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Effects of dietary proteins on cognitive performance and brain vascular function in adults: a systematic review of randomised controlled trials

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Abstract

The incidence of cognitive decline is rising, leading to increased attention on the preventive role of healthy foods on brain function. Previous reviews including primarily observational studies suggested that dietary proteins may improve cognitive performance, but evidence from individual randomised controlled trials (RCT) is less consistent. Therefore, this systematic review examined the long-term effects of dietary proteins from RCT, considering both their amount and type, on cognitive performance (psychomotor speed and attention, executive function, memory and global cognition). Alterations in cerebral blood flow (CBF) – a validated brain vascular function marker – were also considered. A total of 4747 studies were identified through a systematic search, resulting in twenty-three included papers reporting effects on cognitive performance ($n = 23$) and CBF ($n = 3$). Improvements were observed in three out of the nine studies that evaluated psychomotor speed which compared a dietary protein intervention with a non-protein or lower-protein control. Of the six beneficial observations on working memory ($n = 12$), declarative memory ($n = 10$) and visuospatial memory ($n = 10$), five were nut interventions from three different trials. Limited studies focusing on global cognition suggested that specific target populations, namely subacute stroke or dementia, may benefit more than healthy individuals from increased dietary protein intake. From the three studies involving CBF, improvements in regional blood flow were associated with most cognitive performance outcomes. The comparative effects of different protein types warrant further investigation. Overall, this review encourages additional research into protein-rich foods or supplements which could potentially prevent or mitigate cognitive decline.

Key words: brain vascular function: cerebral blood flow: cognitive performance: dietary proteins

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Introduction

Cognitive impairment, which can escalate into worsening cognitive symptoms that could finally culminate in dementia, raises mounting concerns. Notably, as people continue to live longer, rates of dementia are expected to soar from approximately 57 million cases in 2019 to nearly 153 million cases in 2050(1). Currently, no recommendations exist regarding protein intake for cognitive health(2), but higher-protein diets could be a strategic approach to slow down or prevent cognitive decline. Specifically, dietary proteins have been related to cognitive performance improvements in both cross-sectional and longitudinal cohort studies(3–5), but evidence from longer-term randomised controlled trials (RCT) for protein-rich foods(6) and supplements involving different study populations remains less convincing. It is thus pertinent to examine whether changing dietary protein intake could be a strategy to reduce the risk of cognitive decline(4).

Brain vascular function has been suggested to play an important role in cognitive decline, as a reduction in cognitive performance can be a significant consequence following brain vascular dysfunction(7,8). An important marker for brain vascular function is cerebral blood flow (CBF)(9,10). As CBF declines with normal ageing, it is negatively related to changes in cognitive performance, and a reduced CBF is associated with an increased risk of developing dementia(11). CBF can be measured both globally and regionally non-invasively using a variety of techniques such as magnetic resonance imaging (MRI) with arterial spin labelling (ASL), near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) ultrasound(9,10,12,13). MRI with ASL scans is able to quantify CBF(9,10), NIRS evaluates changes in blood oxygenated haemoglobin concentrations(14) and TCD can assess cerebral perfusion in the major cerebral arteries(15). To improve cognitive performance, the mechanisms underlying a protein's ability to enhance CBF may be influenced by both the amount and source of dietary protein. No comprehensive reviews of RCT have evaluated the potential role of dietary proteins in improving CBF and, by extension, cognitive performance, nor have they compared the efficacy of different protein sources in this regard(3–5). These previous reviews, limited by their focus on the effects of specific amino acids and a lack of RCT evidence, have not assessed brain vascular function. This omission leaves questions about how intact dietary proteins influence cognitive performance and brain vascular function.

This systematic review will address these critical gaps by focusing on RCT that investigated the longer-term effects of

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dietary protein interventions on cognitive performance and brain vascular function in both healthy adults and specific target populations that may benefit more from dietary protein interventions. We examined studies which (i) evaluated the effects of dietary protein intake by comparing a dietary protein with a non-protein or lower-protein control or (ii) evaluated the dietary protein type by comparing two dietary proteins with the same protein amount with one another to determine if one was more beneficial than another. Changes in CBF were assessed in relation to cognitive performance tests on three cognitive domains (i.e. psychomotor speed and attention, executive function and memory) and global cognition.

Methods

Eligibility criteria

Studies were included if they (i) were an RCT, (ii) involved only adults, (iii) provided protein-rich foods(6) or supplemental protein interventions, (iv) investigated cognitive performance, (v) were published in a peer-reviewed journal, (vi) were written in English, (vii) compared either an intact protein supplement or protein-rich food with a non-protein or lower-protein control OR compared two intact proteins with one another, (viii) reported total protein amount or total protein amount could be calculated and (ix) were longer term (>1 d). If a paper reported on brain vascular function but not on cognitive performance, it was excluded. Brain vascular function outcomes were included only if they evaluated CBF at rest or while engaged in a cognitive task (i.e. not during exercise or hypercapnia).

Identification of studies

A literature search was conducted using Ovid databases including Embase, Medline and Cochrane for studies performed up until July 2023. The search terms used to identify relevant papers are listed in the Supplementary Materials (Table S1). Key search terms included ('Dietary Proteins' (expand)) AND ('cerebr* blood flow or CBF' (multi-purpose) OR 'cogniti* or cogniti* function' (multi-purpose)). All articles were imported into a reference management tool (Citavi 6, Swiss Academic Software, Wädenswil, Switzerland) where they were filtered for duplicates and eligibility. This systematic review followed the PRISMA guidelines and was registered online in PROSPERO (CRD42024507633).

Study selection

Articles were screened for inclusion by two researchers (M.S.A. and P.J.J.), and disagreements on inclusion were resolved by discussion. Only intervention studies which investigated the effects of dietary proteins on cognitive performance and, if assessed, brain vascular function were included. Duplicates, conference papers, commentaries, reviews, meta-analyses, observational studies, animal studies, protein hydrolysate interventions, acute studies (<1 d) and studies involving children or without a control group were excluded. A study that reported the effects in multiple papers was considered as only one study. Additionally, relevant articles were also included through a manual search by checking the references of included papers and website retrieval through a PubMed search.

