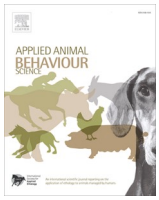
Applied Animal Behaviour Science 269 (2023) 106097

Contents lists available at ScienceDirect

Applied Animal Behaviour Science

journal homepage: www.elsevier.com/locate/applanim



Non-pharmacological interventions for the treatment of canine cognitive dysfunction: A scoping review

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ARTICLE INFO

Keywords:
Senior dog
Supplement
Training
Enrichment
Dementia

ABSTRACT

Canine cognitive dysfunction (CCD) is a neurodegenerative disease, likened to Alzheimer's, most commonly seen in dogs over the age of 10 years. CCD is difficult to diagnose and there is no cure, consequently research efforts are focused on maintaining a good quality of life for these dogs for as long as possible. Our scoping review aimed to identify, critically appraise, and map the existing literature on the impact of non-pharmacological treatments for CCD. We followed a systematic approach and utilised established tools to assess the literature. Thirty-one papers were extracted for full review. Of these, 29 investigated supplements or diets as their intervention, with the most common a combination of antioxidants and omega 3 fatty acids, which are known for their neuroprotective qualities. There were almost twice as many experiments conducted on laboratory dogs than on pet dogs. The inclusion and exclusion criteria for each study varied widely and was often not well-defined, making comparisons between treatments difficult. This scoping review highlights the need for an accepted measure to determine the presence of CCD, standardised testing methods for cognitive ability in senior canines that translates between laboratory and pet dog populations, and a broader view of non-pharmacological interventions that go beyond supplements or diets.

1. Introduction

Canine Cognitive Dysfunction (CCD) is a neurodegenerative disease most commonly seen in dogs over the age of 10 years (Turcsán and Kubinyi, 2023; Yarborough et al., 2022), and is likened to Alzheimer's in humans (Mihevc and Majdic, 2019). Diagnosis of CCD can be challenging, as the symptoms are similar to other age-related conditions or diseases (Salvin et al., 2010). In addition, there is no definitive antemortem test for CCD, and a diagnosis is typically made through a combination of physical examination, behavioural observation, and exclusion of other conditions (Fefer et al., 2022). Consequently, the prevalence of CCD is unclear, although studies have estimated rates of around 25% of dogs aged between 8 and 12 years, increasing to 70% of dogs over 15 years (Azkona et al., 2009; Neilson et al., 2001; Salvin et al., 2010). Breed does not seem to be a risk factor for the disease (Salvin et al., 2010), however as smaller dogs tend to live longer than larger ones clinical signs of CCD are more often observed in smaller dogs (Schmidt et al., 2015).

Canine Cognitive Dysfunction is characterised by behavioural signs such as changes in social interactions, disorientation in familiar environments, changes in sleep-wake cycles, deficits in learning, memory and toilet training, and changes in anxiety and activity levels (Madari et al., 2015). Affect is not always seen equally across these domains, with one area often being more impacted than another (Azkona et al., 2009; Fast et al., 2013). The exact physiology of CCD is still not fully understood, however signs consistent with the disease include an accumulation of amyloid-beta plaques in the brain (Schütt et al., 2015; Urfer et al., 2021), brain atrophy (Head, 2011), neurofibrillary tangles of the peptide tau (Mihevc and Majdic, 2019), oxidative stress (Rofina et al., 2006), and chronic inflammation (Ozawa et al., 2016). There is no known cure or preventative interventions for CCD. Treatment of the disease is currently focused on alleviating symptoms and improving quality of life. Medications such as selegiline, adrafinil and propentofylline have been used to slow the progression of the disease and improve cognitive function (Campbell et al., 2001; Landsberg, 2005). Other treatments, such as environmental enrichment and dietary changes, have also been shown to have beneficial effects (Milgrama et al., 2004; Nippak et al., 2007).

In humans, the lack of a cure for Alzheimer's has prompted research into non-pharmacological treatments to improve the quality of life for

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https://doi.org/10.1016/j.applanim.2023.106097
Received 1 September 2023; Received in revised form 19 October 2023; Accepted 24 October 2023
Available online 31 October 2023

those living with dementia symptoms (Abraha et al., 2017; Klimova et al., 2019). As dogs demonstrate a natural decline in cognition in older age, have comparable brain structures to humans, and have often been used as a model for Alzheimer's disease research (Mihevc and Majdic, 2019), it is reasonable to investigate if similar interventions may be beneficial in the treatment of CCD. Thus, the purpose of our review is to identify, critically appraise, and map the existing literature on the impact of non-pharmacological treatments for canine cognitive dysfunction. This will be a valuable resource for veterinary practitioners and dog owners.

2. Methods

Our scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)(Tricco et al., 2018) framework as well as the Guidance for conducting systematic scoping reviews by Peters *et al.* (Peters et al., 2015). The first author (TLT) pre-identified a small number of seed papers and relevant databases. In consultation with two collaborating authors (SJH and EJF), initial key search concepts were determined: dog, canine cognitive dysfunction and non-pharmacological. In consultation with a librarian from the University of Adelaide, a logic grid mapping the search terms was constructed, and from this a targeted search strategy was developed. The first author tested and refined the strategy until all authors agreed on the final version. A thorough search of multiple databases was undertaken (see below), as well as a manual search of reference lists. The inclusion criteria for this review are studies that have investigated non-pharmacological treatments for CCD in dogs and are written in English, with further detail on inclusion provided below. The data from the studies will be characterised using established tools and the findings will be synthesised using a narrative approach.

2.1. Protocol and registration

A protocol was written and agreed to by the research team. This was not submitted for publication but used as a guide to ensure a planned approach.

2.2. Eligibility criteria

Studies eligible for inclusion included those conducted in both laboratory and field settings in which non-pharmacological treatments were directly applied to aged dogs diagnosed with CCD or showing signs of cognitive impairment related to aging. For the purposes of this review:

- 'Non-pharmacological' was defined as any intervention not directly involving the administration of registered drugs requiring a veterinary prescription (e.g., nutraceuticals, exercise, training).
- Canine cognitive dysfunction and Cognitive Dysfunction Syndrome were treated as equivalent.
- The study design must include at least one treatment condition, that is, a direct intervention applied to senior dogs
- Outcome parameters of interest included CCD scores using a validated tool, as well as standardised tests used to determine cognitive ability.
- Senior dogs were considered as older than 8 years unless nominated and substantiated in the inclusion criteria of the study.

There were no geographic restrictions regarding study location, but the evidence needed to be published in English (or an English version available). There were no time limitations applied to the review.

