



## Review Article

# Effects of Curcumin on Cognitive Function—A Systematic Review of Randomized Controlled Trials

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## Abstract

Curcumin is a polyphenol present in turmeric and is credited with anti-inflammatory, antioxidant, and chemoprotective properties. Questions remain surrounding curcumin’s bioavailability and the mechanism by which it may exert neuroprotective effects. Following PRISMA 2009 guidelines, a systematic review was conducted to identify randomized, placebo-controlled trials investigating the effects of curcumin supplementation on cognitive function in older adults (>50 years). Five databases were searched (CINAHL, Cochrane Library, PubMed, SCOPUS, Web of Science) with five studies identified, each using different forms of curcumin and validated cognitive screening measures, meeting inclusion criteria. Curcumin doses ranged from between 90 and 4,000 mg/day, with significant improvements found in three of the five studies. Firstly, the most recent study found improvements with 90 mg of curcumin twice daily in tests of selective reminding ( $p = 0.002$ ), visual memory ( $p = 0.01$ ), and attention ( $p < 0.0001$ ) over 18 months in non-demented individuals. The second study found improvement in Montreal Cognitive Assessment tool with 1,500 mg/day curcumin over 52 weeks ( $p = 0.02$ ). Another study found improvement in serial three subtraction task responses after 4 weeks compared with the placebo group ( $p = 0.044$ ). Of the adverse events reported ( $n = 58$ ), gastrointestinal symptoms were most common ( $n = 34$ ). Before curcumin can be recommended to treat or reduce rates of cognitive decline, well-designed trials with standardization in dose, method of assessing cognition, and duration, are required to determine the most bioavailable form of curcumin with minimal adverse effects.

**Keywords:** Curcumin; Cognition; Dementia; Alzheimer’s disease; Dietary supplements; Nutraceuticals.

**Abbreviations:** A $\beta$ , amyloid-beta; AD, Alzheimer’s disease; FDDNP-PET, 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthylethylidene)malononitrile positron emission tomography; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RCT, randomized controlled trial.

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## Introduction

The rapid global growth in our ageing population has resulted in an increase in neurodegenerative conditions, such as dementia, which results in cognitive decline, loss of functional capacity and reduced quality of life.<sup>1</sup> However, subtle cognitive changes associated with ageing are common even in the absence of dementia or mild cognitive impairment (MCI).<sup>2</sup> The maintenance of cognitive function is vital for healthy ageing and daily functioning. Cognitive functions including memory, attention, processing speed, visuospatial perception, and problem-solving decline with ageing and are impacted by both non-modifiable and modifiable risk factors.<sup>3,4</sup> Non-modifiable risk factors include age, sex, and genetics, influencing the likelihood of impaired cognitive function, while modifiable risk factors include lifestyle, education, and disease management,

such as diabetes mellitus and hypertension.<sup>2-4</sup> There is increasing recognition that addressing modifiable risk and lifestyle factors can preserve cognitive function later into life, potentially delaying the onset of dementia.

While the prevalence of dementia, particularly its most common form of Alzheimer's disease (AD), may be stabilizing in some countries, cases of younger-onset AD are increasing, and the global rate of people living with dementia has more than doubled from 1990 to 2016.<sup>5,6</sup> Declining cognitive function, memory and behavior are indicative of progressive AD, and at a physiological level, AD is characterized by the formation of amyloid plaques and neurofibrillary tangles in brain tissue, which contribute to neurodegeneration by blocking cell-signaling activity.<sup>7,8</sup> The amyloid-beta (A) protein is the main component of the plaques, which are formed in response to cellular degeneration.<sup>9</sup> Hyperphosphorylated tau proteins are the main component of neurofibrillary tangles, and increased tau synthesis is similarly initiated by cellular degeneration.<sup>9</sup> The neurodegeneration and presence of abnormal physiological structures are intermediary stimulants for neuroinflammation.<sup>10</sup> The inhibition of and tau formation, and their subsequent disestablishment of plaques and neurofibrillary tangles is a current target for pharmacological interventions, which to date have proven to be mostly unsuccessful.<sup>11</sup>

Established treatments for AD include cholinesterase inhibitors, such as galantamine, rivastigmine and donepezil, which are widely prescribed to treat symptoms of cognitive decline. However, difficulty in achieving a correct dosage, the timing of intervention, and potential adverse events limit the overall effectiveness of such treatments.<sup>12</sup> Therefore, non-pharmacological treatments, such as dietary supplements and nutraceuticals, have come into focus for the potential treatment of neurodegenerative conditions.<sup>13</sup> In particular, plant polyphenols are increasingly being investigated for their potential in the prevention or treatment neurodegenerative conditions, due to their pleotropic activities in the human body.<sup>14</sup>

Polyphenolic compounds, such as curcumin, are being acknowledged for their associations with various beneficial health effects. In particular, the consumption of foods containing polyphenol-rich turmeric (*Curcuma longa*), such as curry, is associated with reduced incidence of cognitive decline. In 2006, a cross-sectional study of older people found that participants who 'occasionally' and 'often or very often' consumed curry had higher Mini-Mental State Examination (MMSE) scores compared to those who 'never or rarely' consumed curry.<sup>15</sup> Turmeric supplementation has been associated with alleviation of incontinence, improved recognition of family, and reductions in agitation, anxiety and irritability in people with dementia.<sup>16</sup> Together, these findings have led to a greater examination of the primary bioactives present in turmeric.