Data extraction

Information regarding the study population, intervention and outcome parameters were extracted into a custom-made summary table. Additional information such as the study design, intervention duration, wash-out period (if applicable), baseline characteristics and health status of the study participants (including their body mass index (BMI) and age), type of study product, control(s), protein amount, frequency and tests for cognitive performance and/or brain vascular function were also extracted when provided. When data were available to calculate parameters such as average BMI (from height and body weight) or protein amount, then this was performed and included in the table. Whenever possible, only the study characteristics for the participants who completed the cognitive performance and brain vascular function outcomes were included (per-protocol analysis). If the study consisted of more than two arms, two arms were selected. The arms to be compared were prioritised in order of the research questions (protein amount then protein type), meaning that the arms with the highest and the lowest protein intakes were selected to determine if protein amount has an impact on the outcome parameters. In cases where a co-intervention (e.g. exercise) or a potentially confounding nutrient (e.g. isoflavone) was involved, those two arms were selected that mitigated the potential impact of these co-interventions to isolate effects of the protein as much as possible. For example, if there were three arms including a milk protein, a milk protein with isoflavones and a soy protein with isoflavones, then the two arms containing isoflavones would be compared with one another.

In this review, we focused on three main cognitive domains: psychomotor speed and attention, executive function and memory(16). The executive function domain was further subdivided into working memory, planning and inhibitory control subdomains. The memory domain was organised on the basis of declarative memory (e.g. episodic such as verbal short-term memory), visuospatial and non-declarative memory (e.g. emotional and procedural memory). Studies which used tests that integrated multiple cognitive domains into a composite cognitive performance score were also incorporated and defined as global cognition, referring to an individual's comprehensive cognitive functioning. These tests often screen for dementia in the elderly who may be experiencing decline(17–19). If a single cognitive test was also divided as subscores across different domains, these subscores were reported in their associated subdomains.

Cognitive performance tasks often fall under these subdomains. However, subdomains in which tests are categorised may have areas of overlap, and there are inconsistencies in the literature about what these subdomains are(16). For clarity, tests primarily evaluating reaction time, information processing speed and fine motor skills were organised under the psychomotor speed subdomain. In the attention subdomain, we included tasks assessing alertness, simple and complex attention, and selective, focused and sustained attention. Under the executive function domain, tasks evaluating working memory included spatial, verbal and numerical working memory as well as (language) fluency. Planning included constructions and ideational praxis, while inhibitory control included multitasking and cognitive flexibility (e.g. task switching). In the memory domain, declarative memory was evaluated using verbal short-term and longer-term memory recall tests, and visuospatial memory included shorter- and longer-term memorisation of pictures, picture identification, and orientation and mental rotation tasks. Non-declarative memory comprised emotional and procedural memory.

To assess the dietary protein's effects on cognitive performance, studies were categorised on the basis of the comparator: comparing a dietary protein with a non-protein or lower-protein control or comparing two different dietary proteins with identical total protein amount. In Tables 1 and 2, a statistically significant ($p \leq 0{\cdot}05$) improvement (up arrow) indicates that the first study arm improved compared with the second arm, unless otherwise stated in the footnotes. If improvements were observed in subgroup analyses (e.g. improvements were observed in only one sex), these were also indicated as up arrows in the tables, with specific details about the subgroups provided in a footnote. Studies may have used multiple tests to examine intervention effects for the same subdomain. If we observed improvements on any of those tests, then we indicated that an improvement was observed for that specific subdomain. An equal sign denoted that there were not statistically significant ($p > 0{\cdot}05$) improvements in the intervention (first arm) compared with the control (second arm).

Studies which investigated healthy participants are reported first, followed by specific target populations. Specific target populations were defined as any cohort that the authors did not exclusively categorise as healthy. For example, people who were otherwise healthy but were aware of cognitive decline were categorised as a specific target population. The impact of protein interventions on brain vascular function is presented alongside cognitive performance data.

Results

Study characteristics

A PRISMA flow diagram is shown in Figure 1. A total of 4747 studies were retrieved by the systematic search. Duplicates were first removed, and the remaining 4344 articles were screened by their title and abstract. After reading the full text of the remaining 107 potential papers, four had no control group, two were not in English, twenty-four were acute, fifteen were protein hydrolysates and forty-four were excluded for other reasons such as investigating soy isoflavone extracts instead of soy proteins. Five additional records were manually added. This resulted in a total of twenty-three papers reporting effects on cognitive performance ($n = 23$) and brain vascular function (MRI with ASL: $n = 2$, TCD: $n = 1$). Different dietary protein types were examined: intact proteins stemming from protein-rich diets, animal (e.g. milk, meat, whey), and plant (e.g. soy, nuts) sources. No papers were retrieved that used NIRS to evaluate brain vascular function, and no studies evaluated non-declarative memory. In the Supplementary Materials (Tables S2 and S3), the types of cognitive tests which were used are reported.

Studies comparing a dietary protein with a non-protein or lower-protein control

An overview of study characteristics can be found in Table 3.

Psychomotor speed and attention. Nine studies comparing a dietary protein with a non-protein or lower-protein control investigated psychomotor speed. Seven studies reported outcomes in healthy participants, and one of those studies also evaluated brain vascular function using MRI with ASL after a soy nut intervention(20) (Table 1, Figure 2a). In that study, CBF improved in the ventral network involved in motor processing skills, which corresponded to improvements in psychomotor speed. One study involving peanuts reported improvements in a processing speed test(21), although another study did not observe any benefits after a peanut intervention(22). The four other studies in healthy participants investigating psychomotor speed did not detect any significant changes after the interventions(23–26). In frail and pre-frail elderly, however, a milk protein concentrate improved reaction time(27). Conversely, in patients with type II diabetes (T2D), psychomotor speed worsened after a carbohydrate-reduced high-protein diet compared with a conventional diabetes diet(28).

Eight studies evaluated attention, with six of those studies involving healthy participants. No differences were found between the intervention and control groups in healthy(22,24–26,29,30), frail and pre-frail elderly(27) and T2D populations(28).

Executive function. Twelve studies were identified which evaluated working memory, of which ten were conducted in healthy participants. Among the studies focusing on healthy participants, improvements in this subdomain were observed following a peanut(21) and walnut intervention(31). However, no other beneficial effects on working memory were noted from protein interventions in eight additional studies involving healthy individuals(20,23–26,29,32,33) in frail and pre-frail elderly(27) and T2D populations(28). In the only intervention which evaluated planning, no changes were observed(26).