2.3. Information sources

Four databases were searched: CAB Abstracts, Web of Science, Scopus and ProQuest. Searches were conducted between October 2022 and January 2023. During the full-text review stage the reference list for each extracted article was looked through for additional relevant items. Grey literature identified through the search process, including unpublished conference proceedings, book chapters, theses and dissertations, and other non-peer reviewed publications were included in the initial data capture.

2.4. Search

The search strategy for each database is shown in Table 1.

All identified articles were then uploaded to Covidence ("Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org,"), a web-based collaboration software platform that streamlines the production of systematic and other literature reviews. Covidence removed all duplicates leaving 2494 for initial screening by title and abstract. Title and abstract screening for relevance was conducted by the first (TLT) and second (KNH) authors based on the terms and conditions outlined in the eligibility criteria. Most commonly studies were removed at this step because the content did not relate to ageing/cognition, the experimental subject was not aged dogs, or the focus was canine assisted therapies.

Articles that moved to full-text screening were assessed by authors' TLT and KNH, and prior to extraction, were reviewed by SJH in the first instance and EJF if there were any that required a fourth opinion/particular expertise.

Table 1
Search strategy terms and conjunctions for each database. The Web of Science strategy was developed and tested first and then adjusted for each database as required.

Database	Search strategy
Web of Science	Dogs (Topic) AND "Non-pharmacological" OR "non-pharmaceutical" OR "Nutraceutical" OR "Supplement" OR "Therap*" OR "Nutrition" OR "Exercise" OR "Sleep" OR "Circadian" OR "Behav*" OR "Enrich*" OR "Learn*" OR "Physio*" OR "Melatonin" OR "Train*" (Abstract) AND "Canine cognitive dysfunction" OR "cognitive dysfunction syndrome" OR "cognitive disorder" OR "cognitive decline" OR "senile" OR "cognit*" (Abstract)
CAB Abstracts	Dogs (Topic) AND "Non-pharmacological" OR "non-pharmaceutical" OR "Nutraceutical" OR "Supplement" OR "Therap*" OR "Nutrition" OR "Exercise" OR "Sleep" OR "Circadian" OR "Behav*" OR "Enrich*" OR "Learn*" OR "Physio*" OR "Melatonin" OR "Train*" (Abstract) AND "Canine cognitive dysfunction" OR "cognitive dysfunction syndrome" OR "cognitive disorder" OR "cognitive decline" OR "senile" OR "cognit*" (Abstract)
Scopus	(TITLE-ABS-KEY (dog) AND TITLE-ABS-KEY ("Canine cognitive dysfunction" OR "Cognitive dysfunction syndrome" OR "Cognitive decline" OR senile OR "cognit*") AND TITLE-ABS-KEY ("Non-pharma*" OR nutraceutical OR supplement OR therap* OR nutrition OR exercise OR sleep AND circadian OR behav* OR enrich* OR learn* OR physio* OR melatonin OR train*)) AND (LIMIT-TO (LANGUAGE, "English"))
Proquest	abstract(dog) AND abstract("Canine cognitive dysfunction" OR "Cognitive dysfunction syndrome" OR "Cognitive decline" OR Senile OR Cognit*) AND abstract(Non- pharmacological OR Non-pharmaceutical OR Nutraceutical OR Supplement OR Therap* OR Nutrition OR Exercise OR Sleep OR Circadian OR Behav* OR Enrich* OR Learn* OR Physio* OR Melatonin OR Train*)

2.5. Data characterisation and extraction

A data extraction template was developed in Covidence (www.covidence.org) and the following information was extracted from each paper: authors, title, year of publication, journal, country in which the study was conducted, aim, study design, population description, type of intervention (category), inclusion/exclusion criteria, number of participants, baseline population characteristics, intervention descriptions, cognitive tests used, number of treatments within each paper and key findings. Only original research papers were included (ie. not reviews or narratives). Exclusion criteria was typically labelled by Covidence as 'wrong' and papers were excluded for a number of reasons. For instance, wrong intervention usually indicated that a pharmaceutical drug had been administered as the treatment. Wrong patient population usually indicated that the treatment had been tested on subjects other than dogs (eg. humans or rats). Wrong study design or wrong outcomes were usually allocated to papers that were focused on better understanding or defining elements of CCD and not attempting to treat the disease.

3. Results

Our search strategy identified 6486 abstracts of which 3991 were duplicates and subsequently removed. After abstract screening of the remaining 2494 studies, 138 records were identified for full-text assessment. Twenty-seven papers were extracted and included in this review. Four additional papers were included post-extraction as found through extracted paper reference lists. This resulted in a total of 31 papers included in this review. Fig. 1 shows the study screening flowchart.

3.1. Study characteristics

Table 2 shows the characteristics of the extracted studies. All studies were published between 2001 and 2022. Overwhelmingly the most