Curcumin is the primary polyphenolic compound of turmeric, a bright yellow-colored spice widely used as a flavor and coloring agent in gastronomy.<sup>8,17</sup> The term 'curcuminoid' is used to describe the functional group of biochemical agents found in turmeric, of which curcumin is the most abundant, while demethoxycurcumin, bisdemethoxycurcumin and cyclic curcumin forms are less common occurring curcuminoids of turmeric.<sup>17</sup> Today, curcumin is recognized for its potential to contribute to improved outcomes in the treatment of metabolic syndrome,<sup>18</sup> diabetes mellitus,<sup>19</sup> pain,<sup>20</sup> arthritis,<sup>21</sup> and symptoms of depression and anxiety.<sup>22</sup>

The health benefits of curcumin are reported to be due to its anti-inflammatory,<sup>23-25</sup> antioxidant and chemoprotective properties,<sup>25-27</sup> suggesting that curcumin may also have a role in the prevention of AD. Mechanistically, curcumin has been shown to inhibit the formation of amyloid-beta (A $\beta$ ) fibrils, de-establish preformed fibrils and inhibit tau phosphorylation in *in vivo* and

*in vitro* animal models.<sup>28-31</sup> Moreover, transgenic mouse models of AD have indicated that supplementation with curcumin lowers oxidized proteins and inflammatory cytokines in the brain,<sup>32</sup> prevents memory deficits,<sup>33</sup> cognitive decline and suppresses behavioral deficits.<sup>34,35</sup> However, the evidence supporting curcumin supplementation in humans to prevent or delay cognitive decline remains unclear.

Numerous curcumin formulations aimed to enhance its bioactivity and absorbability have been developed, which may enhance neuroprotective effects due to the ability to cross the blood-brain barrier. However, the debate remains as to whether curcumin promotes brain health and cognitive function through its activity in the brain, or systemically through its effects on gastrointestinal health possibly via interactions with the microbiome.<sup>36,37</sup> This systematic review aims to assess the current evidence surrounding curcumin from human randomized controlled trials (RCTs) and its effects on cognitive function.

## Methods

The review was preregistered with PROSPERO (Registration: CRD42017084518; [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=84518](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=84518)) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for systematic reviews.<sup>38</sup> The Population, Intervention, Comparator, Outcomes and Setting (PICOS) systematic review approach was used to guide the systematic review. The criteria within each of these categories were as follows:

- Population: Human populations aged 50 years or over that were either healthy older people, people with subjective memory complaints, MCI or a diagnosed form of dementia;
- Intervention: RCTs investigating the effects of curcumin supplementation for 4 weeks or longer;
- Comparator: Human comparators were required, using a placebo or control intervention;
- Outcomes: Human data were analyzed according to validated cognitive measures, biochemical measures, and adverse effects reported; and
- Setting: Any.

## Literature search

Literature searches were conducted across five electronic databases (CINAHL, Cochrane Library, PubMed, SCOPUS and Web of Science) for studies published from January 2000 to November 2017. Searches were re-run again in August 2018, with two additional articles undergoing full-text review, and only one article meeting the inclusion criteria.<sup>39</sup> The literature search intended to identify the highest quality evidence from double-blind, placebo-controlled, human clinical trials investigating the effect of curcumin supplementation on cognitive function in older adults. Searches were performed using the following search terms "curcumin\*", "curcuma", "*Curcumin longa*", "turmeric", "bisdemethoxycurcumin", "desmethoxycurcumin", "cyclic curcumin" and "cognit\*" as well as "elder\*", "geriatric", "older", "aged" in conjunction with "Alzheimer's disease", "Alzheimer\*", "dementia", "neurocognitive impairment", "mild cognitive impairment", "memory loss", using Boolean operators AND and OR; the (\*) indicates the use of wildcard operators. Further studies of interest were identified through examination of the reference lists of relevant studies and previously published review articles. A summary of the search