Inhibitory control was assessed in nine studies. Among them, one study involving healthy participants reported improvements following a high-protein meat diet compared with a usual-protein diet(29). In contrast, seven other studies in healthy participants(20–23,25,30,33), and one in frail and pre-frail elderly(27), did not observe changes in this subdomain. In one of these studies using a whey protein isolate intervention, where the cognitive performance test was simultaneously performed with TCD(30), no significant intervention effects were found on the middle cerebral artery. Notably, although no improvements were observed in a mixed-nut study on cognitive performance for this subdomain, an improvement in CBF was observed in prefrontal areas involved in executive function(23). Similarly, improvements in CBF were observed in brain regions without changes in cognitive performance for the soy nut study(20).

Table 1. Results from the cognitive performance subdomains and brain vascular function outcomes for studies comparing a dietary protein with non-protein or lower-protein control

Author (year)	Study population	Intervention	Control	Brain vascular function			Cognitive domains								
				TCD	NIRS	ASL	Attention and psychomotor speed		Executive function			Memory			Global cognition
							PS	Attention	Working memory	Planning	Inhibitory control	Declarative	Visuospatial	Non-declarative	
Barbour (2017)	Healthy	Peanuts	Nut-free diet				↑		↑		=	↑			
Charlton (2016)	Healthy	Pork	Chicken						=			=			
Formica (2002)[*]	Healthy	Red meat and exercise	Carbohydrate meal and exercise				=	=	=[†]				=		=
Fournier (2007)	Healthy	Cow milk and isoflavone supplement	Soy milk and isoflavone supplement						=		=	=	=		
Jakobsen (2011)	Healthy	HP meat diet	UP diet					=	=		↑		↑		=
Kleinloog (2021)	Healthy	Soy nut	No nuts			↑	↑		=		=		=		
Lefferts (2020)	Healthy	WPI	Maltodextrin	=				=			=	=	=		
Nijssen (2023)	Healthy	Mixed nuts	No nuts			↑	=		=		=	↑	↑		
Pribis (2011)	Healthy	Walnuts	No walnuts						↑			=	=		=
Mustra Rakic (2021)	Healthy	Almonds	Snack mix				=	=	=	=			=		
Reeder (2022)	Healthy	Peanuts	No peanuts				=[‡]	=			=	=	=		=
Sala-Vila (2020)	Healthy	Walnuts	No walnuts				=	=	=		=	=	=		=
Aquilani (2008)	Subacute stroke (and cognitive dysfunction)	Protein-calorie supplementation	No supplementation												↑
Jensen (2022)	T2D	CRHP	CD				=[§]	=	=			=			=
Mohamed (2019)	AD	LF	No LF												↑
Van der Zwaluw (2013)	Frail and pre-frail	Milk protein concentrate	Non-protein supplement				↑	=	=		=	=			

Note: Improvements in each subdomain based on significant ($p \leq 0.05$) differences between the intervention (first arm) and control groups (second arm) over the entire intervention period are denoted by an up arrow. No significant improvements ($p > 0.05$) of the intervention (first arm) over the control (second arm) are indicated by an equal sign.

TCD, transcranial Doppler ultrasound; NIRS, near-infrared spectroscopy; ASL, arterial spin labelling; PS, psychomotor speed; HP, high protein; UP, usual protein; WPI, whey protein isolate; T2D, type II diabetes; CRHP, carbohydrate-reduced high-protein diet; CD, conventional diabetes diet; AD, Alzheimer's disease; LF, lactoferrin.

[*] Formica (2002): Authors combined the results into z-scores across subdomains.

[†] Formica (2002): Second arm (carbohydrate meal and exercise) significantly improved over red meat and exercise (first arm).

[‡] Reeder (2022) Control period (no peanuts) significantly improved over intervention period (peanuts).

[§] Jensen (2022): Second arm (conventional diabetes diet) significantly improved over first arm (carbohydrate-reduced high-protein diet).

Table 2. Results from the cognitive performance subdomains and brain vascular function outcomes for studies comparing two different dietary proteins with identical total protein amount

Author (year)	Study population	Intervention	Control	Brain vascular function			Cognitive domains								
				TCD	NIRS	ASL	Attention and psychomotor speed		Executive function			Memory			Global cognition
							PS	Attention	Working memory	Planning	Inhibitory control	Declarative	Visuospatial	Non-declarative	
Basaria (2009)	Healthy	Soy protein	Whole milk protein				=	=	=			=	=		=
Henderson (2012)	Healthy	Soy protein	Milk protein				=	=	=			=	↑		=
Kreijkamp-Kaspers (2004)	Healthy	Soy protein	Milk protein				=	=	=			=	=		=
Nagai (2020)	Healthy	RWL	Soy protein					↑	=		=		=		=
Jadczak (2021)	Frail and pre-frail	Whey protein	Rice protein					=	=						
Sharma (2009)	Prostate cancer (undergoing ADT)	Soy protein	Whole milk protein				=		=			=	↑*		=
Zajac (2018)	Low vitamin B_{12}	WPI	SPI				↑†		=			=			

Note: Improvements in each subdomain based on significant ($p \leq 0.05$) differences between the intervention (first arm) and control groups (second arm) over the entire intervention period are denoted by an up arrow. No significant improvements ($p > 0.05$) of the intervention (first arm) over the control (second arm) are indicated by an equal sign.

TCD, transcranial Doppler ultrasound; NIRS, near-infrared spectroscopy; ASL, arterial spin labelling; PS, psychomotor speed; RWL, rice wine lees; ADT, androgen deprivation therapy; WPI, whey protein isolate; SPI, soy protein isolate.

* Sharma (2009): Second arm (whole milk protein) significantly improved over the first arm (soy protein).

† Zajac (2018): Observed improvements for women only in the soy protein isolate group for reaction time and reasoning speed.