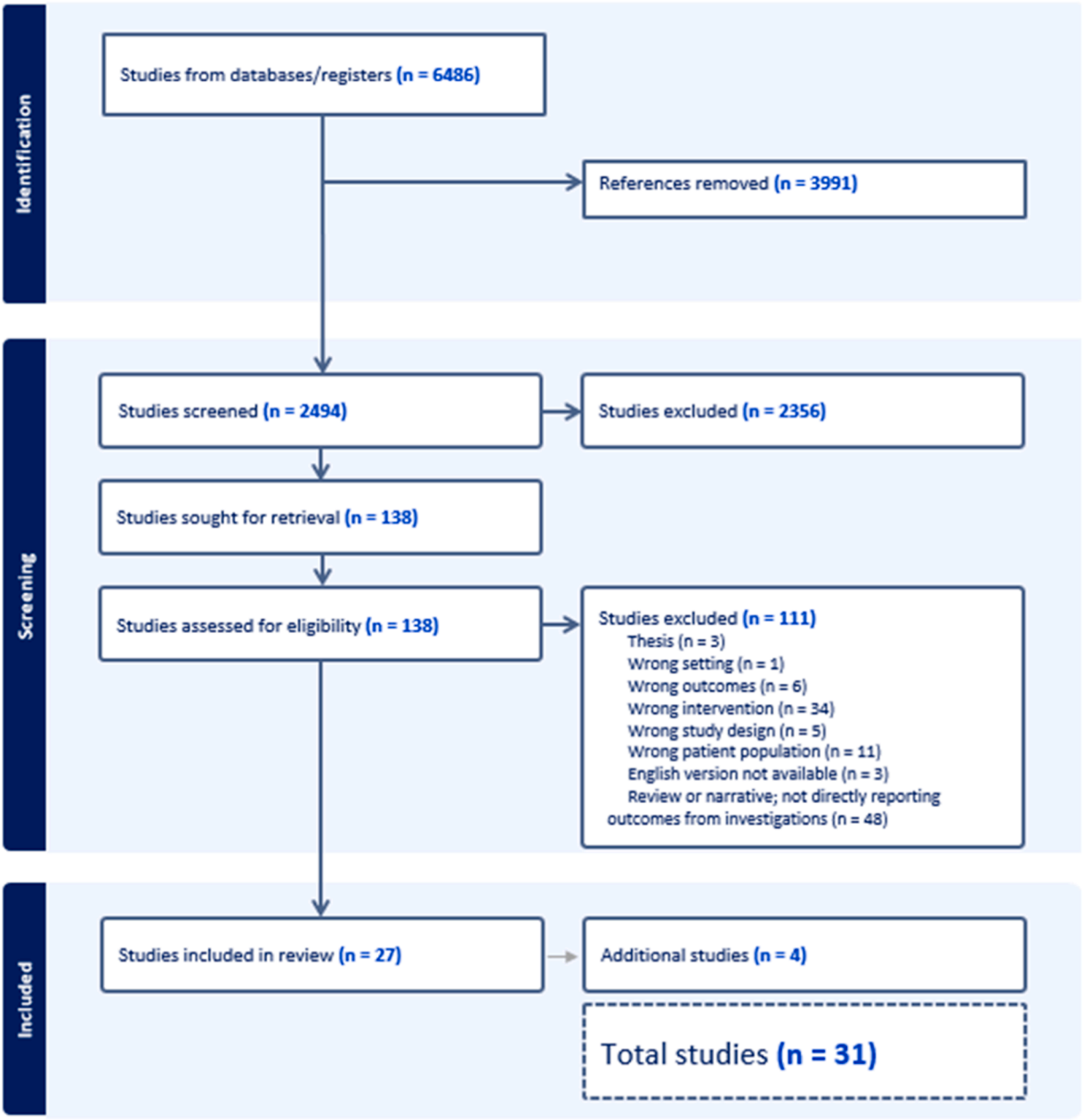

Fig. 1. PRISMA-ScR flow chart produced through Covidence showing the screening process for this review.

Table 2
This table shows key details from all extracted studies in this review. Most studies tested supplements as the intervention, were set in laboratories as randomised control trials and varied in length from as little as 14 days to 3 years. Inclusion and exclusion criteria varied between studies and in some cases was not defined.

Authors	Title	Sample size	Type of intervention	Experimental design	Inclusion/exclusion criteria	Length of intervention	Age range of experimental subjects
Laboratory dogs							
Araujo et al 2008	Improvement of short-term memory performance in aged beagles by a nutraceutical supplement containing phosphatidylserine, Ginkgo biloba, vitamin E, and pyridoxine	9	Supplement/ Diet	RCT Blinded crossover design	Inc – healthy, had previous experience of cognitive tests	70 days	7–12.7 yrs
	Behavioural output measures Delayed stimulus discrimination tests			**Key findings** Supplementation improved short-term memory performance, but the impact decreased with longer delays. However, improved performance was maintained even after discontinuation for 70 days.			
Araujo et al 2022	Sphingolipids and DHA improve cognitive deficits in aged Beagle dogs	24	Supplement/ Diet	RCT Blinded	Ex – declining health, greatest number of non-responses during baseline testing	6 months	6.5–13.9 yrs
	Behavioural output measures Stimulus discrimination test Spatial recognition test Delayed stimulus discrimination test			**Key findings** Supplementation improved cognitive performance in dogs and cats while placebos led to a decline in overall performance.			
Araujo et al 2012	NOVIFIT (NoviSAMe) Tablets improve executive function in aged dogs and cats: implications for treatment of cognitive dysfunction syndrome	30	Supplement/ Diet	RCT Blinded	Inc – adequate health and body condition	55 days	9.2–12.8 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** Novifit had no impact on memory function but reduced errors in reversal learning tasks in both dogs and cats.			
Milgram et al 2007	Acetyl-L-carnitine and alpha-lipoic acid supplementation of aged beagle dogs improves learning in two landmark discrimination tests	12	Supplement/ Diet	RCT Blinded	Inc – dogs aged between 7.6 and 8.8 years, test sophisticated from previous studies	2 months	7.6–8.8 yrs
	Behavioural output measures Spatial recognition test Delayed stimulus discrimination test			**Key findings** Some supplements improved the ability of dogs to learn and remember rules long-term but did not have a significant impact on short-term memory.			
Snigdha et al 2015	Effect of mitochondrial cofactors and antioxidants supplementation on cognition in the aged canine	46	Supplement/ Diet	Allocation to groups balanced for cognitive scoring	Inc - successful acquisition of the pretraining protocol, passing of veterinary health exams	3 years	6.8–8 yrs
	Behavioural output measures Stimulus discrimination test Spatial recognition test Delayed stimulus discrimination test			**Key findings** Aged dogs that received the mitochondrial cofactor enriched diet – co-supplemented with LA and ALCAR but not either of those alone - showed improved delayed recall in the DNMP task. Those supplemented with LA alone showed significant impairments compared with age-matched controls.			
Hadley et al 2017	The oil-rich alga Schizochytrium sp. as a dietary source of docosahexaenoic acid improves shape discrimination learning associated with visual processing in a canine model of senescence	26	Supplement/ Diet	RCT Blinded	Inc - passed veterinary health exam	175 days	8.6–11.1 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** A diet fortified with DHA-rich algae improved healthy brain function in aged dogs, particularly enhancing initial learning of tasks but not long-term recall.			
Pan et al 2010	Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs	24	Supplement/ Diet	RCT	Inc - Passed veterinary health exam, previous cognitive testing experience	225 days	7.5–11.6 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** MCT supplemented group showed significantly better performance on most of the tests than the control group. The more difficult the task the greater supplementation effects shown.			
Pan et al 2018A	Cognitive enhancement in old dogs from dietary supplementation with a nutrient blend containing	87	Supplement/ Diet	RCT Blinded	Inc - completing a pre-training protocol and training on a DNMP task	6 months	9.1–11.5 yrs

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Table 2 (*continued*)