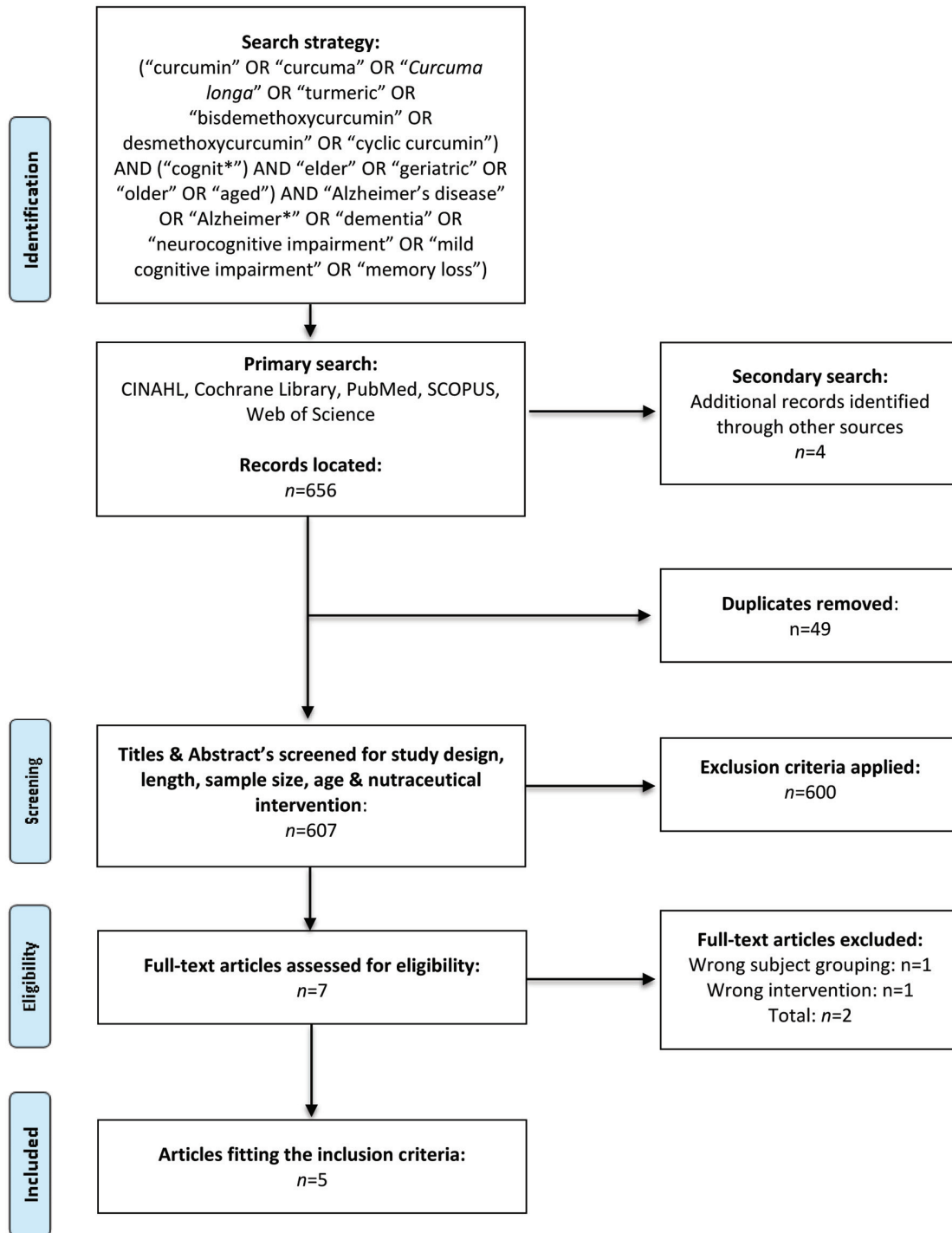


Fig. 1. Search strategy and journal selection process flowchart.

strategy can be found in [Figure 1](#).

#### Selection criteria

Peer-reviewed journal articles of studies conducted in humans and

published in the English language after January 2000 were eligible for inclusion. Studies investigating participants with a mean age over 50 years were of interest to this review due to the increased likelihood of impaired cognitive function. Studies were included if curcumin supplementation was completed for a minimum duration of 4 weeks to assess effects on symptoms of cognitive decline.

**Table 1. Assessment of bias risk in reviewed studies**

Bias classification	Baum <i>et al.</i> <sup>44</sup>	Ringman <i>et al.</i> <sup>42</sup>	Cox <i>et al.</i> <sup>43</sup>	Rainey-Smith <i>et al.</i> <sup>41</sup>	Small <i>et al.</i> <sup>39</sup>
Random sequence generation	Low	Low	Low	Low	Low
Allocation concealment	Low	Low	Low	Low	Low
Blinding of participants and personnel	Unclear	Low	Unclear	Low	Low
Blinding of outcome assessment	Unclear	Low	Unclear	Low	Low
Incomplete outcome data	Low	Low	Low	Low	Low
Selective reporting	Low	Low	Low	Low	Low
Other bias	High	Low	Low	Low	Low
Country	Hong Kong	USA	Australia	Australia	USA
Funding source	University research grant/Private grant	Research foundation/Research grant/government/Private institution	Private institution	Research foundation/Research grant	Research foundation/Research grant/Private institution/Private company

The primary outcomes of interest were studies reporting cognitive function outcomes via validated cognitive screening methods (*e.g.*, MMSE, Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)) or diagnosis of a form of dementia. The secondary outcomes were biochemical markers, including A plasma levels, t-tau, p-tau, and lipids. Biomarkers were used to evaluate the association between curcumin supplementation and changes in cognitive function. Adverse effects were also of interest to examine the safety of the curcumin supplements used.

Two researchers (N.S. and N.M.D.) independently conducted the searches. Using the eligibility criteria, both authors first screened based on titles and abstracts. For any articles where this was unclear, the article was included in the full-text review. The full text of the remaining papers was independently reviewed by both authors, and eligible studies were included in the review. Disagreements were discussed to reach consensus with mediation by a third researcher (N.N.), when appropriate.

#### Data extraction and risk of bias assessment

The included articles were extracted (N.S.) and checked for consistency (N.M.D.). Data extraction was completed for study design, descriptive statistics, type, dose, and timing of the intervention, and results of the primary and secondary outcomes. The Cochrane Risk of Bias Tool was used to assess the potential for bias by two researchers (N.S. and N.M.D.),<sup>40</sup> as it is established as the most appropriate assessment tool due to its specificity for bias in RCTs (Table 1<sup>39,41-43</sup>). Disagreements were discussed with a third researcher (E.N.G). Country of study and funding source were also deemed suitable additions to assess the risk of bias.

## Results

A total of 652 studies were identified during the initial elec-

tronic database search. Four additional articles were located by manual searching ( $n = 4$ ). After the removal of articles due to duplicates ( $n = 49$ ), inappropriate population ( $n = 205$ ), incorrect study design ( $n = 333$ ) and insufficient intervention ( $n = 62$ ), seven studies remained for full-text assessment. Five trials met the inclusion criteria with the remaining two excluded due to investigating turmeric and curry consumption.<sup>22,39,41-45</sup> All included studies were randomized, placebo-controlled, double-blind, clinical trials.

#### Study characteristics

The total number of participants enrolled in the included studies was 292, with sample sizes ranging from 34 to 96 participants (Table 2). The primary outcome for all five studies was validated screening measures of cognitive function, while all also measured biochemical outcomes,<sup>39,41-44</sup> and four reported adverse events (Table 3).<sup>39,41,42,44</sup> The mean age range of participants was 53.5 to 85.5 years of age. The combined average age of participants was 69.9 years, with three studies assessing Caucasian individuals,<sup>41-43</sup> one study assessing ethnic Chinese individuals and one study that did not define racial demographics.<sup>39,44</sup> Three of the studies included participants experiencing cognitive decline. Two studies included healthy participants,<sup>41,43</sup> two recruited participants with mild to moderate AD,<sup>42,44</sup> and one included individuals with MCI.<sup>39</sup> Duration of curcumin supplementation ranged from 4 weeks to 78 weeks.