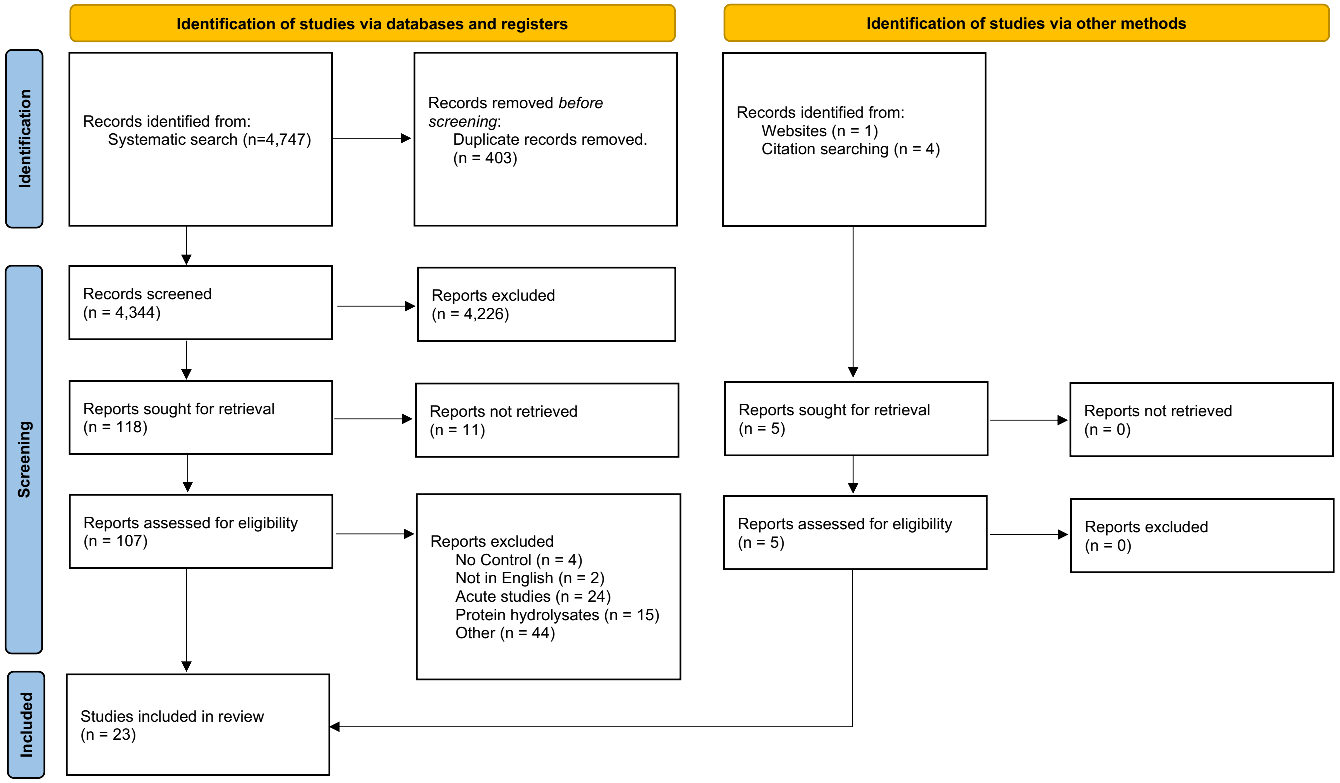

Fig. 1. PRISMA 2020 flow diagram showing the study selection procedures of human intervention studies for the systematic review of dietary proteins and brain function. *Note*: After a systematic search in which 4747 papers were identified and five papers were manually added, twenty-three studies were included in the analysis.

Memory. Ten studies evaluated declarative memory, with eight focusing on a healthy population. Interventions using peanuts(21) and mixed nuts(23) observed improvements in this subdomain. The improvements in task performance for the mixed-nut intervention also observed improvements in CBF via ASL in the pre-central gyrus, a region linked to declarative memory(23). The remaining six studies in healthy participants(22,25,30–33), frail and pre-frail elderly(27) and T2D populations(28) did not observe any changes in declarative memory.

Ten studies assessed visuospatial memory, all of which involved healthy populations. Among them, two studies demonstrated improvements(23,29). Additionally, the intervention with mixed nuts reported enhancements in CBF in the superior/middle frontal gyrus, a brain region associated with visuospatial memory(23). Conversely, the remaining eight studies(20,22,24–26,30,31,33) did not report significant improvements in visuospatial memory.

Global cognition. Eight studies assessed cognitive performance through tests which combined several cognitive domains into a global cognitive performance score. Among these, five studies involving healthy populations reported no enhancements(22,24,25,29,31). In contrast, protein supplementation demonstrated an improvement in global cognition among patients recovering from subacute stroke(34), and individuals with Alzheimer's disease (AD) exhibited improvements following a lactoferrin intervention(35). However, a carbohydrate-reduced high-protein diet compared with a conventional diabetes diet found no discernible changes in global cognition in a T2D population(28).

Studies comparing two different dietary proteins with identical total protein intakes

Study characteristics for studies comparing two different dietary proteins with identical total protein intake are presented in Table 4. No studies reporting on both cognitive performance outcomes and brain vascular function were retrieved.

Psychomotor speed and attention. Five studies which compared dietary proteins with one another investigated psychomotor speed (Table 2; Figure 2b), with three of those studies comparing soy versus milk proteins in healthy populations. In those three studies(36–38), no significant changes were observed. Furthermore, in patients with prostate cancer undergoing androgen deprivation therapy (ADT), a comparison between soy and whole milk protein did not demonstrate any changes(39). However, in a cohort with a low vitamin B_{12} status based on serum concentrations, a target group for whom whey fractions containing vitamin B_{12} might theoretically offer benefits to reduce AD risk(40), women consuming a soy protein isolate instead of a whey protein isolate demonstrated improved reaction times(41).

Table 3. Overview of the study characteristics for studies comparing a dietary protein with a non-protein or lower-protein control