Authors	Title	Sample size	Type of intervention	Experimental design	Inclusion/exclusion criteria	Length of intervention	Age range of experimental subjects
	arginine, antioxidants, B vitamins and fish oil						
	Behavioural output measures Spatial recognition test Delayed stimulus discrimination test			**Key findings** The supplemented group showed significantly better performance than the controls on the second component of the landmark discrimination task, and on reversal learning of an egocentric discrimination task (the more complex tests). The groups did not differ on the other two tests which suggests the beneficial effects are positively linked to task complexity.			
Christie et al 2009	Short-term supplementation with acetyl-L-carnitine and lipoic acid alters plasma protein carbonyl levels but does not improve cognition in aged beagles	29	Supplement/ Diet	RCT Blinded	Inc - successful acquisition of the pre-training protocol and consistent responsiveness during baseline cognitive testing Ex - compromised visual, auditory or motor functioning, one dog removed due to cervical disc disease	273 days	7.8–11.2 yrs
	Behavioural output measures Stimulus discrimination test Spatial recognition test Delayed stimulus discrimination test			**Key findings** Acetyl-L-carnitine alone resulted in increased error scores on spatial tasks, which were reduced when combined with lipoic acid, but the findings were not significant.			
Milgram et al 2004A	Learning ability in aged beagle dogs is preserved by behavioral enrichment and dietary fortification: a two-year longitudinal study	65	Supplement/ Diet Enrichment	RCT	Inc - passed physical and neurological veterinary exams. Also examined by slit-lamp for ocular abnormalities that might have impaired the animals' visual capabilities	2 years	8.05–12.04 yrs 1.95–4.6 yrs
	Behavioural output measures Stimulus discrimination test			**Key findings** After one and two years of treatment the aged, combined treatment group showed more accurate learning than the other aged groups. Discrimination learning was significantly improved by behavioural enrichment. Reversal learning was improved by both behavioural enrichment and dietary supplementation. The fortified food had no effect on the young dogs.			
Milgram et al 2004B	Long-term treatment with antioxidants and a program of behavioral enrichment reduces age-dependent impairment in discrimination and reversal learning in beagle dogs	60	Supplement/ Diet Enrichment	Allocation to groups not clearly defined	Inc - Passed full physical and neurological exam	1 year	8.05–12.6 yrs 1.95–4.9 yrs
	Behavioural output measures Stimulus discrimination test Spatial recognition test			**Key findings** Young dogs performed better in size discrimination learning and reversal tasks than older dogs. The two tasks were improved by both the fortified food and the behavioural enrichment, as well as in the combined (food + enrichment) group.			
Benedetti et al 2019	Effects of chronic supplementation of homotaurine on cognitive processes and spatial cognition in aged dogs: Preliminary results	24	Supplement/ Diet	RCT	Inc - Aged between 10 and 16 yrs Absence of behavioural or clinical conditions that could negatively influence the study	1 year	10–16 yrs
	Behavioural output measures Spatial recognition test			**Key findings** Homotaurine dietary supplementation showed promise in limiting age-related deterioration of learning and memory processes in aged dogs.			
Pop et al 2010	Synergistic effects of long-term antioxidant diet and behavioral enrichment on beta-amyloid load and non-amyloidogenic processing in aged canines	24	Supplement/ Diet Enrichment	Allocation to groups not clearly defined Blinded	Inc – age	2.69 yrs	8.05–12.35 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** Enrichment alone did not affect amyloid-beta, but a combination of antioxidants and enrichment had the most effect on reducing amyloid-beta load in the frontal cortices of aged dogs, correlating with improved cognitive scores.			
Snigdha et al 2012	Effects of diet and behavioral enrichment on free fatty acids in the aged canine brain	24	Supplement/ Diet Enrichment	Allocation to groups not clearly defined	Inc – passed veterinary health examination	>2 yrs	8.05–12.35 yrs
	Behavioural output measures Stimulus discrimination test			**Key findings** Antioxidants plus mitochondrial cofactors either alone or in combination with environmental enrichment attenuates lipid abnormalities in the frontal cortices of aged dogs which correlated to their improved cognitive scores.			
Milgram et al 2002	Dietary enrichment counteracts age-associated cognitive dysfunction in canines	39	Supplement/ Diet	Allocation to groups not well defined	Inc – passed full physical and neurological veterinary exam	6 months	8.5–12.5 yrs 1.95–4.9 yrs

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Table 2 (*continued*)

Authors	Title	Sample size	Type of intervention	Experimental design	Inclusion/exclusion criteria	Length of intervention	Age range of experimental subjects
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** Superior learning by aged dogs on supplemented diet versus aged dogs on control diet – particularly on more difficult tasks. Older animals learned more slowly than the young, making significantly more errors.			
Siwak et al 2005	Chronic antioxidant and mitochondrial cofactor administration improves discrimination learning in aged but not young dogs	39	Supplement/ Diet	RCT	Inc - Previous cognitive testing, passed veterinary exam	1.5yrs	9.5–14 yrs
	Behavioural output measures Stimulus discrimination test Spatial recognition test Delayed stimulus discrimination test			**Key findings** The combined antioxidant-mitochondrial cofactor treatment led to significantly improved performance in aged dogs on the easier discrimination tasks but not on the more complex. Treated aged dogs did not significantly differ from the young. The antioxidant treated group performed better on some tasks than others suggesting a selective improvement rather than general cognitive enhancement.			
Nippak et al 2007	Enhanced spatial ability in aged dogs following dietary and behavioural enrichment	64	Supplement/ Diet Enrichment Exercise	Allocation to groups balanced for cognitive scoring	Inc – passed full physical and neurological veterinary exam	3 years	8.05–12.04 yrs 1.95–4.6 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** Dietary intervention improved delay memory task performance in aged dogs Aged dogs exposed to a combination of cognitive enrichment, increased physical activity and environmental enrichment improved across all cognitive domains Enriched and supplemented aged dogs showed most improvement long term.			
Davis et al 2016	A beta vaccination in combination with behavioral enrichment in aged beagles: effects on cognition, A beta, and microhemorrhages	34	Enrichment Vaccine	Allocation to groups balanced for cognitive scoring	Inc – Overall good health, passed full physical and neurological veterinary exam	20 months	10.5–13.6 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** The combination treatment led to maintenance of learning over time and reduced amyloid-beta, but no benefits to memory were observed.			
Fragua et al 2017	Effects of dietary supplementation with a mixed blueberry and grape extract on working memory in aged beagle dogs	35	Supplement/ diet	Allocation to groups balanced for cognitive scoring	Inc – >8yrs, passed health examination	75 days	8–14.5 yrs
	Behavioural output measures Delayed stimulus discrimination test			**Key findings** The proportion of dogs showing cognitive improvements relative to their baseline level was significantly higher in dogs fed the grape and blueberry extract, regardless of dosage, than in dogs receiving no supplementation			
Milgram et al 2015	A novel mechanism for cognitive enhancement in aged dogs with the use of a calcium-buffering protein	23 (1st study) 24 (2nd study)	Supplement/ diet	Allocation to groups balanced for cognitive scoring	Inc – healthy, had previous testing experience	32 days	9.48–17.33 yrs
	Behavioural output measures Stimulus discrimination test Delayed stimulus discrimination test			**Key findings** The apoaequorin-treated animals showed improved performance on both the discrimination learning and attention tasks			
Pet dogs							
Pan et al 2018B	Efficacy of a therapeutic diet on dogs with signs of cognitive dysfunction syndrome (CDS): a prospective double blinded placebo controlled clinical study	87	Supplement/ Diet	RCT Blinded	Inc - CDS signs as determined by completing a Senior Canine Behaviour Questionnaire and a Canine Medical Health Questionnaire, > 9yrs	90 days	9–16 yrs
	Behavioural output measures Spatial recognition test Delayed stimulus discrimination test Observational			**Key findings** Dogs that were fed the 6.5% MCT diet improved in all 6 categories of CDS signs. Control improved in 4 out of 6. The group on 9% MCT diet only improved if they accepted the diet.			
Pero et al 2019	Effects of a Nutritional Supplement on Cognitive Function in Aged Dogs and on Synaptic Function of Primary Cultured Neurons	22	Supplement/ Diet	RCT	Inc – passed physical and neurological veterinary exam Ex – neurological diseases, endocrinopathies	50 days	10–17 yrs
	Behavioural output measures Stimulus discrimination test Spatial recognition test			**Key findings** No adverse effects on dogs' health and a positive effect on learning. Also showed positive effects on neuronal functions.			