The included studies used a range of cognitive screening measures. Two studies used the MoCA to evaluate global cognition,<sup>39,41</sup> two used the MMSE,<sup>42,44</sup> and one used the ADAS-cog.<sup>42</sup> Additional measures for executive functioning were used in three studies,<sup>39,41,43</sup> visual processing in three studies,<sup>39,41,43</sup> verbal memory in two studies,<sup>39,41</sup> and delayed recall in two studies.<sup>39,43</sup> Due to the small number of articles identified, and considerable heterogeneity across studies, we did not deem the inclusion of a meta-analysis to be appropriate at this time.

Table 2. Summary of clinical trials assessing the effect of curcumin on cognition

Reference	Aim	Participants	Mean age	Duration	Dose	Outcomes
Baum <i>et al.</i> <sup>44</sup>	Examine safety and effects of curcumin on biochemical and cognitive measures in AD	Chinese adults with progressive decline in memory and cognitive function N = 34 (27 F & 7 M)	73.4 y	24 w	1 g per day Or 4 g per day curcumin capsules or powder	No difference on MMSE (baseline: placebo = 15.4 ± 5.8, 1 g = 15.4 ± 5.0, 4 g = 15.6 ± 7.9) to 6 m follow-up (change: placebo = 1.3 ± 0.6, 1 g = -0.6 ± 1.0, 4 g = 0.7 ± 1.1) ( <i>p</i> = 0.43) Serum Aβ did not significantly differ among doses 0 g (30 ± 6.0 ng/L to 26 ± 3.0 ng/L) and 4 g (28 ± 6.0 ng/L to 35 ± 7.0 ng/L) between baseline and 6 m ( <i>p</i> = 0.15) Plasma IsoPs between baseline and 6 m did not change between dosage 9 g (-11 ± 10%), 1 g (12 ± 10%) and 4 g (6.0 ± 8%) ( <i>p</i> = 0.23) No difference between treatment groups in change in ADAS-cog ( <i>p</i> = 0.26), NPI ( <i>p</i> = 0.35), ADCS-ADL ( <i>p</i> = 0.72) or MMSE ( <i>p</i> = 0.08) scores Intervention subjects had lower hematocrit (placebo = 42.9% (SEM = 0.49), 2 g = 41.8% (SEM = 0.55), 4 g = 42.3% (SEM = 0.54) ( <i>p</i> = 0.014) Intervention subjects had higher glucose levels (placebo 85.8 mg/dL (SEM = 4.2), 2 g = 91.6 mg/dL (SEM = 4.5), 4 g = 90.5 mg/dL (SEM = 4.5) ( <i>p</i> = 0.043) No significant change in intervention group on plasma A <sub>42</sub> ( <i>p</i> = 0.98) and A <sub>40</sub> ( <i>p</i> = 0.29), CSF A <sub>42</sub> ( <i>p</i> = 0.96), CSF total tau ( <i>p</i> = 0.97), CSF p-tau ( <i>p</i> = 0.83), and CSF F <sub>2</sub> -isoPs ( <i>p</i> = 0.08) Plasma curcumin levels were undetectable in intervention groups Improvement in serial three subtraction task responses from baseline to 4 w in intervention group (17% increase) vs. control (3% increase) ( <i>p</i> = 0.044, after adjustment for demographic variable) Physical fatigue levels lower in intervention group compared to placebo ( <i>p</i> = 0.02), mental fatigue not significant ( <i>p</i> > 0.05) Compared to the placebo group, the intervention group had a significant reduction in calmness and contentedness ( <i>p</i> = 0.047) Intervention significantly lowered total cholesterol levels ( <i>p</i> = 0.032) MoCA scores improved greater in the intervention group (baseline: 25.8 ± 0.30; 6 m: 26.4 ± 0.40; 12 m: 26.5 ± 0.40) compared with placebo (baseline: 26.4 ± 0.30; 6 m: 25.7 ± 0.30; 12 m: 26.5 ± 0.40) ( <i>p</i> = 0.02) No other differences in cognitive screening was observed between groups (all, <i>p</i> > 0.05) No differences between groups were reported regarding physical health ( <i>p</i> = 0.73), mental health ( <i>p</i> = 0.69), depression ( <i>p</i> = 0.80), stress ( <i>p</i> = 0.68), anxiety ( <i>p</i> = 0.87), and self-reported memory function ( <i>p</i> = 0.22) Improvements in SRT Consistent Long-Term Retrieval in the curcumin group (baseline: 72.3 ± 31.6; 18 m: 92.6 ± 30.9; <i>p</i> = 0.002) vs. placebo (baseline: 73.7 ± 31.8; 18 m: 75.6 ± 36.4; <i>p</i> = 0.80) Attention (Trail Making Test Part A) improved in the curcumin group (baseline: 32.6 ± 9.30; 18 m: 24.9 ± 5.30) <i>p</i> < 0.001) vs. placebo (baseline: 30.5 ± 8.30; 18 m: ; <i>p</i> = 0.1) Non-significant improvements in SRT Total ( <i>p</i> = 0.08), visual memory ( <i>p</i> = 0.50) and BVMT-R delay ( <i>p</i> = 0.08) FDDNP-PET binding decreased within the curcumin group in the amygdala (between groups: <i>p</i> = 0.07; within the curcumin group; <i>p</i> = 0.04) and increased in the placebo group in the hypothalamus (between groups: <i>p</i> = 0.02; within the placebo group; <i>p</i> = 0.05)
Ringman <i>et al.</i> <sup>42</sup>	Curcumin C3 Complex in persons with mild-to-moderate AD with an open-label extension to 48 w	Mild-to-moderate probable AD* N = 36 (19 F and 17 M)	73.5 ± 8.3 y	48 w	2 g per day Or 4 g per day Curcumin C3 Complex	
Cox <i>et al.</i> <sup>43</sup>	Effects of acute, chronic and acute-on-chronic curcumin administration in healthy older adults	Healthy older adults N = 60 (38 F and 22 M)	68.5 ± 5.7 y	4 w	400 mg per day Longvida Optimized Curcumin	
Rainey-Smith <i>et al.</i> <sup>41</sup>	Ability of BioCurcumin™ to prevent cognitive decline in a population of community-dwelling older adults	Community-dwelling older adults No significant cognitive impairments No to minimal impairments in daily activities N = 96 (68 F and 28 M)	66.0 ± 6.6 y	52 w	1,500 mg per day BCM-95CG (BioCurcumin™)	
Small <i>et al.</i> <sup>39</sup>	Effect on memory and brain amyloid and tau accumulation with Theracurmin®.	Cognitively healthy adults or people with MCI N = 40 (22 F and 18 M)	63 ± 8.9 y	78 w	2 × 90 mg per day Theracurmin®	