Author (year)	Study duration	Study design	Wash-out (weeks)	Study population	Intervention	Protein amount/d	Control	Control protein amount/d	Sample size	Age (years)	Male (%)	BMI (mean)	Brain vascular function	Cognitive domains
Barbour (2017)	12 weeks	Cross-over	12	Healthy	Peanuts (unsalted with skins)	21·84 g males, 14·04 g females	Nut-free diet	0 g	61	65	48	31	–	Psychomotor speed, executive function (working memory, inhibitory control), memory (declarative)
Charlton (2016)	12 weeks for 4×/wk	Parallel	–	Healthy	Pork	28·1 g	Chicken	25·2 g	31 (19)	78	?	28	–	Executive function (working memory), memory (declarative)
Formica (2002)	24 weeks for 3 d/wk	Parallel	–	Healthy	Red meat and exercise	45 g	Carbohydrate meal and exercise	0 g (<1·1 g/kg/d total)	154 (77)	71	38	28	–	Psychomotor speed and attention, executive function (working memory), memory (visuospatial), global cognition
Fournier (2007)	16 weeks	Parallel	–	Healthy	Cow’s milk and isoflavones supplement	24 g	Soy milk and isoflavone supplement	18 g	52 (27)	56	0	28	–	Executive function (working memory, inhibitory control), memory (declarative, visuospatial)
Jakobsen (2011)	3 weeks	Parallel	–	Healthy	HP meat diet	3·0 g/kg body weight	UP diet	1·5 g/kg body weight	23 (11)	24	100	22	–	Attention, executive function (working memory, inhibitory control), memory (visuospatial), global cognition
Kleinloog (2021)	16 weeks	Cross-over	8	Healthy	Soy nut	25·5 g	No nuts	0 g	23	64	48	26	ASL	Psychomotor speed, executive function (working memory, inhibitory control), memory (visuospatial)
Lefferts (2020)	12 weeks	Parallel	–	Healthy	WPI	50 g	Maltodextrin	0 g	99 (53)	67	55	27	TCD	Attention, executive function (inhibitory control), memory (declarative, visuospatial)
Nijssen (2023)	16 weeks	Cross-over	8	Healthy	Mixed nuts	10·3 g	No nuts	0 g	28	65	50	28	ASL	Psychomotor speed, executive function (working memory, inhibitory control), memory (declarative, visuospatial)
Pribis (2011)	8 weeks	Cross-over	6	Healthy	Walnuts in banana bread	4·2 g	Banana bread without walnuts	3·12 g	64	20	?	23	–	Executive function (working memory), memory (declarative, visuospatial), global cognition
Mustra Rakic (2021)	6 months	Parallel	–	Healthy	Almonds	18 g	Snack mix	9 g	41 (24)	62	56	29	–	Psychomotor speed and attention, executive function (planning, working memory), memory (visuospatial)

Table 3. *(Continued)*

Author (year)	Study duration	Study design	Wash-out (weeks)	Study population	Intervention	Protein amount/d	Control	Control protein amount/d	Sample size	Age (years)	Male (%)	BMI (mean)	Brain vascular function	Cognitive domains
Reeder (2022)	12 weeks	Parallel	–	Healthy	Dry-roasted Peanuts	13 g[†]	No peanuts	0 g	61 (32)	20	0	25	–	Psychomotor speed and attention, executive function (inhibitory control), memory (declarative, visuospatial), global cognition
Sala-Vila (2020)	2 years	Parallel	–	Healthy	Walnuts	4·5–9 g[†] (30–60 g/d walnuts for 15% of EN)	No walnuts	0 g	657 (336)	69	34	27	–	Psychomotor speed and attention, executive function (working memory, inhibitory control), memory (declarative, visuospatial), global cognition
Aquilani (2008)	21 d	Parallel	–	Subacute stroke and cognitive dysfunction	Protein-calorie supplementation regimens*	20 g	No supplementation	0 g	48 (24)	72	56	25	–	Global cognition
Jensen (2022)	6 weeks	Parallel	–	T2D	CRHP	179 g[†] (30% EN)	CD	102 g[†] (17% EN)	55 (27)	67	49	34	–	Psychomotor speed and attention, executive function (working memory), memory (declarative), global cognition
Mohamed (2019)	3 months	Parallel	–	AD	LF	250 mg	No LF	0 mg	50 (25)	70	56	25	–	Global cognition
Van der Zwaluw (2014)*	24 weeks	Parallel	–	Frail and pre-frail elderly	Milk protein concentrate	30 g	Non-protein supplement	0 g	65 (34)	80	45	27	–	Psychomotor speed and attention, executive function (working memory, inhibitory control), memory (declarative)

Note: Age and BMI were determined by averaging the values over only the two arms being compared, and values are based on participants who were analysed (per-protocol analysis) whenever possible. For the sample size, the intervention group (first arm) value is in parentheses. Unknown values are indicated by a '?', and a '–' is used when the column is not applicable.

BMI, body mass index; EN, energy; wk, week; HP, high protein; UP, usual protein; ASL, arterial spin labelling; WPI, whey protein isolate; TCD, transcranial Doppler ultrasound; T2D, type II diabetes; CRHP, carbohydrate-reduced high-protein; CD, conventional diabetes diet; AD, Alzheimer's disease; LF, lactoferrin.

* Aquilani (2008): The nutritional formula consisted of a 200 ml mixture (Cubitan, Nutricia, Italy) providing 250 kcal of energy, 20 g proteins, 28·2 g carbohydrates and 7 g lipids.

† Calculated protein amount.