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Table 2 (*continued*)

Authors	Title	Sample size	Type of intervention	Experimental design	Inclusion/exclusion criteria	Length of intervention	Age range of experimental subjects
Osella et al 2007	Canine cognitive dysfunction syndrome: Prevalence, clinical signs and treatment with a neuroprotective nutraceutical	75 (only 8 treated with Senilife)	Supplement/ Diet	Within-subjects	Inc - >7yrs Ex – primary organ failure, neurological signs, living with owner for <1 yr	3 months	>7yrs
	Behavioural output measures Observational			**Key findings** All dogs treated with Senilife showed a significant improvement in cognitive signs after 84 days			
Amano et al 2022	Equine placental extract supplement as a night barking remedy in dogs with cognitive dysfunction syndrome	3	Supplement/ Diet	Case series	Inc - diagnosed with dementia, dog was causing night-time disturbance by barking	14–35 days	14–17 yrs
	Behavioural output measures Observational			**Key findings** Supplement reduced/eliminated night-time barking, reduced laboured breathing, increased time dog spent sleeping, reduced pacing, increased alertness to environment. No adverse effects seen in any participants.			
Reichling et al 2005	Reduction of behavioural disturbances in elderly dogs supplemented with a standardised Ginkgo leaf extract	42	Supplement/ Diet	Pre-test, post-test	Inc - min 6yrs for large dogs, 8yrs for medium, 10yrs for small, good overall health, geriatric signs in at least two domains Ex – poor condition, body temp >39°C, geriatric signs attributed to conditions other than CCD, on a variety of drugs, recent dietary changes	8 weeks	Mean age 11.4 years
	Behavioural output measures Observational			**Key findings** Gingko leaf extract was effective in reducing behavioural disturbances in dogs with CCD without significant side effects.			
Heath et al 2006	Nutritional supplementation in cases of canine cognitive dysfunction - A clinical trial	44	Supplement/ Diet	RCT Blinded	Inc - >8 yrs, in owner's possession for at least 2 months, displaying signs of cognitive decline for at least 1 month, behavioural symptoms of cognitive dysfunction Ex - dogs displaying signs of clinical disease on vet exam, dogs receiving treatment in relation to old age behaviour change (pharmacological and non-pharmacological), dogs exhibiting any behavioural problems relating to disorientation, social interaction, sleep patterns or house training prior to 8 years of age, dogs showing an appreciable level of aggression toward people	56 days	>8yrs
	Behavioural output measures Observational			**Key findings** Dogs receiving treatment were active for an extra 2hrs per day, had less incidences of lack of recognition, and reduced house soiling. Overall, there was a statistically significant improvement in CCD-affected domains between the treatment and placebo groups (in favour of the treatment).			
Dodd et al 2002	Can a fortified food affect the behavioral manifestations of age-related cognitive decline in dogs?	125	Supplement/ Diet	RCT Blinded	Inc - >7yrs, adequate health and body condition, consistently exhibit at least two characteristics of CCD (defined) Ex – concurrent medical conditions, received steroids or anti-inflammatory medicines in 7 days prior, pregnant, receiving anti-inflammatory supplements	60 days	7–20 yrs
	Behavioural output measures Observational			**Key findings** During the feeding period significant improvements occurred in all five DISHA categories for the supplemented group, and in disorientation and sleep pattern categories for the control group. At the completion of feeding period there were significant differences between groups, with the supplemented group improving in the categories of interaction and activity, and improvement in family recognition, animal recognition, agility and compulsive behaviours.			

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Table 2 (*continued*)

Authors	Title	Sample size	Type of intervention	Experimental design	Inclusion/exclusion criteria	Length of intervention	Age range of experimental subjects
Chapagain et al 2020	Behavioural and cognitive changes in aged pet dogs: No effects of an enriched diet and lifelong training	94	Supplement/ Diet	RCT Blinded	Inc – passed physical and neurological veterinary exam, any level of CCD (including no signs) as determined by CCDR questionnaire Ex - dogs with changes in mobility suspected to be due to osteoarthritis or other underlying painful conditions, dogs with moderate to severe impairment of visual or auditory capacity	12 months	6.1–14 yrs
	Behavioural output measures Mixed battery			**Key findings** Enriched diet or lifelong training did not significantly affect behavioural and cognitive measures.			
O'Brian et al 2021	Effects of a four-week group class created for dogs at least eight years of age on the development and progression of signs of cognitive dysfunction syndrome	86	Enrichment Training	Allocation to groups not clearly defined	Inc - >8yrs old, no CCD and all levels of CCD via DISHAA Ex - history/anticipation of showing aggression towards people	12 months	8–16 yrs
	Behavioural output measures Observational			**Key findings** Within class group CCD scores did not significantly differ between any time points. Within non-class group CCD scores were significantly higher at 12 months than 6 months. This suggests that participation in classes mitigated the progression of CCD.			
Lee et al 2022	Dietary supplemented anthocyanin reduced serum amyloid beta oligomers and improved cognitive dysfunction scores in elderly dogs	9	Supplement/ Diet	Pre-test Post-test	Inc - >7yo, passed physical and neurological veterinary exam, any level of CCD determined by guardian questionnaire	12 weeks	7–14.4 yrs
	Behavioural output measures Observational			**Key findings** Cognitive dysfunction score and serum amyloid-beta oligomers marker levels were significantly reduced after 90 days. No change in weight, body temperature, heart rate or respiratory rate. Inflammation and antioxidant levels were slightly, but not significantly, changed.			
Rème et al 2008	Effect of S-Adenosylmethionine tables on the reduction of age-related mental decline in dogs: a double-blinded, placebo-controlled trial	36	Supplement/ diet	RCT Blinded	Inc - >8yrs, detection of at least two behavioral problems relating to old age (these were defined) present for at least one month Ex – primary neurologic disease, severe sensory decline, heart failure, renal failure, diabetes, clinical hypothyroidism, hypercorticism, cancer, infectious disease.	8 weeks	7–15 yrs
	Behavioural output measures Observational			**Key findings** Dogs treated with SAMe showed greater improvement in activity and awareness. The aggregate mental impairment score was reduced by more than 50% in 41.2% and 15.8% of dogs treated with SAMe and placebo respectively after 8 weeks.			
RCT = Randomised control trial	Inc = Inclusion criteria Ex = Exclusion criteria						

