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Low-carbohydrate and ketogenic diets: a scoping review of neurological and inflammatory outcomes in human studies and their relevance to chronic pain

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Abstract

Dietary restriction of carbohydrate has been demonstrated to be beneficial for nervous system dysfunction in animal models and may be beneficial for human chronic pain. The purpose of this review is to assess the impact of a low-carbohydrate/ketogenic diet on the adult nervous system function and inflammatory biomarkers to inform nutritional research for chronic pain. An electronic database search was carried out in May 2021. Publications were screened for prospective research with dietary carbohydrate intake <130 g per day and duration of ≥2 weeks. Studies were categorised into those reporting adult neurological outcomes to be extracted for analysis and those reporting other adult research outcomes. Both groups were screened again for reported inflammatory biomarkers. From 1548 studies, there were 847 studies included. Sixty-four reported neurological outcomes with 83% showing improvement. Five hundred and twenty-three studies had a different research focus (metabolic $n = 394$, sport/performance $n = 51$, cancer $n = 33$, general $n = 30$, neurological with non-neuro outcomes $n = 12$, or gastrointestinal $n = 4$). The second screen identified sixty-three studies reporting on inflammatory biomarkers, with 71% reporting a reduction in inflammation. The overall results suggest a favourable outcome on the nervous system and inflammatory biomarkers from a reduction in dietary carbohydrates. Both nervous system sensitisation and inflammation occur in chronic pain, and the results from this review indicate it may be improved by low-carbohydrate nutritional therapy. More clinical trials within this population are required to build on the few human trials that have been done.

Key words: **ketogenic diet: low-carbohydrate: human: neurological: beta-hydroxybutyrate: inflammation: nervous system: chronic pain**

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Introduction

Adoption of a low-carbohydrate diet (LCD) or ketogenic diet (KD) is gaining popularity as a nutritional therapy for many dysfunctions, including those within the nervous system[1–3]. Both diets focus on the restriction of dietary carbohydrate. An LCD typically reduces intake to below 130 g per day, with a KD further reducing intake to below 50 g per day to induce nutritional ketosis[4] not necessarily achieved with an LCD.

Ketosis is the elevation of ketones in the blood, with a therapeutic KD generally in the range of 0·5–3·0 mmol/l from a reduction in carbohydrate to <50 g per day[5]. The production of ketone bodies from fat oxidation can influence neurons in several ways: as an alternate fuel source with potential efficiency gains and reduced oxidative stress compared with glucose metabolism, as a regulator of neurotransmitter production and clearance, as a signalling molecule promoting neuroprotection, and as an epigenetic modulator to up-regulate gene expression of antioxidant, mitochondrial and anti-inflammatory functions[4,6,7]. As such, ketones have a dual action, both as a fuel source assisting with bioenergetic stability and a signalling molecule regulating many pathways within the nervous system.

An LCD allows for up to 130 g of carbohydrate per day but does not necessarily produce the same level of fat oxidation and may not result in blood ketone elevation. Despite this, smaller reductions in carbohydrate intake still produce favourable metabolic consequences. These include reducing high blood glucose levels that can sensitise sensory neurons and stimulate pro-inflammatory pathways via receptors and channels on the neuron and microglia[8–11]. Overall, whether the mechanism is glucose reduction, ketone formation or a synergistic relationship between them, the impact of an LCD or a KD on the nervous system is potentially favourable.

Chronic pain is characterised by increased sensitivity within the nervous system and an inflammatory profile[12,13] and as such may respond to an LCD or a KD. There is limited research on how low-carbohydrate nutrition influences neurobiology in this population. We have recently reported relevant pre-clinical research which identified 170 animal model studies using a ketogenic diet to produce changes within the nervous system[7]. These studies investigated the mechanisms reported to occur with nutritional ketosis and how these alter nervous system function, with fourteen broad mechanistic themes emerging. These included: (a) metabolic, energetic and biochemical changes, (b) restoration of cortical excitability to homoeostatic levels,

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(c) gene regulation, (d) improved mitochondrial function and number, (e) reduced neuroinflammation, (f) adaptive neuroplasticity, (g) neurotransmitter and synaptic regulation, (h) reduced oxidative stress and (i) activation of signalling pathways. We have also more recently identified a significant and clinically meaningful reduction in reported pain of patients undergoing a whole-food ketogenic diet intervention in a pilot clinical trial[14].

We lacked the capacity to investigate potential neurological mechanisms in that pilot and as such conducted this scoping review. The primary aim of this scoping review was to identify any clinical trials that report changes in adult nervous system function and report outcomes that may be relevant to drivers of chronic pain. The secondary aim was to more broadly identify clinical trials across any research area that report changes in inflammation in response to an LCD or a KD. As such, this scoping review is a more comprehensive approach than other recent neurological reviews that limited their focus to particular diseases or focused on paediatric populations[1,15–17]. It also considers LCD/KD research focused on other body systems or populations (such as metabolic studies or athletes) that report on how the diet influences inflammatory biomarkers.

Methods

Protocol

The primary research question for this review was: 'How does an LCD or a KD influence the human adult nervous system?', with the secondary research question being 'Does an LCD or a KD influence inflammatory processes?'. Relevant items from the scoping review protocol and PRISMA-ScR checklist from the Joanna Briggs Institute[18,19] were used as the framework. Studies were reviewed in three phases. Phase one captured all publications reporting a human ketogenic diet that met the criteria for daily carbohydrate intake, research type and diet duration. Phase two sorted the retrieved papers into either research reporting adult neurological outcomes for the primary analysis or allocated the remaining studies into categories based on reported research focus. Research papers on paediatric populations that met the eligibility criteria were also grouped to allow for simple quantification but not further analysed. Phase three re-examined all adult papers from phase two for studies reporting common inflammatory biomarkers. The purpose of this broad approach was to avoid missing studies with a different research focus that also reported a neurological or inflammatory outcome, to establish the breadth of research in the neurological area within the context of all ketogenic diet research, and to quantify the extent of ketogenic research in human adult populations.

Eligibility criteria

For the first screen, studies were included if they met the following criteria: (a) human studies that reported a low-carbohydrate diet (LCD) (≤130 g per day and/or <26% of total energy intake (TEI)) or ketogenic diet (KD) (≤50 g per day and/or <15% of total energy intake)[20], (b) the LCD/KD was an intervention, (c) the diet lasted ≥14 days to allow for adaptation to the new diet and (d) the study design was prospective (observational prospective cohorts where the KD/LCD was a treatment, or experimental, longitudinal pre–post intervention trials including randomised controlled trials). Full texts were reviewed if the abstract did not contain this information. Studies were excluded if they: (a) were single case reports, (b) were retrospective reviews, (c) were cross-sectional or associational studies, (d) used exogenous ketones rather than diet, (e) were reviews, commentaries, letters or conference papers, or (f) were not in English where the required information was not in the abstract (Fig. 1).

For the second screen, studies were then sorted into three groups: (a) any research on adult populations reporting objective outcomes related to nervous system function, pain, cognitive functioning or psychological outcomes (including mood, anxiety, depression and cognitive processing, but not food cravings or hunger); (b) other adult studies which were categorised by research area: metabolic, cancer, sports/performance, general, gastrointestinal or neurological studies with non-neurological outcomes (for quantification, but did not have data extracted); or (c) paediatric papers (for quantification, but did not have data extracted). Many studies evaluate the effect of a low-carbohydrate or ketogenic diet on child and adolescent development. As this was not the focus of this study, paediatric studies were not included for data extraction to eliminate this confounding variable. We do, however, report the number of studies retrieved.

The third screen searched the two adult groups for any research that reported changes in common biomarkers associated with increased inflammation, including reactive oxygen species (ROS), oxidative stress, C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α), leptin, interleukin (IL)1, 6 or 8, or decreased inflammation (adiponectin, fibroblast growth factor 21 (FGF-21), IL10). A concise summary of the PICOS criteria can be found in Table 1.