\*Classified via the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the National Institute of Neurological and Communicative Disorders Association (NINCDS-ADRDA). Abbreviations: A, amyloid beta; AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease Assessment Scale—cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study—Activities of Daily Living; BVMT-R, Brief Visual Memory Test-Revised; CSF, cerebrospinal fluid; F<sub>2</sub>isoPs, cerebrospinal fluid isoprostanes; F, female; FDDNP-PET, 2-(1-(6-[(2-[18F]fluoroethyl)(methyl)amino]-2-naphthyl) ethylidene)malonitrile-positron emission tomography; isoPs, isoprostanes; NPI, Neuropsychiatric Inventory; M, male; MCI, mild cognitive impairment; mg, milligram; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SEM, standard error of the mean; SRT, Selective Reminding Test; w, weeks; y, years.

**Table 3. Adverse events reported**

Adverse Event	Reference	Curcumin, n (%)	Placebo, n (%)
Gastrointestinal symptoms	Baum <i>et al.</i> <sup>44</sup>	4(11.8)	0
	Rainey-Smith <i>et al.</i> <sup>41</sup>	23(0)*	0
	Ringman <i>et al.</i> <sup>42</sup>	3(8.3)	0
	Small <i>et al.</i> <sup>39</sup>	4(19)	2(10.5)
Edema	Baum <i>et al.</i> <sup>44</sup>	1(2.9)	1(2.9)
Fall or dizziness	Baum <i>et al.</i> <sup>44</sup>	2(5.9)	1(2.9)
Hearing impairment	Baum <i>et al.</i> <sup>44</sup>	0	1(2.9)
Respiratory tract infection	Baum <i>et al.</i> <sup>44</sup>	1(2.9)	2(5.9)
Dysphagia like symptoms	Ringman <i>et al.</i> <sup>42</sup>	2	0

\*Participants' results excluded from the final statistical analysis.

### Dosage and type of curcumin supplementation

The dosage of supplemental curcumin ranged from 0.09 g to 4 g per day, and four studies used a bioenhanced curcumin supplement while the study by Baum *et al.* used pure curcumin at two different dosages (1 g/day or 4 g/day) (Table 2).<sup>39,41–44</sup> One study used Curcumin C3 Complex<sup>®</sup> (2 or 4 g/day), a combination of curcumin, bisdemethoxycurcumin and demethoxycurcumin standardized for minimum 95% curcuminoids.<sup>42</sup> The study by Cox *et al.*<sup>43</sup> used Longvida<sup>®</sup> curcumin (400 mg/day), an encapsulated lipophilic formulation with 80 mg of curcumin. Rainey-Smith *et al.*<sup>41</sup> used BCM-95<sup>®</sup>CG (Biocurcumin<sup>™</sup>) (1.5 g/day) containing 88% total curcuminoids (curcumin, bisdemethoxycurcumin, demethoxycurcumin and 7% volatile oils from *Curcuma longa*) and the trial by Small *et al.*<sup>39</sup> used Theracurmin<sup>™</sup> (2 × 90 mg/day), a nanoencapsulated submicron crystal solid dispersion of curcumin. The trial by Baum *et al.*<sup>44</sup> included 120 mg of Ginkgo leaf extract in both the two curcumin and comparator groups as a standard treatment for AD. The study by Ringman *et al.*<sup>42</sup> also permitted vitamin E supplementation up to 2,000 i.u./day and vitamin C up to 0.5 g per day. All studies included a placebo group who were treated in an identical manner to the intervention group but were given capsules,<sup>39,41–43</sup> or packets of powder that contained no active ingredients and were identical in appearance to those provided to the intervention group.<sup>44</sup>

### Results of cognitive outcomes

All five included studies reported on an outcome of cognitive function (Table 2), with varying results. A study by Baum *et al.*<sup>44</sup> ( $n = 34$ ) found no difference between the intervention groups and control groups in the MMSE at the 6-month follow up ( $p = 0.43$ ). The trial by Ringman *et al.*<sup>42</sup> ( $n = 36$ ) showed no difference between groups in the ADAS-cog ( $p = 0.26$ ), NPI ( $p = 0.35$ ) or ADCS-ADL ( $p = 0.72$ ). However, the intervention groups performed worse than the placebo group on the MMSE (placebo = 23.2 vs. 2 g = 21.4 and 4 g = 22.8;  $p = 0.08$ ). The three more recent trials used bioenhanced versions of curcumin.

In 2015, Cox *et al.*<sup>43</sup> ( $n = 60$ ) used a liposomal encapsulated form of curcumin (Longvida<sup>®</sup>) and reported improvements on measures of sustained attention and working memory compared with placebo over a 4-week duration. The curcumin group had a 17% nonsignificant increase in the number of correct responses in the serial three subtraction task compared to baseline, whereas the

placebo group only improved by 3%. However, when the results were adjusted for demographic variables, the effect was significant ( $p = 0.044$ ), suggesting the intervention improved working memory, psychomotor speed and attention when controlling for education and work status.