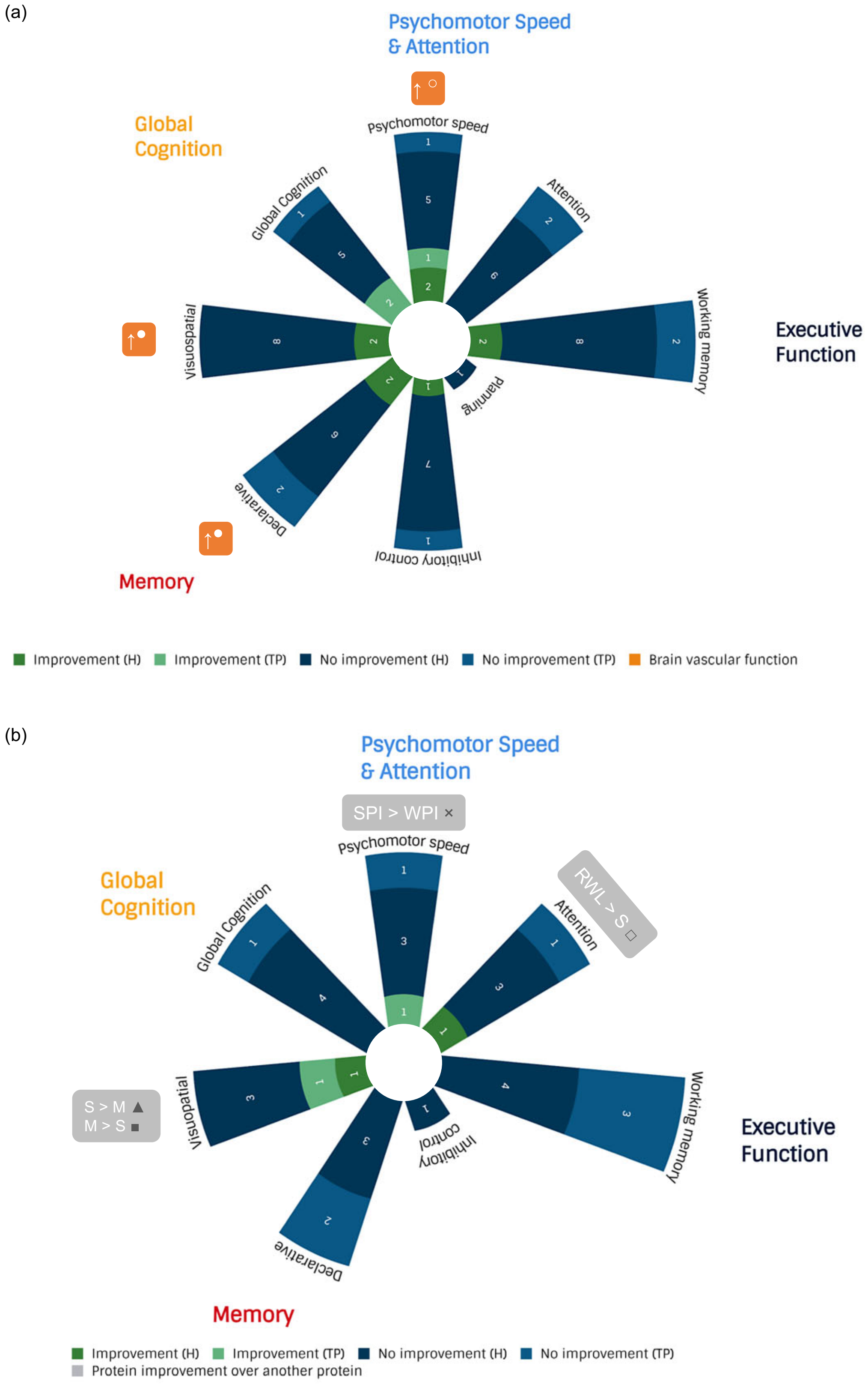

Fig. 2. Results of studies which compared a dietary protein versus a non-protein or lower-protein control or two different dietary proteins with identical total protein amount. *Note*: Polar charts (Vizzlo, Leipzig, Germany) indicate the number of studies that observed significant improvements ($p \leq 0{\cdot}05$, shown in green) or no improvement ($p > 0{\cdot}05$, shown in blue) in subdomains in the intervention (first arm) compared with the control group (second arm). H indicates healthy participants, and TP indicates a specific target population. Improvements included subgroup analyses, but not changes over entire domains. Orange descriptions alongside a cognitive domain specify whether a connection was made between a study which investigated brain vascular function and an associated cognitive domain. Up arrows indicate there was an improvement in brain vascular function. Grey descriptions in Figure 2 (b) specify which dietary proteins demonstrated an improvement over the other.

Five studies evaluated attention, with four studies involving healthy populations. In three soy compared with milk protein studies, no significant differences were observed between groups(36–38). In contrast, visual selective attention improved after a rice wine lees over a soy protein intervention(42). One frail and pre-frail elderly population comparing whey versus rice proteins did not observe any significant differences between the groups(43).

Executive function. Among seven studies examining working memory, four were conducted in healthy populations. However, across all healthy(36–38,42) and specific target populations(39,41,43), no significant changes were detected. Furthermore, the only study evaluating inhibitory control did not find benefits in rice wine lees over soy protein(42).

Memory. A total of five studies examined declarative memory, with three involving healthy participants. No significant changes were observed between proteins for both healthy(36–38) and specific target populations(39,41). Five studies examined effects on visuospatial memory, with four studies involving healthy populations. Notably, one study in healthy participants favoured soy protein over milk protein(37), while in a population with prostate cancer undergoing ADT, whole milk protein demonstrated greater improvements compared with soy protein(39). None of the remaining studies in healthy participants observed any changes, including two studies which also compared soy versus milk protein(36,38) and another comparing rice wine lees versus soy protein(42).

Global cognition. Across four studies conducted with healthy populations(36–38,42) as well as in one study involving individuals with prostate cancer undergoing ADT(39), no significant differences were identified in global cognitive function between the different protein interventions.

Discussion

In this systematic review, we provided a comprehensive overview of the effects of dietary proteins on cognitive performance (psychomotor speed and attention, executive function, memory and global cognition) and brain vascular function. When comparing dietary proteins with a non-protein or lower-protein control, we primarily observed enhancements in psychomotor speed. Improvements in other cognitive subdomains (working, declarative and visuospatial memory) were mainly detected following the intake of dietary proteins from nuts. Limited research suggested that certain target groups, specifically those with subacute stroke or dementia, might derive greater benefits from dietary protein interventions, as was evident in global cognition. Three studies comparing a dietary protein with a non-protein or lower-protein control utilised MRI with ASL or TCD to assess brain vascular function in relation to cognitive performance outcomes. Two studies found that increases in CBF in specific regions were linked to improvements in related cognitive performance domains(20,23). In one study, cognitive performance remained unchanged, and there was also no change in CBF(30). Further research is necessary to determine the comparative effects between different protein types.

Studies comparing a dietary protein and non-protein or lower-protein control

Psychomotor speed improved in three distinct dietary protein interventions: after a peanut(21) and soy nut(20) intervention in healthy participants, as well as after a milk protein concentrate intervention in frail and pre-frail elderly(27). These studies were all conducted in older populations (mean: >64 years old). Interestingly, another peanut study which did not observe improvements in psychomotor speed(22) featured a much younger population (mean: 20 years old). Both peanut studies were 12 weeks long; however, protein intake from peanuts was lower in the study that did not yield positive results (13 g versus 30 g), potentially explaining the discrepancies in outcomes. Additionally, as normal ageing leads to a decline in CBF which may contribute to age-related cognitive decline(11), we have hypothesised on the basis of previous research that older adults may have more room to improve in certain cognitive domains, such as psychomotor speed and memory(44). Furthermore, psychomotor speed worsened after a 6-week high-protein diet in participants with T2D compared with a conventional diabetes diet(28). The authors discussed that the test used to evaluate this domain (Symbol Digit Modalities Test) is responsive in T2D for detecting changes in hypoglycaemia(45). However, attention, declarative memory and global cognition were not changed in this study, which would also be expected from hypoglycaemia(46), indicating that further research is needed to confirm or refute these findings regarding the effects of dietary proteins on psychomotor speed in T2D.