Information sources and search strategy

An electronic database search including Medline, EMBASE, Cochrane Library for controlled trials, AMED via OVID, CINAHL via EBSCO, Web of Science and PubMed was carried out on 24 May 2021 and included publication dates from database inception to search date. The search targeted any reference to an LCD or a KD intervention using the terms 'ketogenic', 'Atkins', 'carbohydrate-restricted diet' or 'low-carbohydrate diet'. Additional searches included Google Scholar to check identified articles 'cited by' and 'related articles' links, and reference checks on identified articles with subsequent hand search for these and inclusion if they met the criteria. Retrieved references were downloaded into EndNote reference management software (Endnote X7·7·1, Thomson Reuters 2016) and then imported using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

Study selection and screening

Duplicates were removed, then titles and abstracts were assessed against the eligibility criteria in Covidence by two reviewers independently (R.F. and T.F.). Full texts of identified studies were then screened and categorised by RF. Studies

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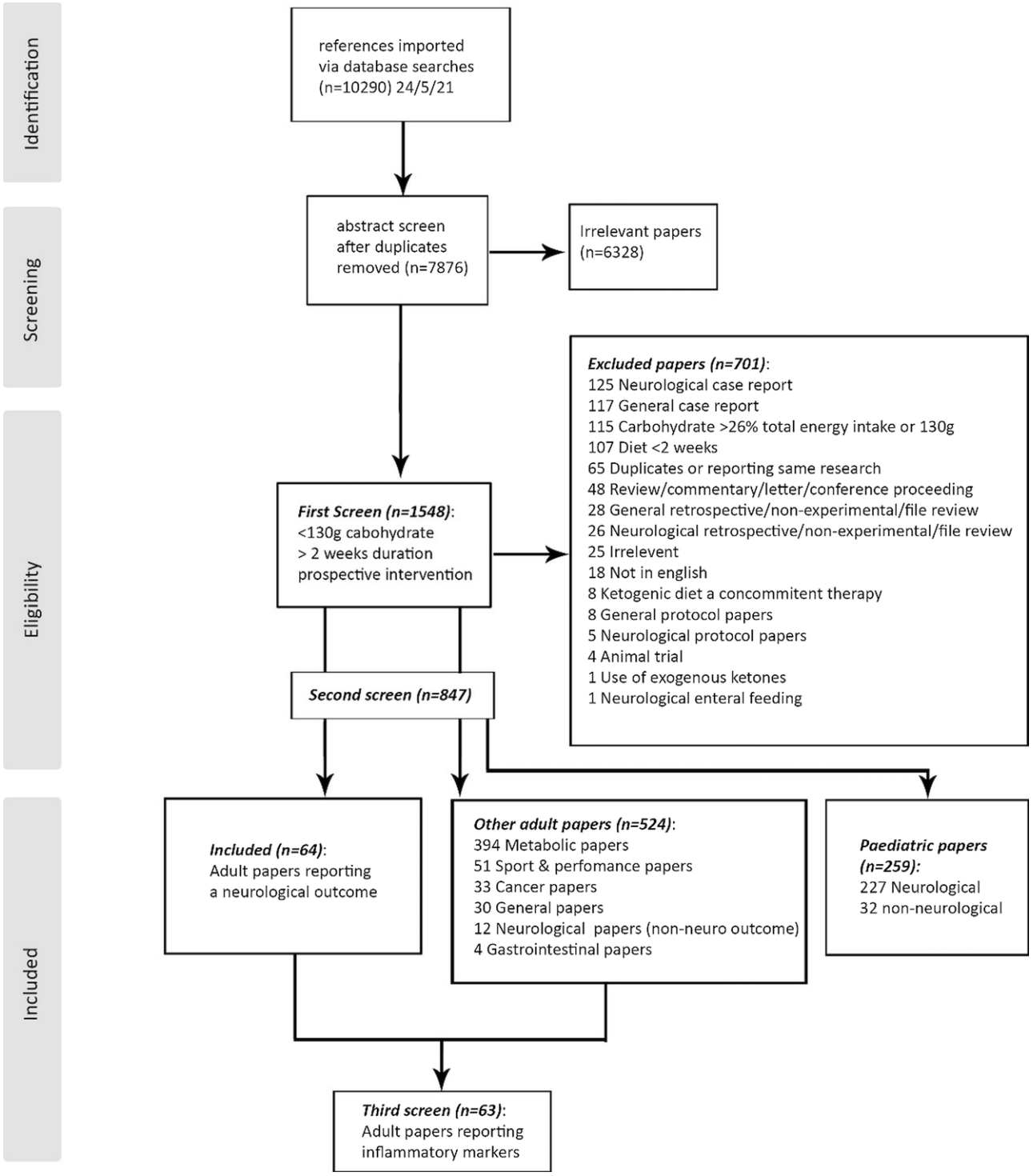

Fig. 1. Inclusion/Exclusion flow chart.

combining paediatric and adult subjects were included if the data identified the adult results of interest separately or if the mean/median age was ≥18 years. Studies included in the second phase were imported into Endnote with their full reference and abstract. Then the inflammatory biomarker search terms were used to extract any study with these terms in any reference field.

Data items

The primary outcome of interest was changes in adult nervous system function (such as excitability, seizure frequency/duration/magnitude, nerve conduction, neuroinflammation, cognitive function or psychological changes). Additional data extracted included: author, study title, year of study, trial type,

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Table 1. PICOS criteria for inclusion and exclusion of studies

Criteria	Phase/Screen 1	Phase/Screen 2	Phase/Screen 3
Participants	Any adult population Any paediatric population (for quantification, not data extraction)	Any adult population	Any adult population
Intervention	Low-carbohydrate diet (<130 g per day and/or <26% of total energy intake lasting ≥14 days	Low-carbohydrate diet (<130 g per day and/or <26% of total energy intake lasting ≥14 days	Low-carbohydrate diet (<130 g per day and/or <26% of total energy intake lasting ≥14 days
Comparator	Any comparator was considered	Any comparator was considered	Any comparator was considered
Outcome	All outcomes	1. Any nervous system function for data extraction 2. Other outcomes categorised for quantification but not extraction.	Any inflammatory biomarkers
Study design	Prospective cohorts where the diet was a treatment, or experimental, longitudinal pre–post intervention trials including randomised controlled trials	Prospective cohorts where the diet was a treatment, or experimental, longitudinal pre–post intervention trials including randomised controlled trials	Prospective cohorts where the diet was a treatment, or experimental, longitudinal pre–post intervention trials including randomised controlled trials

diet description, enrolment/completion numbers for the LCD/KD, comparator diet if applicable, age of participants and weight loss. These data items were repeated for inflammatory biomarkers.

Data charting process and synthesis of results

An excel sheet was used to compile extracted data items and generate a table of primary outcomes reported. Primary outcomes were reviewed and summarised by R.F. on the basis of whether the LCD/KD produced positive, neutral or negative outcomes, and whether the comparator diet also had significant positive outcomes.

Results

A systematic database search on 24 May 2021 retrieved 7876 publications after the removal of duplicates. Title and abstract screen extracted 1548 papers that were potentially eligible, with full text review excluding 701. The included studies were sorted into publications reporting a neurological outcome ($n = 64$), other adult research with a different focus ($n = 524$: metabolic $n = 394$, sport/performance $n = 51$, cancer $n = 33$, general $n = 30$, neurological with non-neuro outcomes $n = 12$, or gastrointestinal $n = 4$), or paediatric papers (paediatric neurological $n = 227$, other $n = 32$). A re-screen of all included papers excluding the paediatric populations ($n = 588$) for the key inflammatory terms retrieved sixty-three studies reporting on inflammatory outcomes (Fig. 1).

Characteristics of included studies

Neurological outcomes. The primary outcome of interest was results pertaining to adult nervous system function. Of the sixty-four publications reporting neurological outcomes (Table 2), twenty-two provided measures on cortical excitability (nineteen epilepsy studies[21–39], one narcolepsy[40], one glucose transporter-1 deficiency syndrome[41] and one general physiology[42]). Additional categories included fifteen psychological publications (eleven mood and/or cognition[43–55], one schizophrenia[56] and one orexinergic system[57]), twelve neurodegenerative disease publications (three Alzheimer's disease[58–60], three multiple sclerosis[61–63], three cognitive impairment[64–66] and three Parkinson's disease[67–69]), seven migraine publications[70–76], two musculoskeletal studies (one hip osteoarthritis/pain[77] and one knee osteoarthritis/pain[78]), two autonomic nervous system studies (one sympathetic activation[79] and one heart rate variability[80]), two nervous system bioenergetics papers (one cerebral glucose uptake[81] and one cerebral blood flow[82]), one spinal cord injury paper[83] and one traumatic brain injury paper[84]. Half of the included studies were randomised controlled trials (RCT) ($n = 32$), thirty were prospective single or two-arm studies, and two were case series[41,70]. Time on the diet ranged between 2 weeks[42,56] and 112 weeks[23] (mean 18 weeks, standard deviation (SD) ± 19), with fifty-seven studies (90%) considered KD <50 g carbohydrate per day, four considered LCD[63,77,79,82] (between 50 g and 130 g), two unclear[56,70] and one including LCD and KD[55]. Overall, a total of 1729 participants commenced an LCD or a KD that

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Table 2. Reported neurological outcomes from human studies utilising low-carbohydrate (LCD) or ketogenic (KD) diets $n = 64$