common treatment or intervention was a supplement or enriched diet (94%). Twenty studies were conducted on laboratory dogs (65%) and 11 studies (35%) on pet dogs. Most studies had sample sizes less than 50 and used randomised control trial experimental designs. Thirteen studies included multiple treatments, often testing interventions on their own and then in conjunction with each other (e.g., supplement; enrichment; supplement + enrichment) or varying dosages. In total, 57 treatments were included in the 31 papers. Less than half (13) of the studies specified that the experimenters were blinded in their experimental design. Inclusion and exclusion criteria varied between studies and were often not well described. Fourteen studies were conducted in Canada, eight in the United States of America, three in Italy, one each in Switzerland, Japan, United Kingdom, Korea, Austria and France, Belgium and Spain (these three combined in one study).

3.2. Participant characteristics

There were a total of 1298 individual experimental subjects across all 31 studies. The majority of studies were undertaken on laboratory dogs, with beagles the most common breed tested. Where pet dogs were studied the breeds included were often not stated. Four studies included young dogs as a comparator with ages ranging from 2.0 to 4.9 years. All other studies singularly tested senior dogs older than 6 years. The inclusion and exclusion criteria for participants in each study varied greatly. Some papers did not define their inclusion criteria beyond an age limit and the dog being generally healthy, while others detailed a rigorous process including veterinary diagnosis of CCD, physiological and behavioural examination, and the use of validated questionnaires. Only 6 studies specifically tested for the presence of CCD, all others

ranked their participants according to their cognitive abilities against their success on cognitive tests.

A summary of the key findings from the extracted papers is shown in Table 2. Almost all studies showed some level of efficacy in their intervention. Two studies found no improvement in dogs supplemented singularly with lipoic acid or acetyl-L-carnitine, with a positive effect only seen when given together (Christie et al., 2009; Snigdha et al., 2016). One study found that enrichment alone did not reduce amyloid-beta load in the brain but was efficacious when combined with an antioxidant-based supplement (Pop et al., 2010). A single study found training slowed the progression of the disease (O'Brian et al., 2021).

3.3. Intervention characteristics and effects

The results of the studies showed variability in efficacy of the interventions with some being task-specific (i.e., they showed improvement in one cognitive domain, but not in others). Most interventions were supplement or diet based (29 papers; 94%), seven used some type

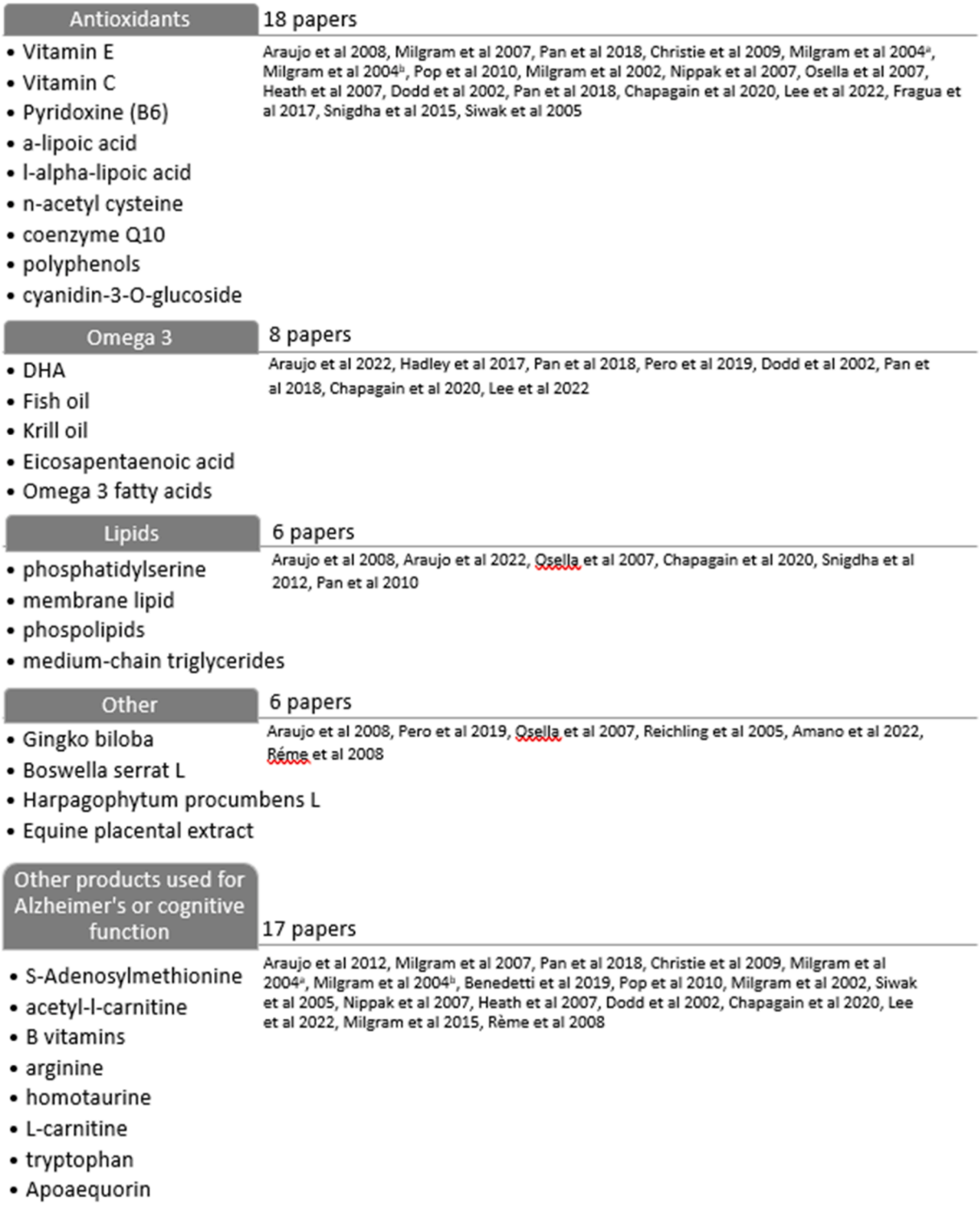

Fig. 2. Types of dietary supplements used in the included studies.