Several beneficial changes were also observed in working memory, declarative memory and visuospatial memory. These beneficial effects were primarily observed after nut interventions(21,23,31), but also in a study that compared a high-protein

(a) Studies comparing a dietary protein and non-protein or lower-protein control **(b)** Studies comparing two different dietary proteins with identical total protein amount. Note that for (a) Reeder (2022), Jensen (2022), and Formica (2002) found improvements in the second arm (lower or non-protein control) over the first arm (protein intervention) and for (b) Sharma (2009) the second arm improved over the first arm. Abbreviations: S, soy protein; M, milk protein; RWL, rice wine lees; SPI, soy protein isolate; WPI, whey protein isolate. **(a)** ○ Kleinloog (2021) observed improvements in psychomotor speed, alongside improvements in CBF related to these brain regions. Additionally, improvements in CBF were observed in brain regions without changes in cognitive performance (not shown). ● Nijssen (2023) observed improvements in declarative and visuospatial memory, alongside improvements in CBF related to these brain regions. Additionally, an improvement in CBF was observed in pre-frontal areas involved in executive function, without changes in cognitive performance (not shown). *Note*: Lefferts (2020) no changes in TCD or cognitive performance including attention, declarative memory, inhibitory control and visuospatial subdomains were observed (not shown). **(b)** ▲ Henderson (2012) Improvements were observed for soy protein over milk protein. □ Nagai (2020) Improvements were observed for rice wine lees over soy protein. ■ Sharma (2009) Improvements were observed for milk protein over soy protein in patients with prostate cancer undergoing androgen deprivation therapy. × Zajac (2018) Improvements were observed for SPI over WPI only for women with low serum vitamin B_{12} concentrations.

Table 4. Overview of the study characteristics for studies comparing two different dietary proteins with identical total protein amount

Author (year)	Study duration	Study design	Wash-out	Study population	Intervention	Protein amount/d	Control	Control amount/d	Sample size	Age (years)	Male (%)	BMI (mean)	Brain vascular function	Cognitive domains
Basaria (2009)	12 weeks	Parallel	–	Healthy	Soy protein	20 g	Whole milk protein	20 g	84 (38)	56	0	26	–	Psychomotor speed and attention, executive function (working memory), memory (declarative, visuospatial), global cognition
Henderson (2012)	2·5 years	Parallel	–	Healthy	Soy protein	25 g	Milk protein	25 g	313 (154)	61	0	27	–	Psychomotor speed and attention, executive function (working memory), memory (declarative, visuospatial), global cognition
Kreijkamp-Kaspers (2004)*	1 year	Parallel	–	Healthy	Soy protein	25·6 g	Milk protein	25·6 g	175 (88)	67	0	26	–	Psychomotor speed and attention, executive function (working memory), memory (declarative, visuospatial), global cognition
Nagai (2020)	12 weeks	Parallel	–	Healthy	RWL	15·2 g	Soy protein	15·2 g	35 (17)	71	77	23	–	Attention, executive function (working memory, inhibitory control), memory (visuospatial), global cognition
Jadczak (2021)	6 months	Parallel	–	Pre-frail and frail	Whey protein	40 g	Rice protein	40 g	70 (34)	73	33	?	–	Attention, executive function (working memory)
Sharma (2009)	12 weeks	Parallel	–	Prostate cancer (undergoing ADT)	Soy protein	20 g	Whole milk protein	20 g	33 (17)	69	100	29	–	Psychomotor speed, executive function (working memory), memory (declarative, visuospatial), global cognition
Zajac (2018)	8 weeks	Cross-over	16 weeks	Low vitamin B_{12}	WPI	50 g	SPI	50 g	44	61	45	27	–	Psychomotor, executive function (working memory), memory (declarative)

Note: Age and BMI were determined by averaging the values over only the two arms being compared, and values are based on participants who were analysed (per-protocol analysis) whenever possible. For the sample size, the intervention group (first arm) value is in parentheses. Unknown values are indicated by a '?', and a '–' is used when the column is not applicable.

RWL, rice wine lees; ADT, androgen deprivation therapy; WPI, whey protein isolate; SPI, soy protein isolate.

* Study characteristics include intent-to-treat.

meat diet with a usual-protein diet(29). Nuts, a key food of the Mediterranean diet, have been linked to cognitive benefits, including enhanced memory(47,48). Furthermore, in a recent longer-term study, the Mediterranean diet has also shown positive effects on regional CBF in adults with normal cognition(49). However, the question remains why results are conflicting for studies using the same protein source. Specifically, an 8-week-long study on walnuts improved verbal reasoning among a younger cohort (mean: 20 years old)(31), while another 2-year-long study with walnuts in an older population (mean: 69 years old) did not observe any beneficial effects in executive function(25). As mentioned before, we would have expected greater improvements in an older compared with a younger population, so differences in these results could potentially be attributed to the varying amounts of consumption: the prior study used a fixed amount of 60 g/d, whereas the latter ranged anywhere from 30 to 60 g/d, aiming to provide 15% of energy from walnuts.

Underscoring the potential influence of health status, studies comparing a dietary protein intervention with a non-protein or lower-protein control revealed no changes in global cognition among healthy participants. However, despite the limited number of studies, most specific target populations did exhibit beneficial changes. In one study, the authors concluded that 21-d protein supplementation in patients with subacute stroke could positively aid in the recovery of cognitive processes through higher amino acid bioavailability in the brain(34). Animal studies have shown that stroke can lead to significant decreases in brain protein synthesis(50,51). Potential improvements in brain protein synthesis and rehabilitation, neuron energy formation and neurotransmitter synthesis through improvements in amino acid bioavailability(34,52) could, in turn, lead to improvements in CBF. However, this theory remains to be elucidated. Furthermore, a 21-d lactoferrin intervention on patients with AD suggested that lactoferrin could influence pathways related to AD pathology(35), potentially enhancing global cognition. In the peanut study performed by Barbour *et al.*(21), cerebrovascular reactivity, a measurement of brain endothelial function, was measured using TCD. They reported a 5% increase in the left middle cerebral artery and a 7% increase in the right middle cerebral artery compared with the nut-free diet. These changes were correlated with a 5% increase in declarative memory, suggesting that changes in cognitive performance may result from changes in other aspects of brain vascular function as well.