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm n = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
CORTICAL EXCITABILITY ($n = 22$)									
Randomised controlled trials									
Kishk[26]	2021	Outpatient clinic, epilepsy, median 20 (17–30) years	RCT (KD with two arms, or control sham meals)	2:1 (phase 1) 2:1 or 3:1	1 month 2 months	40/31 (78%) 31/29 (94%)	*Ad libitum*	N	Significant improvement in seizure severity and frequency for both ketogenic diets but not for the sham diet. (positive)
Kverneland[30]	2018	Tertiary centre, epilepsy, 36 (32–40) years	RCT (KD or habitual)	16 g	12 weeks	37/24 (65%)	*Ad libitum*	BL: 78 kg, loss −4 kg (95% CI −6, −2)	Median difference for the sum of seizures between baseline and intervention was −1·0 (−13·7, 8·8) for the KD group and +4·5 (−4·8, 33·5) for the habitual diet. (positive)
McDonald[32]	2018	Epilepsy Centre, epilepsy, 32 ± 14 years	RCT cross-over (KD or KD + supplement)	20 g	1 month each arm	80/56 (70% at 1 month) 80/49 (61% at 2 months)	*Ad libitum*	N	13/25 ≥50% seizure reduction on KD alone at 1 month, 10/22 ≥50% seizure reduction on KD alone at 2 months, 10/12 at 6 months. (positive #)
Zare[39]	2017	Neurology clinic, epilepsy, 29 ± 9 years	RCT (KD + AEDs or AEDs only	15 g	2 months	34/22 (65%)	*Ad libitum*	BL BMI: 23 ± 3·6 kg/m^2, loss to 22 ± 3·52 kg/m^2	Significant difference between groups for seizure frequency, 12/34 had 50% reduction by 2 months with KD. 0/32 reduced frequency in control. (positive)
Non-randomised or non-controlled trials									
Cantello[42]	2007	Uni/hospital healthy volunteers 36 ± 8·5 years	Prospective, single-arm KD	4:1	2 weeks	8/8 (100%)	*Ad libitum*	BL 66 ± 3·6 kg, loss to 63 ± 3·7 kg	Cortical physiology altered, reflecting a lower level of neural excitability based on EEG and TMS measures. (positive)
Carrette[21]	2008	Uni hospital, epilepsy, 42 (31–55) years	Prospective, single-arm KD	20 g	6 months	8/3 (38%)	*Ad libitum*	BL NR, loss −10 (−8 to 8·5–13·5) kg	30–50% seizure reduction in two out of three completers. (positive)
Cervenka[22]	2012	Epilepsy Centre, epilepsy, median 30 (18–66) years	Prospective, single-arm KD	20 g	3 months	25/14 (56%)	*Ad libitum*	BL NR, loss −3·1 (0–8·2) kg	At 1 month >50% seizure reduction ($n = 9$). At 3 months >90% seizure reduction ($n = 3$), 50–90% seizure reduction ($n = 3$). (positive)
Cervenka[23]	2016	Epilepsy Centre, epilepsy, 32 (18–70) years	Prospective, two arms (new to KD or on established KD)	20 g	2 months to 5 years (average 28 months)	101/44 (new to KD) (44%)	*Ad libitum*	56% new to diet lost weight, amount NR	On analysis, 17/44 >50% seizure reduction, 22/44 were seizure free. (positive)
De Souza Neves[24]	2020	Hospital, epilepsy (middle income), 31 ± 9 years	Prospective, single-arm KD	20 g	24 weeks	14/8 (57%)	*Ad libitum*	BL BMI 26·4 ± 1·8 kg/m^2, loss −9·4%	55·5% median seizure reduction by 12 weeks with >50% reduction for 4/8 participants. (positive)

Table 2. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm *n* = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
Green[25]	2020	Epilepsy tertiary centre, epilepsy, 37 ± 11 years	Prospective, single-arm KD	10–25 g	1 year	42/20 (48% at 6 months) 42/14 (33% at 1 year)	*Ad libitum*	NR	60% of patients reported an improvement in seizure frequency, 38% reported a >50% reduction, and 13% reported a seizure-free period. (positive)
Husain[40]	2004	Narcolepsy clinic, narcolepsy, 48 ± 11 years	Prospective, single-arm KD	20 g	8 weeks	9/8 (89%)	*Ad libitum*	BL: 99·3 ± 20·7 kg, loss to 92·2 ± 19·8 kg	NSSQ decreased by 18% with modest improvements in daytime sleepiness. (positive)
Klein[27]	2010	Hospital, epilepsy, 40 (24–65) years	Prospective, single-arm KD	3:1	4 months	12/9 (75%)	CR: 1600 kcal per day	BL BMI 33·8 ± 6·8 kg/m^2, loss −18%	Average monthly seizure frequency for the 11 subjects treated for >1 week declined by 38·4%. 5/12 had a >50% seizure reduction. (positive)
Kossoff[28]	2008	Epilepsy centre, epilepsy median 31 (18–53) years	Prospective, single-arm KD	15 g	6 months	30/14 (47%)	*Ad libitum*	BL 80 kg, loss −6·8 kg	3% were seizure free, 30% >50% seizure reduction, 17% <50% reduction and 50% no reduction. (positive)
Kverneland[29]	2015	Epilepsy outpatient clinic, epilepsy, 37 (16–58) years	Prospective, single-arm KD	15–20 g	12 weeks	13/6 (46%)	*Ad libitum*	BL NR, loss −6·5 kg (−4·3 to −8·1)	>50% seizure reduction ($n = 4$) with reduced severity (range 1–70%). (positive)
Lambrechts[31]	2012	Epilepsy centre, epilepsy, 28 (18–41) years	Prospective, single-arm KD	3:1–4:1	1 year	15/5 (33%)	*Ad libitum*	BL NR, 60% lost ≥2 kg,	2/5 had seizure reduction between 50% and 90% at 12 months. 27% of patients completing at least 1 month of KD had ≥50% seizure reduction. (positive)
Leen[41]	2013	Uni medical centre, GLUT1DS, three adults (21, 28, 30 years)	Prospective, case series KD	<20 g	3–16 months (average 9 months)	3/3 (adults) (100%)	*Ad libitum*	BL and amount NR, 2/3 lost weight	Significant improvement of paroxysmal movements between 24 h and a few weeks. Subjective improvement in cognitive function. (positive)
McDonald[33]	2021	Epilepsy Centre, epilepsy, 36 years	Prospective, single-arm KD	20 g	6 months	65/40 (3 months) (62%) 65/31 (6 months) (48%)	*Ad libitum*	BL 86 kg, weight loss significant but NR	Significant reduction in median seizures per week at 3 months and 6 months. (positive)
Mosek[34]	2009	Medical centre, epilepsy, 28 ± 6 years	Prospective, single-arm KD	4:1	12 weeks	9/2 (22%)	*Ad libitum*	BL: 20·7 ± 7 kg, loss −2·8 kg at 6 weeks	Two completers ≥50% seizure reduction. (positive)
Nei[35]	2014	Epilepsy centre, epilepsy, 32 (11–51) years	Prospective, single-arm KD	4:1	0·13–35 months (mean 9 months)	29/18 (3 months) (62%)	*Ad libitum*	BL: NR, loss −7·98 ± 10·6 kg	Overall seizure improvement 52%, no improvement 31%, increased 10%, unable to initiate diet 7%. (positive)
Sirven[36]	1999	Uni hospital, epilepsy, 32 (19–45) years	Prospective, single-arm KD	4:1	8 months	11/7 (64%)	Weight maintenance	N	3/7 had 90% seizure frequency decrease, 3/7 had 50–89% decrease, 1/7 had 40% decrease. (positive)

Table 2. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm *n* = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
Smith[37]	2011	Outpatient clinic, epilepsy median 29 (18–55) years	Prospective, single-arm KD	20 g	12 months	18/14 (78%)	CR: weight loss encouraged	BL: 88·9 ± 2 kg, loss to 78 k± 19·6 kg	12% had >50% seizure reduction after 3 months; 28% after 6 months, and 21% after 12 months. (positive)
Van Egmond[38]	2017	Uni clinic, NSPME, 20 years	Prospective, single-arm KD	20 g	3 months	2/2 (male adults) (100%)	*Ad libitum*	N	No relevant changes in seizures, EEG or mood. (equivocal)
PSYCHOLOGICAL (*n* = 15)									
Randomised controlled trials									
Brinkworth[43]	2009a	Community obese, mood/cognition, 50 ± 8 years	RCT (KD or HC 46%)	<20 g	12 months	55/33 (60%)	CR: 30% per day energy restriction	BL: 93·9 ± 16 kg, loss −14·5 ± 1·7 kg	Significant improvement in psychological mood states for both diets at 8 weeks. At 12 months, KD returned to baseline and LF remained significantly better. (positive #)
Brinkworth[44] (Tay 2016[166])	2016	Community obese + T2D, mood/ cognition, 59 ± 7 years	RCT (KD or HC 53%)	<50 g/14%	12 months	58/41 (71%)	CR: 2–4 MJ per day restriction	BL: 101·8 ± 2·0 kg, loss to 92·6 ± 2·0 kg	Both diets achieved comparable improvements in mood state and affect. (positive #)
Butki[45]	2003	Uni clinic, mood/cognition, 41 ± 7 years	RCT cross-over (KD or HC 55%)	<20 g	3 weeks each arm, 1 week washout	22/17 (77%)	*Ad libitum*	NR	Significant increase in negative affect, decrease in positive affect and fatigue following exercise while on the KD. (negative)
Gorkos[54]	2019	Community obese, cognition, 41 ± 20 years	RCT cross-over (KD or KD + exercise)	<50 g/15%	4 weeks each arm 4 weeks washout	12/12 (100%)	*Ad libitum*	BL BMI: 35·4 ± 4·3 kg/m^2 to 33·2 ± 5·4 kg/m^2 (KD, no exercise)	Improvement on cognitive function measures (speed and flexibility) and self-perceived cognitive symptoms, 20–38% increase BDNF. (positive)
Halyburton[47]	2007	Community obese, mood/cognition, 50 (24–64) years	RCT (KD or HC 46%)	<4%	8 weeks	58/48 (83%)	CR: 30% energy restriction	BL: 93·6 ± 2·1 kg, loss −7·6%	Significantly improved psychological wellbeing for both groups. High-carbohydrate group improved significantly more on processing speed. (positive #)
Harvey[55,167]	2019	Community health, mood, 38 ± 7 years	RCT three arms (KD$^{(1)}$, KD$^{(2)}$ or LCD)	5%, 15% or 25%	12 weeks	77/75 (97%)	Eucaloric 3 weeks *Ad libitum* 9 w	BL: 81·2 ± 16·6 kg, loss: KD$^{(1)}$ −4·1 kg, KD$^{(2)}$ −3·9 kg, LCD −3·0 kg	Consistent improvement in mood disturbance for KD$^{(1)}$ and KD$^{(2)}$. Overall significant improvement with no difference between groups. (positive)
Iacovides[48]	2019	Community healthy, mood/cognition, 30 ± 9 years	RCT cross-over (KD or HC 55%)	15%	3 weeks each arm 1 week washout	11/10 (91%)	*Ad libitum*	N	Diet had no effect on vigilance, accuracy, visual learning/memory, working memory, executive function or mood. (equivocal)
Makris[49]	2013	Community obese, Cognition, 47 ± 9 years	RCT (KD or HC 55%)	20 g	24 weeks	47/47 (100%)	*Ad libitum*	BL: NR, loss −11·4 ± 5·6%	No effect was seen on cognitive function from weight loss, with both diets showing similar cognitive performance. (equivocal #)