of environmental enrichment (23%), and one used a training intervention (0.03%) (Table 2). Dietary changes, focusing on the use of antioxidant-rich diets and omega-3 fatty acid supplementation known for their neuroprotective effects (Lee et al., 2020), were shown to reduce oxidative stress and improve cognitive function (Amano et al., 2022; Araujo et al., 2012, 2008, 2022; Benedetti et al., 2019; Chapagain et al., 2020; Christie et al., 2009; Dodd et al., 2003, 2002; Hadley et al., 2017; Heath et al., 2007; Milgram et al., 2007, 2002; Milgrama et al., 2004; Milgramb et al., 2004; Nippak et al., 2007; Osella et al., 2007; Pan, Kennedy, et al., 2018; Pan, Landsberg, et al., 2018; Pan et al., 2010; Pero et al., 2019; Pop et al., 2010; Reichling et al., 2006; Siwak et al., 2005; Snigdha et al., 2012, 2016). Fig. 2 shows the categories of ingredients for the supplements tested.

Using a combination of ingredients showed positive effects more consistently than single interventions, with increased cognitive impairment even shown in some instances in response to a single constituent (Christie et al., 2009; Snigdha et al., 2016). Improvements in ability were often seen in one domain or at one task but not another (Davis et al., 2017; Pan, Kennedy, et al., 2018; Siwak et al., 2005). For example, the supplement Novifit® had no impact on memory function but reduced errors in reversal learning (Araujo et al., 2012). Another combined supplement led to improved performance on easier discrimination tasks but not on the more complex (Siwak et al., 2005). In a third study, supplemented dogs showed improvements in all five DISHA categories (disorientation, interactions, sleep-wake cycles, house soiling, anxiety), but the control group also had improvements in the sleep and disorientation categories (Dodd et al., 2002).

Seven studies investigated the effects of environmental enrichment on CCD (Davis et al., 2017; Milgrama et al., 2004; Milgramb et al., 2004; Nippak et al., 2007; O'Brian et al., 2021; Pop et al., 2010; Snigdha et al., 2012). These interventions included providing toys, increased social interactions with conspecifics, regular exercise, and ongoing cognitive testing. Some studies reported improvements in cognitive function, including increased learning ability, improved memory, and reduced anxiety from enrichment alone (Milgrama et al., 2004; Milgramb et al., 2004), but others suggested the pairing of enrichment and dietary supplementation was required to produce optimum results in improving cognitive function and reducing CCD symptoms (Davis et al., 2017; Milgrama et al., 2004; Milgramb et al., 2004; Nippak et al., 2007; Pop et al., 2010; Snigdha et al., 2012). All but one of these studies was undertaken in a laboratory environment making it difficult to draw definitive conclusions for the application to pet dogs who already live in a highly enriched environment.

Only one study tested training as an intervention for CCD (O'Brian et al., 2021). In this study dogs participated in a 4-week group training class, and when tested, their CCD scores were not significantly different at 3 months post-treatment and 12 months post-treatment. In contrast the control group did see a significant increase in CCD scores over that same time period suggesting that the training may have slowed the progression of the disease.

3.4. Main outcome measures

Cognitive ability was measured using a variety of tests, veterinary diagnosis, and owner questionnaire. The most frequent measure was a discrimination and reversal learning task, followed by a delayed non-matching to position task. The tests used to measure changes in cognitive responses were categorised as: stimulus discrimination tests (including discrimination learning and reversal, selective attention, contrast sensitivity and oddity tasks), spatial recognition tests (including spatial discrimination, landmark discrimination, egocentric and spatial navigation tests), delayed stimulus discrimination tests (including delayed non-matching to position, object recognition memory and delayed non-matching to sample tasks), mixed battery and observational (including pet owner questionnaire and veterinary diagnosis) (Fig. 3). Observational tests were used solely with pet dog participants, and in only one study were they paired with a standardised cognitive test (Pan, Landsberg, et al., 2018). The behavioural tests used in each study can be found in Table 2.

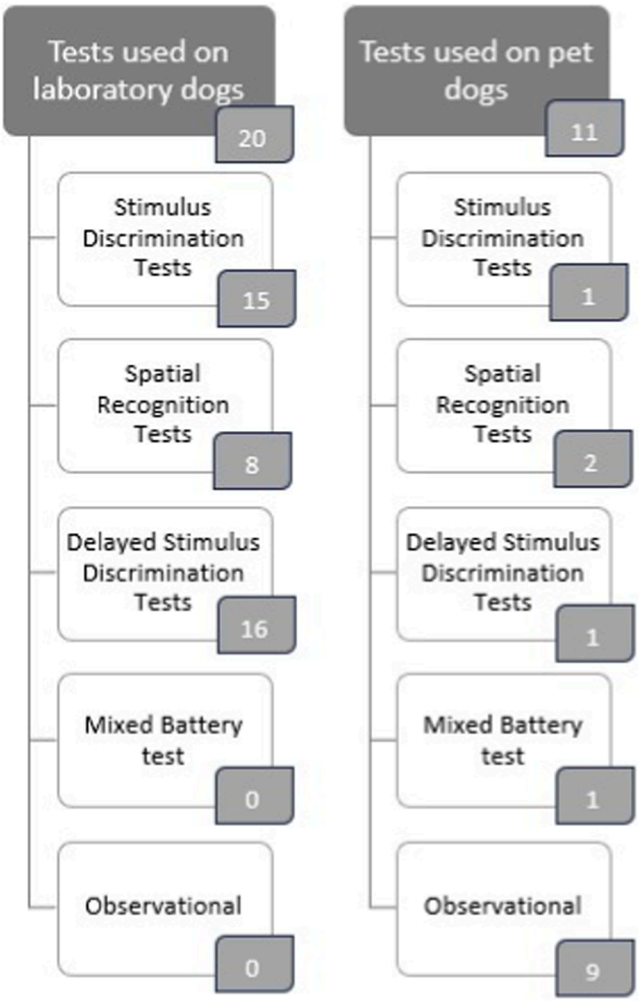

Fig. 3. The cognitive test categories used to determine the range of cognitive ability in experimental subjects before and after treatment. Tests were grouped by the authors into five categories: stimulus discrimination, spatial recognition, delayed stimulus discrimination, mixed battery and observational. The numbers indicate how many papers used these tests. Pet dog studies relied mostly on observational tests, while laboratory studies focused on tests which showed changes in learning and memory.