In 2016, Rainey-Smith *et al.*<sup>41</sup> ( $n = 96$ ) reported a time-by-treatment group interaction in the MoCA with Biocurcumin<sup>™</sup> supplementation over 52 weeks compared to the placebo group ( $p = 0.02$ ). However, no other differences between groups were observed in cognition according to the Rey Auditory Verbal Learning Test (all,  $p > 0.05$ ), Wechsler Digit Symbol Scale ( $p = 0.91$ ), or Controlled Oral Word Association Task, for both a noncomputerized ( $p = 0.09$ ) and computerized composite score ( $p = 0.46$ ).

The most recent study by Small *et al.*<sup>39</sup> showed improvement from baseline to 18 months in the Buschke-Fuld Selective Reminding Test of verbal memory for the group by time interaction and the total score (both,  $p = 0.002$ ), with no change in the control group following 18 months of Theracurmin supplementation. Only the intervention group displayed improvements in visual memory (Brief Visuospatial Memory Test-Revised) from baseline to 18 months ( $p = 0.01$ ). The Theracurmin group also improved in attention (Trail Making Test A) after 18 months compared with placebo ( $p < 0.0001$ ). However, it is important to note that both groups exhibited improvements in their verbal memory score at 6 months, representing a potential learning effect. With the Theracurmin group performing better at 18 months, the results suggest that curcumin supplementation prevented a decline in cognition compared with the control group. Overall, these results suggest greater improvements in cognitive function with more recent trials using bioenhanced versions of curcumin.

### Biochemical outcomes

Four of the five studies provided results on the outcomes of different biochemical markers, with varying results.<sup>39,42–44</sup> Baum *et al.*<sup>44</sup> reported that serum A did not differ by dosage of curcumin, and plasma isoprostanes did not change by dosage from baseline to 6 months ( $p = 0.23$ ). Ringman *et al.*<sup>42</sup> reported that the intervention groups had lower hematocrit than the control group (control = 42%, 2 g = 41.8%, 4 g = 42.3%;  $p = 0.014$ ) and the intervention groups also had higher blood glucose levels (control = 85.9 mg/dL, 2 g = 91.6 mg/dL, 4 g = 90.5 mg/dL;  $p = 0.043$ ) than the control group. There were no significant changes for the intervention groups for A<sub>42</sub> ( $p = 0.98$ ) and A<sub>40</sub> ( $p = 0.29$ ), CSF A<sub>42</sub> ( $p = 0.96$ ),

CSF total tau ( $p = 0.97$ ), CSF p-tau ( $p = 0.83$ ), and CSF F<sub>2</sub>-isoprostanes ( $p = 0.08$ ). The study by Cox *et al.*<sup>43</sup> showed significantly lower total cholesterol levels in the intervention group compared to the control group ( $p = 0.032$ ). No other significant differences on blood biomarkers were noted regarding IL-1, IL-6 and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), as participants had serum levels below measurable evaluation. The study by Small *et al.*<sup>39</sup> performed 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthylethylidene) malononitrile positron emission tomography (FDDNP-PET) scans on participants at baseline and 18 months. Compared with controls, accumulation of A $\beta$  and tau was lower in the Theracumin group ( $p = 0.04$ ). FDDNP-PET binding decreased within the curcumin group in the amygdala (between groups:  $p = 0.07$ ; within curcumin group;  $p = 0.04$ ) and increased in the placebo group in the hypothalamus (between groups:  $p = 0.02$ ; within placebo group:  $p = 0.05$ ). They also measured levels of free curcumin, which increased in the intervention group, confirming compliance with supplementation.

### Adverse events

Adverse events were reported in four studies, with one study reporting that the curcumin was well tolerated overall.<sup>43</sup> A total of 40 (13.7%) adverse events were reported in the intervention groups compared with only 7 (2.40%) in the control groups. The most common adverse event was gastrointestinal symptoms, reported in four studies,<sup>39,41,42,44</sup> with a total of 34 individuals given the curcumin intervention reporting experiencing these symptoms. Two studies showed specific symptoms, including black stools, diarrhea, transient abdominal pain, gastritis, and nausea.<sup>39,42</sup> It is important to note that the 23 intervention participants who reported adverse events in Rainey-Smith *et al.*<sup>41</sup> were excluded from the final statistical analysis. Baum *et al.*<sup>44</sup> reported additional adverse events in both intervention and placebo groups, including falls or dizziness ( $n = 2$  and  $n = 1$ , respectively), edema ( $n = 1$  and  $n = 1$ , respectively) and respiratory tract infections ( $n = 1$  and  $n = 2$ , respectively). Additionally, one participant in the control group experienced hearing impairment. Two participants in the study by Ringman *et al.*<sup>42</sup> experienced difficulty swallowing the capsules. Small *et al.*<sup>39</sup> reported six participants with gastrointestinal symptoms (abdominal pain, gastritis and nausea), comprising four from the intervention group and two from the placebo group. Both the studies by Small *et al.*<sup>39</sup> and Baum *et al.*<sup>44</sup> found adverse events occurring among the control group participants. We can only speculate that these reported events in the control groups were due to the general effects of ageing in populations that may be more susceptible to illness. For the trials of Longvida® and Theracurmin™ that found no or minimal side effects, it is suggested that the issue of gastrointestinal symptoms can be potentially resolved with these forms.<sup>39,43</sup>

### Risk of bias assessment

The reviewed studies indicated low levels of bias among the criteria published in the Cochrane tool.<sup>40</sup> No articles presented with a high, overall risk of overall bias. However, several criteria were deemed as “unclear” for the trials by Baum *et al.*<sup>44</sup> and Cox *et al.*<sup>43</sup> As the study by Baum *et al.*<sup>44</sup> was published as a letter to the editor, this may explain why sufficient detail was not presented to assess the risk of bias clearly. There were apparent commercial links between four of the five studies. Small *et al.*<sup>39</sup>, Ringman *et al.*<sup>42</sup>, Rainey-Smith *et al.*<sup>41</sup> and Cox *et al.*<sup>43</sup> all obtained their in-

tervention products from private companies and these had been provided free of charge. The trials by Ringman *et al.*<sup>42</sup> and Cox *et al.*<sup>43</sup> received direct funding from these organizations, which were acknowledged in the cited papers.