Table 2. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm *n* = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
McClernon[50]	2007	Community overweight, mood, 45 ± 9 years	RCT (KD or low-fat diet) + prospective	<20 g	6 months	59/45 RCT (76%) 51/41 (80%)	*Ad libitum*	BL: 97·8 ± 15·0 kg, loss −12·9 kg	Improvement in negative affect for both diets but significantly more for KD. (positive #)
Rosen[53]	1982	Inpatient female obese, mood (33–35 years)	RCT (KD or HC 29%)	1%	6 weeks	4/4 (100%)	VLED: 800 kcal	BL: 81 kg, loss NR	Psychological states were unchanged from baseline. (equivocal)
Wing[52]	1995	Community obese female, cognition, 47 ± 3 years	RCT (KD and LCD 76 g)	10 g	1 month	11/9 (82%)	VLED: <600 kcal	BL 108·6 ± 5·1, loss −8·1 kg	No difference between groups on attention tasks higher-order processing reduced in the first week for the KD. (equivocal)
Non-randomised or non-controlled trials									
D'Anci[46]	2009	Overweight female Uni staff, mood/cognition, (22–25 years)	Prospective, two arms (KD or low-calorie DG)	0 g (1 week) 16 g (by 3 weeks)	3 weeks	9/9 (100%)	*Ad libitum*	BL BMI: 28·1, loss −1·8 kg	KD performed significantly worse on memory-based tasks, but improvement in attention during the first week. (equivocal)
Mohorko[51]	2018	Community obese, cognition, 37 ± 7 years	Prospective, single-arm KD	5–10%	12 weeks	38/35 (92%)	CR: 2 weeks 1200–1500 kcal then 10 weeks *ad libitum*	BL BMI: 36·5, loss −14·5 kg	Significant increase in working memory and speed of processing. (positive)
Pacheco[56]	1965	Female in-hospital schizophrenia, (19–63 years)	Prospective, single-arm KD	Unclear	2 weeks	10/10 (100%)	NR	NR	Significant improvement in symptom rating scales which partially reverted after ceasing diet for 1 week. (positive)
Valenzano[57]	2019	Uni clinic, orexinergic system, 48 ± 10 years	Prospective, single-arm VLCKD	<50 g per day	8 weeks	20/20 (100%)	VLED: 700–900 kcal	BL: 91·3 ± 17·1 kg, loss to 78·7 ± 13·4 kg	Orexin-A (involved in weight loss, energy homoeostasis, cognition, mood and sleep regulation) significantly increased after dietary treatment. (positive)
NEURODEGENERATIVE (*n* = 12)									
Randomised controlled trials									
Bock[61] Choi[168]	2018 2016	Uni clinic, MS, 43 years	RCT, three arms (KD, 1 week fast then MED, control)	<50 g	6 months	20/18 (90%)	*Ad libitum*	BL BMI: 25·9, loss −0·78 ± 0·3	Reduced pro-inflammatory gene expression in combined treatment groups (both in ketosis at the timepoint) at approximately 2 weeks. 1/20 had relapse (4/20 in control and 3/20 in MED). (positive)
Brandt[64]	2019	Community, MCI/ALZ, 73 ± 6 years	RCT (KD or DG)	<20 g	12 weeks	15/9 (60%)	*Ad libitum*	BL BMI 26·5 kg/m^2, loss NR	Significant increase in memory composite score for those in ketosis. (positive)
Koyuncu[67]	2020	Community, PD (56–81 years)	RCT (KD or habitual)	<10%	3 months	37/34 (92%)	NR	NR	Significant improvement in voice handicap index (VHI) scores. (positive)
Krikorian[65]	2012	Community, MCI, 70 ± 6 years	RCT (KD or >50% HC)	<20 g	6 weeks	12/10 (83%)	*Ad libitum*	BL: 84 ± 17 kg, loss to 81 kg	Ketone levels correlated significantly to memory performance. Significantly improved verbal memory performance. (positive)

Table 2. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm *n* = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
Lee[63]	2021	Uni clinic, MS, 52 ± 10 years	RCT three arms (LCD, Paleo, habitual)	<60–70 g	12 weeks	5/4 (80%)	*Ad libitum*	BL BMI: 24·3 ± 6·1 kg/m^2, loss NR	No clinical outcomes significantly changed. (equivocal)
Morrison[66]	2020	HIV clinic, MCI, 57 ± 6 years	RCT (KD or habitual)	<50 g	12 weeks	7/7 (100%)	Eucaloric	BL: 83·3 ± 13·9 kg, no loss 82·8 ± 13 kg	Significantly improved executive function and speed of processing, which returned to baseline after 6-week washout. (positive)
Neth[58]	2020	Community, pre-diabetic with ALZ risk, 64 ± 3 years	RCT cross-over (MED + KD, AHA diet)	5–10%	6 weeks each arm, 6 weeks washout	23/20 (87%)	Eucaloric	BL BMI: 28·4 ± 5·7 kg, loss −8·5 kg	Increased cerebrospinal fluid β-amyloid 42 and decreased tau. Memory performance improved after both diets. (positive #)
Phillips[68]	2018	Community, PD, 64 ± 7 years	RCT (KD or low fat)	5 g	8 weeks	24/18 (75%)	CR: 1750 kcal per day	BL 83·7 ± 19·4 kg, loss −4·4 ± 3 kg	Significantly improved motor and nonmotor symptoms for both groups; KD significantly more improvement in non-motor daily living experiences symptoms. (positive #)
Phillips[59]	2021	Community, PD, 70 ± 6 years	RCT cross-over (KD or habitual)	6%	12 weeks each arm, 10-week washout	26/21 (81%)	*Ad libitum*	BL: 80·5 ± 15·8 kg, loss −2·2 ± 2·7 kg	Significantly improved in daily function and quality of life, but not cognitive scores. (equivocal)
Non-randomised or non-controlled trials									
Brenton[62]	2019	Community, MS, median 38 (15–50) years	Prospective, single-arm KD	<20 g	6 months	20/18 (90%)	*Ad libitum*	BL BMI: 34·1 ± 6·9 kg/m^2, loss −3·0 ± 2·2 kg/m^2	Significant improvement in fatigue, mood disturbance and depression. No worsening of MS symptoms whilst on the diet. (positive)
Taylor[60]	2018	Community, ALZ, 73 ± 9 years	Prospective, single-arm KD	<10%	3 months	15/10 (67%)	*Ad libitum*	BL: 76·5 ± 17·4 kg to 74·7 ± 16·2 kg	Significant improvement in mean Alzheimer's Disease Assessment Scale-cognitive subscale score, which reverted to baseline after washout. (positive)
VanItallie[69]	2005	Community, PD, 61 ± 11 years	Prospective, single-arm KD	2%	4 weeks	7/5 (71%)	*Ad libitum*	BL BMI: 31 ± 3 kg/m^2, loss −6·1 (4·1 to 9·5) kg	Unified Parkinson's Disease Rating Scale scores improved (resting tremor, freezing, gait, balance, mood and energy level). (positive)
MIGRAINE (*n* = 7)									
Randomised controlled trials									
Di Lorenzo[72]	2015	Community overweight, migraine	RCT (KD or low-calorie, 46% HC)	30 g	4 weeks, 8 weeks increasing carb	45/43 (3 months) (96%)	VLED: <800 kcal	BL BMI: 27·5 ± 3·2 kg/m^2 to 22·2 ± 2·6 kg/m^2	Significant reduction migraine frequency, length and medication use after 1 month KD compared with low-calorie. Symptom worsening with re-introduction of carb to match control diet. NS between groups at 6 months, but both groups significantly improved from baseline. (positive #)