4. Discussion

Our review reveals that most research effort into non-pharmacological treatments has been directed towards supplement/diet interventions for ameliorating the signs of CCD, leaving a significant knowledge gap for how other non-pharmacological interventions may work in conjunction with, or as a replacement for, supplement/diet treatments. A review of the literature relating to non-pharmacological interventions in humans with cognitive impairment and early-stage dementia reveals a focus on cognitive training in the early stages of the disease being most beneficial (Rodakowski et al., 2015), which may point to similarly successful interventions for dogs. Our review also shows that most studies looked at improvements in memory and learning, with very few looking at other signs of CCD, such as changes in social interactions and sleep-wake cycles. This is of interest because our previous research reported significant burden of care in owners caring for dogs with CCD, with disrupted sleep the most difficult thing to live

with (Taylor et al., 2023).

Studies involving senior dogs must grapple with how best to account for the number of co-morbidities commonly present in this population. Investigations into canine cognitive dysfunction are no exception, but they are also impeded by the lack of a definitive way to diagnose the syndrome. How, and even if, researchers have determined if CCD is present in the studies reviewed here is often unclear or distinctly different to each other (Table 2). Further, twice as many studies in this review were undertaken on laboratory dogs versus in pet dogs, and using cognitive testing procedures that are difficult to replicate with pet dogs outside a laboratory. This makes comparisons, generalisations and applications of the research challenging for both clinicians and owners.

The links between progression and severity of CCD and levels of associated biomarkers, such as amyloid-beta and tau proteins, remain unclear (Dewey et al., 2019; González-Martínez et al., 2011; Schutt et al., 2015), this in turn makes developing targeted treatments and measuring their efficacy problematic. Some studies in this review reported improvements in cognitive function, including increased learning ability, improved memory, and reduced anxiety from enrichment alone, but others suggested the pairing of enrichment and dietary supplementation was required to produce optimum results (Davis et al., 2017; Milgrama et al., 2004; Milgramb et al., 2004; Nippak et al., 2007; Pop et al., 2010; Snigdha et al., 2012). As well as reducing signs of CCD, regular exercise has been shown to improve memory consolidation in aging dogs (Snigdha et al., 2014), the rate of CCD progression, and the likelihood of CCD occurring (Bray et al., 2022). However, the optimal type and duration of exercise, and the benefits of combining it with other non-pharmacological interventions for CCD are still unclear as in all studies, exercise was combined with other enrichment activities rather than a stand-alone intervention (Davis et al., 2017; Milgrama et al., 2004; Milgramb et al., 2004; Nippak et al., 2007; Pop et al., 2010; Snigdha et al., 2012). Additionally, exercise used as enrichment was limited to experiments in a laboratory environment and ranged from 15 to 30 minute walks twice a week. Most healthy and mobile pet dogs enjoy more frequent and longer outings than this (Christian et al., 2013), as well as living in a more enriched environment, further limiting the applicability of their findings.

Neuropsychological tests mostly used in laboratory settings (Fig. 3) are objective and comparable, but often require extensive pre-testing training to acquire the task. Further, the laboratory studies included in our scoping review tested dogs up to six times a week, and for months at a time, a methodology not easily replicable in a pet dog population. There were also several studies where the experimenters were not blinded to the treatment of the dogs they were testing (Benedetti et al., 2019; Davis et al., 2017; Milgram et al., 2015, 2002; Milgrama et al., 2004; Milgramb et al., 2004; Nippak et al., 2007; Osella et al., 2007; Pan et al., 2010; Pero et al., 2019; Siwak et al., 2005; Snigdha et al., 2012, 2016), meaning the potential for experimenter bias cannot be ruled out.

This scoping review has several strengths. The review followed a systematic approach and utilised established tools to assess the quality of the studies. The comprehensive search strategy used in the review aimed to minimise the risk of missing relevant studies. One limitation of this scoping review is that only English-language studies were included. This may have resulted in some relevant studies being missed. In addition, while an effort was made to be comprehensive in our search strategy, it is possible that some relevant studies were not identified. The findings of our review have made it clear that future investigations need to find a way to bring together the robust and objective nature of neuropsychological tests, with the ease and accessibility of observational surveys. It is also critical that CCD is well defined in the study methodology so that clear comparisons between senior dogs with and without the disease can be made.

Overall, the results of this scoping review suggest that non-pharmacological interventions may be beneficial for the treatment of CCD in dogs. While the results are optimistic, more research is needed to determine the most effective interventions and optimal durations of treatment. This scoping review will be a valuable guide for future research in this area, as well as for veterinary practitioners and dog owners looking for non-pharmacological interventions to alleviate the signs of canine cognitive dysfunction.

5. Conclusion

Research into non-pharmacological interventions to alleviate the signs of canine cognitive dysfunction is focused mainly on dietary supplementation as an input measure, and improvements in learning and memory as output measures. Broader testing of treatments should be considered for future research, as well as looking at other domains affected by CCD. Most studies in this review were undertaken on laboratory dogs and whether the findings translate to pet dogs is difficult to predict as the testing procedures are not user-friendly or accessible for most pet dog owners. This is an area of research that can have positive implications for animal welfare, burden of care, and clinical practice.

Statement of ethics

This scoping review did not require approval from the University of Adelaide ethics committees.

CRediT authorship contribution statement

Susan J Hazel takes overall responsibility for the accuracy and authenticity of the research. Tracey L Taylor chose the topic, and the scientific question was refined with the input of all authors. Tracey L Taylor and Kimberley N Handley were jointly responsible for the data screening. Tracey L Taylor was responsible for the drafting of the manuscript and data analysis. Editing of the document and overall guidance of the project was provided by Susan J Hazel and Eduardo J Fernandez. All authors were involved in addressing the revisions required by reviewers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Thank you to the Animal Behaviour, Welfare and Anthrozoology Lab (ABWAL) for their support and guidance in the production of this manuscript.

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