Among the three studies that investigated both cognitive performance and brain vascular function, findings suggested an association between specific cognitive domains and brain vascular function. In particular, enhancements in psychomotor speed (soy nut study(20)) and verbal and visuospatial memory (mixed-nut study(23)) were linked to regional CBF. The study by Lefferts *et al.* comparing whey protein isolate with maltodextrin reported no changes in task performance or regional CBF(30). However, it remains to be addressed why CBF improvements can occur in brain areas, without improvements in associated cognitive domains. It could be speculated that the cognitive processes involved in these functions may require additional time for adaptation or translation of these CBF changes into observable behaviour(53).

Studies comparing two different dietary proteins with identical total protein intake

Three different protein comparators were assessed: soy compared with whey, rice wine lees compared with soy, and soy compared with whole milk. Clear evidence emerged that there is no advantage of soy over whole milk protein on psychomotor speed, as indicated in four studies(36–39). With regard to visuospatial memory, the findings were contradictory. Henderson *et al.*(37) identified an improvement in soy milk's impact compared with whole milk for this specific subdomain, whereas Sharma *et al.*(39) observed the opposite effect. It is worth acknowledging that ages were similar (mean: 69 years old(39) compared with 61 years old(37)) and intakes were relatively high (20 g/d(39) compared with 25 g/d(37)), but Sharma *et al.*(39) consisted of only men with prostate cancer undergoing ADT, as opposed to a healthy demographic with only women(37). An additional two studies investigating the same comparators in healthy women did not reveal any notable differences between groups in this subdomain(36,38). Based on the strong similarities in study designs between the studies conducted in only women(36–38), yet with contrary results, more attention should be given to this protein comparison in future studies.

Zajac *et al.*(41) demonstrated that, in individuals with low serum vitamin B_{12} concentrations, women but not men who consumed soy compared with whey protein isolates showed beneficial effects on psychomotor speed. Although isoflavones in soy have been attributed to beneficially impact cognitive performance owing to their oestrogen-like effects(54,55), a 3-week study using oestradiol did not yield cognitive improvements in tasks related to executive function associated with frontal lobe function(56), which is a brain region that is also implicated in psychomotor speed(57). Therefore, it is possible that the beneficial results for women in the present study(41) could be attributed to the amino acid composition instead. Soy and whey both contain components related to cognitive performance including L-arginine, branched-chain amino acids (e.g. leucine, isoleucine, valine) and tryptophan, but in different amounts(58,59). In general, soy contains more arginine than whey(59), an amino acid precursor for nitric oxide involved in endothelial function(60), which could, in turn, improve brain vascular function(61). A potential sex difference in cognitive performance has been observed before in an egg-protein hydrolysate study(62) which was postulated as potentially being related to the participants' higher mean subjective cognitive failures scores at baseline as well as women's quicker reductions in cognitive performance after menopause(63,64). There is also evidence to suggest that women have higher rates of dementia than men at the same age(65). This may allow for a greater window of improvement for older women compared with men. Moreover, differences in cognition between the sexes have also been noted in a cross-sectional study involving people with low serum vitamin B_{12} concentrations(66), which may relate to the differences observed in the present study(41). However, soy may not be superior in other domains or populations. A study with healthy participants comparing rice wine lees and soy protein in attention found rice wine lees to be more beneficial, independent of sex(42). These findings indicate that dietary proteins' effects on cognitive performance may depend on an interplay of factors including amino acid composition and potentially sex-specific responses. However, it is evident that further investigation into how effects differ between protein types is necessary. Unfortunately, for studies comparing a dietary protein and non-protein or lower-protein control, sex differences were not reported.

Limitations and other considerations

This is the first systematic review to evaluate the effects of RCT in dietary proteins on cognitive performance in conjunction with changes in CBF. Strengths of this paper include that the existing literature was systematically reviewed, and the focus included both healthy adult and specific target populations who may benefit more from certain dietary protein interventions. Largely due to differences in study designs (e.g. study duration, target populations), our review faces limitations regarding the ability to assess dose–response effects. It also remains unclear if participants met their recommended protein intake prior to the studies. The diversity in comparators and the array of tests used across studies could influence outcomes as well. It is possible that some studies may have been too short to impact certain cognitive domains. Additionally, certain cognitive performance tests may not be sensitive enough to detect subtle changes(67). Furthermore, attributing effects solely to protein in interventions involving complex food items, such as nuts, is challenging due to other bioactive components such as polyphenols(68). While brain vascular function (as determined by CBF) was a key focus in evaluating the relationship between dietary protein intake and cognitive performance, we acknowledge that additional mechanisms may also play a role, which were beyond the scope of this review and not assessed in the included studies. For instance, the amino acid composition of different protein sources could influence neurotransmitter synthesis(69), brain insulin sensitivity(70), inflammation(71), brain-derived neurotrophic factor(72) and the gut–brain axis(73), which may all affect cognitive function. Given the evidence that specific target populations and sexes may respond differently to dietary protein intake, more long-term studies should compare equivalent doses of various protein types across different domains, ensuring sufficient statistical power to detect any sex differences. This will provide valuable insights into the most effective protein sources for specific populations, as well as the amino acids responsible for cognitive benefits.

Conclusion

Based on the results of RCT involving healthy adult and specific target populations, there is evidence to support beneficial effects of dietary proteins on cognitive performance and brain vascular function. For studies that compared a dietary protein and non-protein or lower-protein control to determine the effects based on the amount of protein, improvements were shown in three out of the nine studies evaluating psychomotor speed. From the six beneficial effects observed in the cognitive subdomains working ($n = 12$), declarative ($n = 10$) and visuospatial memory ($n = 10$), five were following nut consumption assessed in three different trials. Based on limited studies focusing on specific target groups such as patients with subacute stroke or dementia, these populations may derive greater benefit from dietary protein interventions. Changes in regional CBF, as evaluated in three studies, were related to most effects observed on cognitive performance outcomes. Further research is required to understand the differences between protein types. Overall, this review encourages additional research into protein-rich foods or supplements that may help to prevent or alleviate cognitive decline.

Supplementary material

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Authorship

M.S.A. designed the study and conducted the literature review, interpreted the data and wrote the manuscript; R.P.M. designed the study, interpreted the data and wrote the manuscript; P.J.J. designed the study and conducted the literature review, interpreted the data and wrote the manuscript.

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