Table 2. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm *n* = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
Di Lorenzo[76]	2019b	Community obese, migraine, 44 ± 9 years	RCT cross-over (VLCKD or VLCnKD)	30–50 g	4 weeks each arm, 4-week washout	35/29 (83%)	VLED: ≤800 kcal	BL BMI: 35 ± 6 kg/m^2, loss NS b/n arms, total NR	Ketogenic diet had significant reduction in migraine days and attacks. 26/35 responded to the ketogenic arm, 3/35 to the non-ketogenic. (positive)
Non-randomised or non-controlled trials									
Barborka[70]	1930	Clinic patients, migraine, 33 ± 8 years	Prospective, case series KD	Unclear	3–36 months (average 46 weeks)	50/50 (100%)	NR	NR	14/50 controlled migraine, 25/50 decreased severity and frequency, 11/50 no benefit. (positive)
Bongiovanni[71]	2021	Clinic patients, MOH, median 46 (18–57) years	Prospective, single-arm KD	30 g	3 months	50/23 (46%)	Matched to BMI: *ad libitum* to VLED	BL: 63·5 (54–120) kg to 58·5 (51–101) kg	Median migraine duration significant reduction: 24 to 5·5 h per day. Median migraine frequency significant reduction 30 per month to 7·5 per month. Significant intensity reduction. (positive)
Di Lorenzo[73]	2016	Female clinic patients, migraine, 39 ± 9 years	Prospective, single-arm KD	15–30 g	4 weeks	18/18 (100%)	VLED <800 kcal (10 overweight) *Ad libitum* (8)	BL BMI: 25·5 ± 4·6 kg/m^2, loss NR	Significant reduction in mean frequency and duration independent of weight loss. (positive)
Di Lorenzo[74]	2018	Clinic patients, migraine, 38 ± 9 years	Prospective, single-arm KD	10–30 g	12 weeks	18/18 (100%)	*Ad libitum*	NR	11/18 had full resolution of headache, 4/18 had >50% of mean monthly number of attacks. 3/18 were non-responders. (positive)
Di Lorenzo[75]	2019a	Clinic patients, migraine, 41 ± 12 years	Prospective, two arms (KD, healthy volunteer)	15 g	4 weeks	18/18 (100%)	*Ad libitum*	BL BMI: 26·7 ± 4·6 kg/m^2 to 25·3 ± 4·6 kg/m^2	Significant reduction in frequency, duration and disability of headache attacks. (positive)
MUSCULOSKELETAL (*n* = 2)									
Randomised controlled trials									
Strath[78]	2019	Community, knee OA/ pain, 72 ± 2 years	RCT three arms (KD, low fat or habitual)	20–40 g	12 weeks	8/8 (100%)	*Ad libitum*	BL: 98·5 ± 18·5 kg to 89·6 ± 17·9 kg	Both diet groups lost weight, but only KD had improved pain and quality of life outcomes. (positive)
Uncontrolled trials									
Hall[77]	2021	Community, hip OA/ pain, 65 ± 7 years	Prospective, single-arm LCD	<70 g estimated	6 months	18/16 (89%)	VLED <800 kcal	BL 89·8 ± 13·4 kg, 81·4 ± 15·5 kg	Overall hip pain reduced by −3·3. Physical function improved −14·2 (−18·1 to −7·5). 8/16 pain much better, 4/16 moderately better, 4/16 slightly better. (positive)
AUTONOMIC NERVOUS SYSTEM (*n* = 2)									
Randomised controlled trials									
Fagerberg[79]	1984	Outpatient clinic, sympathetic activation 49 ± 3 years	RCT (LCD and HC >50%)	24%	4 weeks	12/12 (100%)	CR: 1400 kcal per day	BL BMI: 29·1 ± 1·8 kg/m^2, no change in weight	Significant decreases in systolic blood pressure, heart rate and plasma noradrenalin concentration. (positive)

Table 2. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate	Diet length	Ketogenic arm *n* = start/finish (retention)	KD/LCD energy intake	KD/LCD weight loss (range)	Reported neurological outcome (overall summary)
Maunder[80] (Shaw 2019[169])	2021	Athletes, Heart rate variability, 30 ± 5 years	RCT cross-over (KD or habitual)	<50 g	4 weeks each arm	8/8 (100%)	*Ad libitum*	BL BMI: 22·4 ± 1·7 kg/m^2, BMI lower on KD	A significant reduction in rMSSD was observed in the KD, along with an increase in day-to-day variability in rMSSD. (positive)
BIOENERGETICS (*n* = 2)									
Randomised controlled trials									
Lobley[81]	2014	Obese men, cerebral glucose uptake (50–74 years)	RCT cross-over (KD or HC 182 g)	22 g	4 weeks each arm, 3-day washout	14/12 (86%)	CR: restricted to 8 MJ per day	BL BMI: 34·9 kg/m^2, loss −6·3 kg	5% lower supply of glucose to the brain with KD. Despite this, the uptake of glucose by the fifty-four regions of the brain analysed remained similar for the two dietary interventions. (equivocal)
Holsen[82]	2021	Recruits weight loss trial, cerebral blood flow 33 ± 11 years	RCT three arms (LCD, HC 40% or HC 60%)	20%	20 weeks	28/28 (100%)	Weight maintenance	BL BMI: 31·7 ± 5 kg/m^2, loss −12·5 ± 2·7%	Significantly higher cerebral blood flow in nucleus accumbens, with HC potentially increasing reward and hunger. (positive)
SPINAL CORD INJURY (*n* = 1)									
Randomised controlled trials									
Yarar-Fisher[83]	2018	Spinal rehab ward, acute SCI, 32 ± 15 years	RCT (KD or 44% HC)	3–8%	5 weeks	4/4 (100%)	*Ad libitum*	NR	Higher upper extremity motor scores showed significant improvement with KD but not with HC. (positive)
TRAUMATIC BRAIN INJURY (*n* = 1)									
Non-randomised or non-controlled trials									
Rippee[84]	2020	Community, post-concussion syndrome 45 ± 12 years	Prospective, single-arm KD	<10%	2 months	14/12 (86%)	*Ad libitum*	BL BMI: 27·0 to 26·2 kg/m^2	Non-significant improvement in visual memory and post-concussion symptom scale. (equivocal)

AED, anti-epileptic drugs; AHA, American Heart Association; ALZ, Alzheimer's disease; BL, baseline; carb, carbohydrate; CR, calorie restriction; CVD, cardiovascular disease; DG, dietary guidelines; EEG, electroencephalogram; GLUT1DS, glucose transporter-1 deficiency syndrome; HC, high carbohydrate; kcal, kilocalorie; KD, ketogenic diet <50 g carbohydrate per day or 15% TEI; LCD, low-carbohydrate diet 50–130 g carbohydrate per day or 16–26% TEI; LCKD, low calorie ketogenic diet (typically between 1000 and 1800 kcal per day); MCI, mild cognitive impairment; MED, Mediterranean diet; MOH, medication overuse headache; MS, multiple sclerosis; N, No; NR, not reported; NS, not significant; NSPME, North Sea Progressive Myoclonus Epilepsy; NSSQ, Narcolepsy Symptom Status Questionnaire; PD, Parkinson's disease; RCT, randomised controlled trial; rMSSD, root mean square of the sum of successive difference in R-R intervals; T2D, type 2 diabetes; TEI, total energy intake; TMS, transcranial; Uni, university; VLCKD, very-low-calorie ketogenic diet (typically below 1000 kcal per day); VLCnKD, very-low-calorie NON ketogenic diet; VLED, very-low-energy diet.

** Carbohydrate presented as either (a) ratio of fat: protein + carbohydrate, (b) grams per day or (c) a daily percentage.

Comparator diet also showed significant positive outcome.

reported a neurological outcome. Number of participants in trials ranged between 2 and 101, with an average of 26 ± 20. Adherence to the diet was reported between 22% and 100% (mean 79 ± 21%).

Most studies ($n = 53$, 83%) reported favourable neurological outcomes attributable to carbohydrate restriction. These included: reduction in seizure frequency, improved psychological mood states with reduced negative affect, better cognitive and memory functions, reduced narcoleptic sleepiness, reduced fatigue, depression and rate of multiple sclerosis relapse, reduced structural changes and improved cognitive function in Alzheimer's disease, improved motor function in Parkinson's disease, reduced migraine frequency and severity, reduced pain in osteoarthritis, reduced sympathetic nervous system activation, improved heart rate variability and improved recovery following spinal cord injury. Ten papers reported neutral results[38,46,48,49,52,53,59,63,81,84] and one trial reported a negative effect on mood[45]. Three papers reported also similar or better improvements for the comparator diet[43,44,47].

Energy intake varied between studies; most reported *ad libitum* food intake or intake formulated for weight maintenance ($n = 43$), eight had mild-to-moderate calorie restriction[27,37,43,44,47,68,79,81], six were very low-calorie (<800 kcal per day)[52,53,57,72,76,77], three had combined protocols[51,71,73] and did not specify energy intake[56,67,70]. Weight loss pre–post intervention was common ($n = 45$), but not always significant. Five studies reported no weight loss[26,32,36,38,48], and nine did not report weight changes[25,45,53,56,63,64,67,70,83].