### Discussion

This is the first systematic review of curcumin supplementation and its association with cognitive function. Together, the results suggest that various formulations of curcumin supplements may improve performance on some cognitive domains in older people and that supplementation may improve biochemical markers associated with AD. Three of the five studies found improvement in cognitive function when supplementing with curcumin. Two studies found improvements in MoCA scores and serial three subtraction task response, respectively.<sup>41,43</sup> However, in the most recent article included in this systematic review, improvements were observed using a new nanoparticle formulation of curcumin in measures of memory and attention, and through less accumulation of A $\beta$  and tau proteins in the hypothalamus and amygdala.<sup>39</sup> This study by Small *et al.*<sup>39</sup> was also the longest trial to date, with a total time of 18 months. However, when assessing the studies together, it is difficult to generalize the results due to considerable heterogeneity across trials and the low number of participants overall. The major limitation of this systematic review, and curcumin research investigating its effects on cognitive function in general, is the small number of clinical trials conducted to date.

Supplementation dosage and duration of intervention greatly differed amongst the included studies. The earliest studies, those by Baum *et al.*<sup>44</sup> and Ringman *et al.*,<sup>42</sup> used between 1–4 g/day curcumin, and the study by Rainey-Smith *et al.*,<sup>41</sup> which resulted in considerable adverse gastrointestinal symptoms, used 1.5 g/day. However, the two studies using bioenhanced versions used much smaller doses.<sup>39,43</sup> Cox *et al.*<sup>43</sup> used 0.4 g/day of Longvida®, which contains only 0.08 g of actual curcumin. Small *et al.*<sup>39</sup> provided 0.09 g of Theracumin twice per day. The development of bioenhanced versions of curcumin resulted in lower dosages in the studies by Cox *et al.*<sup>43</sup> and Small *et al.*,<sup>39</sup> which appear to reduce the likelihood of gastrointestinal distress due to their increased absorption.<sup>25</sup> The high dosages of low-bioavailable curcumin helps to explain the gastrointestinal effects observed by Baum *et al.*<sup>44</sup> and perhaps, the null results reported. Moreover, this study and the study by Ringman *et al.*<sup>42</sup> were the only studies to assess cognitive function in individuals with an established progressive decline in cognitive function. Plausibly, their gastrointestinal function may have been disrupted already as is often observed in people living with dementia.<sup>46</sup> The findings in animal models have suggested that there is gut-brain modulation of cognitive function and this represents a novel and under-researched area in humans.<sup>25</sup> In these two studies, the timing of curcumin supplementation in relation to the disease course may have affected the findings, as progressive cognitive decline was already underway. Nevertheless, gastrointestinal symptoms observed in people living with dementia, consuming newer formulations of curcumin, are yet to be examined.

Curcumin, in its pure form, appears to be poorly tolerated in large dosages (>1 g per day). Participants who consumed more than 1 g per day reported some adverse events manifested as gastrointestinal symptoms. Similar adverse events have been reported in other clinical trials of curcumin. In a systematic review of RCTs of treatment of joint arthritis, Daily *et al.*<sup>21</sup> reported six studies that found curcumin leading to gastrointestinal complaints. Interestingly, joint pain occurrence had a 2.5% decrease per gram of curcum-

in, yet it was accepted that curcumin doses were considered safe if they did not exceed 1.2 g per day for a period of 4 months.<sup>21</sup> As such, the dosages prescribed in three of the five studies included in this review would not be deemed safe. Based on current recommendations, only the Longvida<sup>®</sup> and Theracurmin studies provided safe dosage,<sup>39,43</sup> from among the five included trials. Nevertheless, Cheng *et al.*<sup>47</sup> examined the chemoprotective properties of curcumin on high risk or premalignant lesions in patients with a bioenhanced curcumin with dosages as high as 12 g per day and reported no toxicity in dosages up to 8 g per day. Therefore, the tolerability of specific doses of the different formulations of curcumin needs to be assessed.

It is well established that curcumin has relatively low bioavailability, low intestinal absorption, and rapid liver metabolism, with the majority being excreted through the feces in 3–6 h.<sup>48</sup> This has led to the development of bioenhanced formulations used in recent trials with Longvida<sup>®</sup> that found as much as 100 times more bioavailability than naturally occurring curcumin.<sup>49</sup> Rainey-Smith *et al.*<sup>41</sup> supplemented with BCM-95 CG (Biocurcumax), which is reported to be 6.93 times more bioavailable than pure curcumin purportedly due to the noncurcuminoid compounds.<sup>50</sup> Ringman *et al.*<sup>42</sup> and Cox *et al.*<sup>43</sup> also utilized manufactured curcumin supplements Curcumin C3 Complex, and Longvida<sup>®</sup> Optimized Curcumin, respectively. The study by Small *et al.*<sup>39</sup> measured the kinetics of curcumin absorption over 6 h and found Theracurmin to lead to higher peak concentrations compared with Meriva curcumin and a standardized turmeric extract.

Considerable heterogeneity was seen across trials included in this systematic review, with different curcumin formulations, dosages and cognitive outcomes used. For these reasons, a meta-analysis is not currently considered suitable for this data. Improved standardization of study measures in trials may render this feasible in the future. The length of studies also varied with the study by Cox *et al.*<sup>43</sup> running for 4 weeks, making it difficult to extrapolate the results to the same extent as the longer trials. However, this group is currently testing Longvida<sup>®</sup> in a 12 week trial with improvements in working memory reported recently in an RCT of older Australians (unpublished results).<sup>51</sup> While four studies measured biochemical outcomes, there was no consistency in the markers of interest that were measured. Two studies conducted APOE genotyping.<sup>39,41</sup> The APOE gene has been identified as the most recognized genetic risk for AD and could impact the results through unknown mechanisms.<sup>52</sup> Also, none of the three most recent trials investigated older people that had existing cognitive impairments. This review evaluated both healthy individuals and those with cognitive impairment. Future studies investigating curcumin in both populations of older people are needed to assess curcumin from both a preventative and treatment perspective.

