinated coffees may help increase understanding about possible interactions of caffeine and CGA and the impact on cognitive function.

Conclusions

In summary, the evidence from the meta-analysis does not provide support for coffee-derived CGA benefitting cognition. However, the evidence from the wider systematic review provides some support for a benefit of CGA-rich coffee on cognition in the domains of memory, attention, executive function, alertness and motor activity, and also may decrease the risk of cognitive impairment, dementia and Alzheimer's. Sex differences may exist, with observational studies finding more benefits for women who drink coffee, particularly for memory. Long-term intake of coffee may be needed to see clear effects of coffee CGA as indicated by two RCT that provided CGA for either 12 or 16 weeks, and the observational studies looking at coffee intake over many years. Further RCT studies are warranted to explore the effects of CGA intake duration on cognitive function, as well as dose–response effects. Considering differences in CGA from unroasted, green coffee and roasted coffee while controlling for caffeine could also be useful to investigate.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0954422424000209.

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Author contributions

All authors contributed to this manuscript. K.J., D.L., D.J. and J.A.L. contributed to conception, design and revisions. All authors contributed to analysis and interpretation of data, as well as reviewing, editing and approving the final version to be published.

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