Inflammatory markers. The secondary outcome of interest was measures related to inflammation. A second screen of studies meeting the criteria retrieved sixty-three studies reporting on inflammatory biomarkers (Table 3). These were mostly metabolic studies ($n = 52$) investigating chronic lifestyle diseases such as diabetes, obesity and heart disease[57,85–135]. The remaining studies included three general population[51,136,137], two cancer[138,139], two neurodegenerative disease[61,62], one auto-immune[140], one musculoskeletal[78], one sport/performance[141] and one spinal cord injury[83]. There was a large proportion of RCTs ($n = 45$), seventeen prospective studies and one case series[138]. Time on the diet ranged from 2 weeks[61,89] to 104 weeks[86,88] (mean 16 ± 20 weeks) with fifty-three studies considered a KD, five mixed models[88,92,96,113,117] and five LCDs[107,109,134,135,140]. The most reported inflammatory biomarker was CRP, followed by TNFα, then various ILs. Studies focused on weight loss commonly reported leptin and adiponectin.

Forty-four studies reported positive outcomes (lowered inflammatory markers) from the diet, with fourteen of these also reporting benefits for the comparator diet[91,95,103,106,108,109,113,116,117,122,127,129,131,134]. Fifteen studies presented equivocal results[62,87,90,92,96,100,110,112,114,123,128,132,135,138,140] (no significant change in inflammatory markers), two reported mixed results[51,124] and two studies reported negative results[105,121] (increased inflammatory markers). Total energy intake was similar to the neurological outcomes group; thirty-eight were *ad libitum*/weight maintenance studies, fifteen had mild-to-moderate calorie restriction[91,92,105–109,111,116,125,127,129,132,134], seven were very low-calorie (<800 kcal per day) [57,93,97,102,112,115,120] and three used mixed models[51,94,101]. Fifty-seven studies reported weight loss, two reported no weight loss[98,114] and four did not report a finding[83,90,134,139]. Overall, a total of 2296 participants commenced an LCD or KD trial that reported an inflammatory outcome. Number of participants in trials ranged between 4 and 262, with an average of 35 ± 38. Adherence to the diet was reported between 38% and 100% (mean 87 ± 15%).

Other findings. There are a substantial number of interventional human KD and LCD trials in other research areas reported in the literature that meet the carbohydrate intake criteria and exceed 2 weeks in duration. In addition to the 61 neurological trials, other publications retrieved in the search included: 393 metabolic, 51 sport/performance, 33 cancer, 30 general, 12 neurological (reporting non-neurological outcomes) and 4 gastrointestinal (Supplementary Appendices 2–7).

Discussion

The primary aim of this scoping review was to review adult human studies that report outcomes related to the nervous system in response to an LCD or a KD. The secondary aim was to review the research that reports on changes in inflammatory biomarkers and evaluate the relevance of these findings to chronic pain. The overall results (83% of studies) suggest a favourable outcome on the nervous system from a reduction in dietary carbohydrates. Most studies utilised a KD below 50 g carbohydrate per day (fifty-eight out of sixty-four focused on neurological outcomes (91%), and fifty-five out of sixty-three focused on inflammatory biomarkers (87%)). The more moderate approach to carbohydrate restriction of the LCD also reported positive outcomes, with three out of four LCDs and both 'unclear' diets reporting improved neurological outcomes. Similarly, three out of four LCDs and four out of five mixed protocols also reported favourable reductions in inflammatory biomarkers.

The KD is reported to reduce nervous system excitability through ketone signalling. The actions include: activation of various ion channels (such as ATP-sensitive K^+ channels) where ketones reduce excitability, modulation of neurotransmitter levels via the reduction of excitatory glutamate and/or increase in inhibitory GABA (or changes in clearance rates), and improved mitochondrial respiration and number with reduced reactive oxygen species formation[142,143]. Most studies focused on cortical excitability (twenty-one of twenty-two publications) and reported improvements in seizure measures. Our recent scoping review of animal research using KDs[7] identified fifty-three studies reporting on cortical/neuronal excitability, with forty-two reporting improvements that shifted nervous system excitability back towards homoeostatic levels. Increased neuronal excitability (sensitisation) is common in chronic pain presentations[144–146] and as such may also respond positively to the mechanisms outlined in the review. Additionally, the use of anti-seizure/anti-epileptic medication (such as pregabalin) is commonly prescribed for neuropathic pain, providing further evidence for common pathways being involved in both chronic pain and seizure disorders[147]. Given that poor nutrition potentially triggers mechanisms responsible for driving increased nervous system

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Table 3. Reported inflammatory biomarkers from human studies utilising low-carbohydrate (LCD) or ketogenic (KD) diets, $n = 63$

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm n = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
METABOLIC ($n = 52$) *Randomised controlled trials*									
Al-Sarraj[85]	2009	Hospital/uni contacts, MetS, (18–50 years)	RCT (LCD or LCD then HC 55%)	20–25%	12 weeks LCD or 6 weeks LCD, then 6 weeks HC	28/20 (71%) 28/19 (68%)	*Ad libitum*	BL: 102·8 ± 24·2 kg to 94·2 ± 23 kg, loss −8·4%	LCD (at 6 weeks) significantly decreases in CRP and TNFα, significant increase in adiponectin which persisted at 12 weeks regardless of diet. (positive)
Bluher[88] (Shai 2008[170])	2012	Recruits weight loss trial, obesity, 52 ± 7 years	RCT (LCD, LF or MD)	20 g for 2 months, then increase to 120 g	2 years	109/85 (78%)	*Ad libitum*	BL BMI: 30·9 ± 3·6 kg/m^2, loss −6·5% 6 months, −5% at 2 years	Significant decrease LCD for hsCRP, leptin, and increased adiponectin at 6 months and 2 years. Significant reduction in hsCRP for LCD compared with other diets at 2 years. (positive)
Breukelman[90]	2021	Diabetic clinic, T2D and immune, (31–71 years)	RCT (KD or KD + exercise or control)	<50 g	16 weeks	13/10 KD (77%), 13/12 KD+exercise (92%)	*Ad libitum*	NR	No significant changes in CRP in KD or KD + exercise. (equivocal)
Brinkworth[91]	2009b	Community obese, 50 ± 8 years	RCT (KD or LF)	4%	1 year	55/33 (60%)	CR: 1400–1700 kcal	BL: 93·9 ± 16 kg, loss −14·5 ± 1·7 kg	CRP reduced for both diets, NS b/n groups. (positive [#])
Buscemi[92]	2009	Female community obese CVD and obesity, 38 ± 3 years	RCT (KD or MD)	25 g for 2 weeks, then increase 10 g per week	8 weeks	10/10 (100%)	CR: 20 kcal/kg body weight	BL 87·1 ± 3·8 kg, loss −7·6 ± 0·8 kg	Significant increase in IL6 and prostaglandin F2α in KD at 5 days, which had returned to baseline by end of 8 weeks. (negative/equivocal)
Dansinger[95]	2005	Community overweight, CVD/ obesity, 49 ± 11 years	RCT four arms (Atkins KD, Ornish, Weight Watchers or Zone)	20 g (Atkins)	1 year	40/21 (53%)	*Ad libitum*	BL: 100 ± 15 kg, loss −2·1 ± 4·8 kg	For each diet, decreasing levels of CRP were significantly associated with weight loss, with no significant difference between diets. (positive [#])
Davis[96] (Davis 2009[171])	2011	Recruits weight loss/T2D trial, T2D, 55 ± 1 years	RCT (KD or LF)	20–25 g for 2 weeks 5 g added per week	1 year	55/47 (85%)	*Ad libitum*	BL BMI: 34·2 ± 1·0 kg/m^2, loss −3·1 ± 4·8 kg/ m^2	Testing on KD subset ($n = 27$) of CRP, IL6 were NS. (equivocal)
De Luis[97]	2016	Clinic patients, Obesity, 46 ± 10 years	RCT (VLCKD ± DHA supplementation)	<50 g	6 months	34/29 (85%)	VLED: 600–800 kcal	BL: 92·2 ± 13·1 kg, loss −19·7 ± 5·1 kg	Significant decrease for both KD in CRP, resistin, TNF-α, and leptin. The ratio of pro-resolution/pro-inflammatory lipid markers was increased with DHA supplementation increasing AI effect. (positive)
Ebbeling[98]	2018	Uni campus, overweight, EE, 38 ± 14 years	RCT (LCD, MC 40%, or HC 60%)	20%	20 weeks (after 12% weight loss run in)	57/54 (95%)	Individual weight maintenance	N – designed for weight maintenance	Significantly reduced leptin for LCD. (positive)