There has been a substantial increase in the number of clinical trials investigating curcumin to treat or prevent a range of conditions in recent years. The studies included in the present systematic review were conducted within the last 10 years, indicative of the modern ideology of natural medicine and a response to the lack of new pharmacological treatments for cognitive decline and dementia prevention. This contemporary trend in natural medicine will no doubt result in further human clinical trials, potentially driven by commercial interest and industry funding. Furthermore, curcumin interventions may be more efficacious if the supplementation is given earlier in life as a preventative measure, rather than a curative (or palliative) measure. In 2018, results from RCTs of curcumin improved symptoms associated with rheumatoid arthritis and liver dysfunction.<sup>53,54</sup> Curcumin has also shown promise in improving the metabolic profile of diabetes mellitus, a risk factor

for the development of AD.<sup>19</sup> In recent clinical trials of people with diabetes mellitus, curcumin has led to improvements in the lipid profile, fasting blood glucose, antioxidant status, and inflammatory markers, suggesting that curcumin may be useful as a strategy to reduce the risk of AD related risk factors earlier in life.<sup>19</sup>

Considerable attention has been given to curcumin's bioavailability and testing of new formulations, including several commercially available, proprietary formulations not used in the reviewed studies, such as Meriva<sup>®</sup> (a phytosomal formulation with curcuminoids and lecithin) and CW8 ( $\gamma$ -cyclodextrin).<sup>49</sup> A recent review of curcumin formulation bioavailability compared 11 different formulations, identified as NovaSol<sup>®</sup> (Micellized with Tween-80), CurcuWin<sup>®</sup> (Water-soluble formulation) and Longvida<sup>®</sup> possessing the highest bioavailability relative to pure curcumin. However, while the cell signaling mechanisms have been extensively investigated, dietary polyphenols are starting to come into focus for their benefits, irrespective of low bioavailability. Findings from animal studies have shown that curcumin may impact gut health through the microbiome by the promotion of bacterial diversity, reduced gut permeability and improved tight junction function; all of these contribute to a reduction in inflammation.<sup>36</sup> More research is needed to understand how curcumin exerts protection through modulation of the gut-brain axis.

Curcumin is only one of four curcuminoids present in turmeric, being the most abundant and most well studied. The potential capacity of curcumin as an antioxidant, anti-inflammatory and health promotive agent are far greater than its less known curcuminoids.<sup>55–57</sup> However, lesser-known curcuminoids, such as bisdemethoxycurcumin and desmethoxycurcumin, may also provide health benefits. Furthermore, research will assess the potential for benefits to humans of specific curcumin analogues, such as J147 (which has been shown to reverse cognitive impairment in mice by targeting mitochondrial ATP synthase) and EF24 (which is being explored as a novel senolytic agent).<sup>58–60</sup>

The effects of curcumin on improving cognitive function in combination with other nutraceuticals also represent an important future area for investigation.<sup>25</sup> Recently, curcumin was tested in combination with Huperzine A in an open-label study of individuals with dementia and MCI.<sup>61</sup> A small study ( $n = 15$ ) found improvements in the ADAS-cog (Japanese version) after 12 and 28 weeks with only 60 mg curcumin with 50  $\mu$ g active Huperzine A, 3 mg piperine and other potentially active ingredients. Trials are ongoing, investigating the impact of curcumin in combination with omega-3 fatty acids to promote cerebral endothelial vasodilator function synergistically.<sup>62</sup> Curcumin is also being tested in conjunction with a lifestyle intervention involving yoga.<sup>63</sup> Combining curcumin with compounds that cross the blood-brain barrier, such as beta-hydroxybutyrate, may enhance its effects centrally.<sup>64</sup> Finally, the design of food products or delivery systems that are targeted to specific sites of the small intestine (upper portion of the jejunum) may improve the efficacy of curcumin interventions. Similar to other polyphenolic compounds, absorption rates may differ depending on the method of oral delivery.<sup>65</sup>

### Future research prospect

Curcumin's pleiotropic effects are becoming more widely understood; however, the mechanisms by which it exerts its benefits to cognitive function remain unclear. Curcumin and other polyphenols have low bioavailability but are known to be recycled and reabsorbed, delivering improvements in gut health, and a reduction in systemic inflammation with chronic consumption. To properly



evaluate the effects of curcumin on cognitive function, future acute and long-term trials should be conducted assessing the efficacy of different formulations of curcumin in crossover trials, analyzing by APOE genotype,<sup>13</sup> and controlling for potential gut dysbiosis pre-randomization. A range of other biochemical measures will provide insight into curcumin's benefits, such as microbiome testing, homocysteine, C-reactive protein and other proinflammatory cytokines, and markers of mitochondrial function.

## Conclusions

In this first systematic review to evaluate the effects of curcumin and cognitive function, the results suggest that novel formulations of curcumin are promising strategies to promote cognitive function. However, despite trials of up to 18 months, there is insufficient evidence to support curcumin supplementation as an effective means of both preventing and treating dementia and symptoms of cognitive decline. The current evidence in humans is promising but generalizability of the results is limited by the small number of trials, relatively small sample sizes, and the considerable variation across studies. Future research may focus on examining the role of bioavailability to further elucidate the mechanisms by which curcumin exerts its pleiotropic effects, through examination of the gut-brain axis and relevant biomarkers.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

NN and NMD designed the study and devised the research questions. NMD and NS drafted the manuscript and carried out the literature review and data extraction. NN, NS and NMD were in charge of editing and formatting the final manuscript. NS, NMD, ENG, DP, JK, AJM, DDM and NN contributed to the writing and provided critical feedback. All authors read and contributed to the final manuscript.

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