Table 3. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm *n* = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
Forsythe[99] (Volek 2009[172])	2008	Community overweight, 33 ± 11 years	RCT (VLCKD or LF)	12%	12 weeks	20/20 (100%)	*Ad libitum*	BL: 96·5 ± 13·7 kg to 86·4 ± 12 kg	Significant decrease in TNF-a, IL-6, IL-8, MCP-1, E-selectin, I-CAM and PAI-1 in VLCKD greater than LF and not significantly correlated to weight loss. (positive)
Forsythe[100]	2010	Male overweight, obesity/lipoprotein 45 ± 7·9 years	RCT crossover (KD + SF or KD + USF)	10%	6 weeks each arm	8/8 (100%)	Individual weight maintenance	BL: 95·4 ± 13·5 kg to 94·1 ± 13·7 kg (SF) or 93·1 ± 13·8 kg (USF)	NS hs-CRP, IL-6, IL-8, TNF-a, MCP-1, leptin overall or b/n diets. (equivocal)
Gyorkos[103]	2019	Community obese, MetS, 41 ± 20 years	RCT crossover (KD or KD + exercise)	<50 g/15%	4 weeks each arm 4-week wash-out	12/12 (100%)	*Ad libitum*	BL BMI: 35·4 ± 4·3 kg/m^2 to 33·2 ± 5·4 kg/m^2 (KD, no exercise)	Both arms significantly decreased hsCRP, TNF-α, IL-6 and ICAM-1 compared with baseline. (positive [#])
Hu[104]	2015	Community obese, obesity/CVD, 48 ± 10 years	RCT (KD or LF)	<40 g	12 months	75/59 (79%)	*Ad libitum*	BL: 97·9 ± 13·5 kg, loss −5·3 kg	Significant reduction in ICAM-1 and increase in adiponectin in KD compared with LF. Both diets had equal effects on IL-6, IL-8 and TNF-α. (positive [#])
Johnston[105]	2006	Community obese, 38 ± 4 years	RCT (KD or MC 40%)	5%	6 weeks	9/9 (100%)	CR: 1500 kcal	BL BMI: 34·9 ± 1·6 kg/m^2 to 32·5 ± 1·6 kg/m^2	Inflammatory risk (arachidonic acid: eicosapentaenoic acid ratios in plasma phospholipids) were more adversely affected by the KD. (negative)
Johnstone[106]	2011	Male community obese, CVD risk, 55 ± 14 years	RCT crossover (KD or MC 35%)	4%	4 weeks each arm	18/16 (89%)	CR: 30% restriction	BL: 108·8 kg to 102·0 kg, loss −6·75 kg	Both diets reduced TNF-α and IL-10. (positive [#])
Jonasson[107]	2014	Primary care centre, T2D, 63 ± 11 years	RCT (LCD or LF)	20%	6 months	30/26 (87%)	CR: 1600 kcal	BL BMI: 32 ± 5 kg/m^2 to 30 ± 5 kg/m^2	Significant decrease in IL-1 receptor agonist and IL-6. No change in CRP. (positive)
Keogh[108]	2008	Community overweight, 50 ± 8 years	RCT (KD or HC 55%)	4%	8 weeks	57/52 (91%)	CR: 30% restriction	BL BMI: 33·5 ± 4·1 kg/m^2, loss 7·9 ± 2·0%	Significant decrease in CRP, but less for KD than HC. (positive [#])
Kerksick[109]	2010	Female community obese, CVD risk, 39 ± 8 years	RCT six arms (LCD + HP, LCD + MP, HC 55% + LP, high calorie or control ± exercise)	<20%	14 weeks	116/75 (65%)	CR: 1200 kcal	BL: LCD + HP 95 ± 18 to 90 ± 18, LCD + MP 95 ± 15 to 91 ± 14	Significant reduction in leptin for all calorie-restricted diets. (positive [#])

Table 3. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm *n* = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
Merra[112]	2017	Uni medical clinic, MetS, 45 ± 15 years	RCT crossover three arms (VLCKD[1], VLCKD[2] with simple sugars or VLCKD[3] complex sugars)	<20 g/15%[1] or 20–35 g/20–25%[2,3]	3 weeks each arm with 3-week washout	60/54 (90%)	VLED: <500 kcal	BL BMI 30·5 kg/m^2 to mean of groups 28·5 kg/m^2	Significant reduction in CRP in VLKCD[3] but not VLCKD[1,2]. (positive/equivocal #)
Miller[113]	2009	Uni campus, obesity, 39 ± 3 years	RCT (KD or HC 60%)	<20 g for 2 weeks then + 5 g per week	12 w	13/13 (100%)	*Ad libitum*	BL: 85·6 ± 12·8 kg to 78·3 ± 11·5 kg	Significant reduction in leptin for both groups, NS b/n groups. (positive #)
Miller M[114]	2009	Community healthy, CVD risk, 31 ± 10 years	RCT crossover (KD, MD and HC 70%)	<20 g	4 weeks each arm, 4-week washout	26/18 (69%)	*Ad libitum*	N, weight maintenance	No significant changes in CRP for any dietary group. (equivocal)
Noakes[116]	2006	Community obese, CVD risk, 48 ± 8 years	RCT (KD, HC/ HUF 50% or HC 70%)	4%	8 weeks	28/24 (86%)	CR: 30% restriction	BL: 46·5 ± 1·9 kg to 43·9 ± 1·8 kg, loss −2·6%	Decreased CRP in all diets. (positive #)
O'Brien[117]	2005	Female community obese, CVD risk, 44 ± 8 years	RCT (KD or LF)	20 for 2 weeks, then <60 g	3 months	22/22 (100%)	*Ad libitum*	BL BMI: 33·6 ± 1·86 kg/m^2, loss −7·6 ± 3·2 kg	CRP decreased for both diets and significantly correlated with weight loss. (positive #)
Paoli[118]	2015	Male community overweight, CVD risk, 56 ± 5 years	RCT (KD + MD + O3 or KD + MD)	10%	4 weeks	38/34 (89%)	*Ad libitum*	BL: 92·3 ± 12·5 kg, loss −4·7 kg	Significant decrease in IL-1β, IL-6 and TNF-α and increase in adiponectin on KD + O3. Significant decrease in TNF-α only for KD. O3 improved AI qualities of KD. (positive)
Perissiou[173]	2020	Community obese, CVD risk, 35 ± 9 years	RCT (KD + exercise or DG + exercise)	<50 g	8 weeks	46/33 (72%)	*Ad libitum*	BL: 87·8 ± 16 kg, loss −4·4 ± 4 kg	Significantly greater reduction in CRP for KD. CRP reductions correlated with higher ketosis. (positive)
Perticone[120]	2019	Hospital clinic obese, 47 ± 11 years	RCT (VLCKD or low-calorie MD)	<50 g/20%	12 months	28/28 (100%)	VLED: 600 kcal	BL: 113·9 ± 31·0 kg to 87·3 ± 22·8 kg	Significantly greater reduction in hsCRP in VLCKD compared with MD. (positive)
Rankin[121]	2007	Female community overweight, 39 ± 4 years	RCT (KD or HC 60%)	<20 g	4 weeks	Unclear, *n* = 32 total	*Ad libitum*	BL: 87·3 ± 15·2 kg to 83·5 ± 14·8 kg	Significant increase in CRP in KD and significant decrease in HC. (negative)
Ratliff[122,174]	2008, 2009	Male community overweight (40–70 years)	RCT (KD or KD + egg)	10%	12 weeks	31/28 (90%)	*Ad libitum*	BL NR, mean loss −6·3 kg	Significant reduction in fasting leptin for both groups. (positive #)

Table 3. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm *n* = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
Retterstol[123]	2018	Uni normal weight, lipids 24 ± 4 years	RCT (KD or habitual)	<20 g	3 weeks	19/15 (79%)	*Ad libitum*	BL: 61 ± 8·6 kg to 59·8 ± 8·4 kg	No change in CRP. (equivocal)
Ruth[125]	2013	Community obese, CVD risk 42 ± 13 years	RCT (KD or HC 55%)	10%/40 g	12 weeks	29/18 (62%)	CR: 500 kcal deficit	BL: 99·3 ± 14·5 kg, loss −5·3 ± 4·7%	hsCRP significantly decreased and adiponectin increased for KD. (positive)
Seshadri[126,175]	2004, 2005	Medical centre, obesity, 54 ± 9 years	RCT (KD or DG)	<30 g	6 months	NR/40 (unclear %)	*Ad libitum*	BL BMI: 43·7 ± 6 kg/m^2, loss −2·7 ± 3 kg	Significantly greater reductions in TNF-α and leptin for KD; no significant change in adiponectin. (positive)
Sharman[127]	2004	Male community obese, 33 ± 11 years	RCT crossover (KD or LF/HC 55%	<10%	6 weeks each arm	15/15 (100%)	CR: −2·1 MJ per day	BL: 109·1 ± 7·8 kg, loss −6·5 ± 3 kg	Both diets significantly decreased TNF-α, IL-6, CRP and sICAM-1. (positive [#])
Stoernell[128]	2008	Uni medical centre, lipids, 57 ± 10 years	RCT (KD or LF/ HC 55%)	<15%	8 weeks	14/10 (71%)	*Ad libitum*	BL: 91·3 ± 26·9 kg, loss −1·7 ± 1·5 kg	No significant difference in hsCRP. (equivocal)
Tay[129]	2008	Community obese, CVD risk, 50 ± 8 years	RCT (KD or LF/ HC 46%)	4%	24 weeks	55/45 (82%)	CR: 30% restriction	BL: 94·4 ± 15·5 kg, loss −11·9 ± 6·3 kg	CRP reduced with both diets. (positive [#])
Vetter[131]	2010	Outpatient clinic, obesity/T2D, 61 ± 10 years	RCT (KD or LF/ HC)	<30 g	6 months	70/37 (53%)	*Ad libitum*	BL: 118·7 ± 24·4 kg, loss −4 ± 6·3 kg	Significant decrease in leptin and increase in adiponectin for both groups. No change in TNF-α. (positive [#])
Volek[132]	2003	Community healthy, lipids, 26 ± 6 years	RCT crossover (KD or LF/HC 55%)	<10%	4 weeks each arm 4-week washout	10/10 (100%)	CR: isoenergetic (7 MJ)	BL: 59·8 ± 4·6 kg, loss −1·2 ± 0·8 kg	No significant effect of KD on CRP, TNF-α or IL-6. (equivocal)
Wekesa[133]	2016	Female overweight, CVD risk, 48 ± 1 years	RCT crossover (KD or habitual)	40 g	24 weeks each arm	28/24 (86%)	*Ad libitum*	BL BMI: 27·1 ± 0·6 kg/m^2, loss −3·7 ± 0·8 kg	CRP levels were significantly lower on KD. (positive)
Zadeh[134]	2018	Community obesity + T2D, 47 ± 5 years	RCT four arms (LCD, LF/HC 50%, HF/HC 30% or control)	20%	8-week diet 12-week diet + exercise 4-week diet	11/11 (100%)	CR: 1800 kcal	BL BMI: 104·1 ± 9 kg/m^2, loss −8·9 kg	Significant reduction LCD and LF for IL-6, TNF-α, leptin, resistin and adiponectin, and FGF21 (AI). (positive [#])

Table 3. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm *n* = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
Non-randomised or non-controlled trials									
Athinarayanan[86] (Bhanpuri[176])	2019	Diabetes clinic, T2D, 54 ± 8 years	Prospective, two arms (KD and ADA)	30 g	1 year	262/218 (1 year) (83%)	*Ad libitum*	BL:114·6 ± 0·6 kg, 1 year 100·3 ± 0·9 kg, 2 years 102·6 kg	Significant reduction in hsCRP at 1 year and 2 years in KD. (positive)
(Hallberg[177])	2018 2018				2 years	262/194 (2 years) (74%)			
Ballard[87]	2013	Community statin users, CVD, 59 ± 10 years	Prospective, single-arm KD	<50 g/10%	6 weeks	21/21 (100%)	*Ad libitum*	BL: 30·5 ± 3·2 kg, loss −3·6 kg	No significant effect on CRP, TNFα or ILs 6 and 8. (equivocal)
Boden[89]	2005	Community obese with T2D, 51 ± 10 years	Prospective, two arms (KD or habitual)	21 g	2 weeks	10/10 (100%)	*Ad libitum*	BL: 114·4 ± 12·9 kg, loss −2·2 kg	Mean 24-h serum leptin levels profiles were significantly lower after LCD. (positive)
Castaldo[94]	2020	Community obese with psoriasis, 43 ± 14 years	Prospective, single-arm VLCKD then MD	VLCKD 10–20 g MD 54%	4 weeks VLCKD 6 weeks MD	37/37 (100%)	VLED: <500 kcal then CR: 25–30 kcal/kg bodyweight	BL: 86·3 ± 19·6 kg, loss −10·6 kg	Significant decrease in TNF-α, IFN-γ, IL-1β, and IL-2 at 4 weeks. (positive)
Castaldo[93]	2021	Hospital obese, psoriasis, 43 ± 14 years	Prospective, two arms (VLCKD or habitual)	10–20 g	4 weeks	30/30 (100%)	VLED: <500 kcal	BL BMI: 30·8 ± 6 kg/m^2, loss −10%	Significant decrease in the levels of the cytokines IL-2 and IL-1β. Significant improvement in pain. (positive)
Gomez-Arbelaez[101]	2018	Obesity clinic, female, metabolic rate, 47 ± 10 years	Prospective, single-arm VLCKD	<50 g	4 months	20/20 (100%)	VLED: <800 kcal to target then maintain	BL: 95·9 ± 16·3 kg to 76·6 ± 11·1 kg	Leptin values were significantly reduced at each timepoint in line with fat mass reduction. (positive)
Gu[102]	2013	Hospital clinic, Obesity, 32 ± 9 years	Prospective, two arms (VLCKD and control)	<20 g	8 weeks	45/38 (84%)	VLED: <800 kcal	BL: 95·7 ± 18·7 kg to 88·5 ± 18 kg	Altered metabolites involved in inflammatory and oxidative processes independent of weight loss. (positive)
Kong[110]	2020	Uni female overweight, 21 ± 4 years	Prospective, single-arm KD	<10%	4 weeks	24/20 (83%)	*Ad libitum*	BL BMI: 24·9 ± 2·7 kg/m^2 to 23·6 ± 2·6 kg/m^2	Fasting leptin levels significantly reduced, TNF-α and MCP-1 unchanged. (equivocal)
Kreider[111]	2011	Female obese community, 45 ± 11 years	Prospective, two arms (LCD + HP or HC 55%)	7%	10 weeks	NR/129 [unclear %]	CR: 1200 kcal 1 week, then 1600 kcal	BL: 93·8 ± 17 kg, loss −4·4 ± 3·6 kg	Greater significant decreases in leptin for LCD. (positive)
Monda[115]	2020	Community obese, Obesity, 48 ± 8 years	Prospective, single-arm VLCKD	14%	8 weeks	20/20 (100%)	VLED: ~800 kcal	BL: 91·3 ± 17 kg to 78·7 ± 13 kg	Significant increase in adiponectin and IL-10; significant decrease in CRP and TNFα. (positive)

Table 3. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm *n* = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
Rosenbaum[124]	2019	Overweight males, metabolic function, 34 ± 7 years	Prospective, single-arm KD	5%	4 weeks run-in 50% 4 weeks KD 5%	17/17 (100%)	2400 kcal	BL: 85·7 ± 14·9 kg to 85·1 ± 14·6 kg	Increased adiponectin on KD; increased CRP on KD. (positive/ negative)
Tendler[130]	2007	Outpatient NAFLD clinic, 36 (24–50) years	Prospective, single-arm KD	<20 g	6 months	5/5 (100%)	*Ad libitum*	BL: 102·2 kg, loss −12·8 kg	Significantly reduced inflammatory grade on liver biopsy in 4/5. (positive)
Waldman[135]	2020	Firefighters, male, CVD risk	Prospective, single arm, LCD	25%	4 weeks	21/15 (71%)	*Ad libitum*	BL: 89·2 ± 12·8 kg to 86·5 ± 12·5 kg	Significant reduction in adiponectin and NS decrease in CRP. (equivocal)
Valenzano[57]	2019	Uni clinic, obesity, 48 ± 10 years	Prospective, single-arm VLCKD	<50 per day	8 weeks	20/20 (100%)	VLED: ~800 kcal	BL: 91·3 ± 17·1 kg, loss to 78·7 ± 13·4 kg	Significant decrease in CRP and increase in Orexin-A (involved in regulating the inflammatory response). (positive)
GENERAL (*n* = 3)									
Non-randomised or non-controlled trials									
Cipryan[136,178]	2020 2018	Healthy males, Inflammation, 24 ± 2 years	Prospective, two arms (KD and habitual)	<50 g	4 weeks	9/9 (100%)	*Ad libitum*	BL: 83·2 ± 17·7 kg, loss −6%	Lowered leptin concentration KD but no other significant b/n groups in inflammatory markers. (positive)
Cipryan[137]	2021	Adiponectin/ leptin ratio, 25 ± 2 years	Prospective, two arms (KD and habitual)	<50 g	1 week	15/12 (80%)	*Ad libitum*	BL: 72·7 ± 15·0 kg, loss −5·4%	Significant increase in adiponectin–leptin ratio from increased adiponectin and decreased leptin KD. (positive)
Mohorko[51]	2018	Community obese, cognition, 37 ± 7 years	Prospective, single-arm KD	5–10%	12 weeks	38/35 (92%)	CR: 1500 kcal 2 weeks, *ad libitum* 10 weeks	BL BMI: 36·5 kg/m^2, loss −14·5 kg	Increased CRP for 2 weeks, then return to baseline. Significant reduction in leptin levels and increase in adiponectin (AI) (positive)
CANCER (*n* = 2)									
Randomised controlled trials									
Khodabakhshi[139]	2021	Female oncology clinic, breast cancer 45 ± 8 years	RCT (KD or HC 55%)	6%	12 weeks	40/30 (75%)	Eucaloric	NR	Significant decrease of TNF-α and increase of IL-10 (AI) with KD. No significant differences for ESR or CRP within or between groups. (positive)
Non-randomised or non-controlled trials									
Hagihara[138]	2020	Oncology clinic, Stage IV cancer, 55 ± 13 years	Case series (KD)	10–30 g	3 months	55/37 (67%)	CR: 1500kcal+MCT oil + KD formula	BL: fat mass 12·4 ± 6·4 kg to 10·3 ± 4·8 kg	CRP levels showed no significant changes. (equivocal)

Table 3. (*Continued*)

Author	Date	Research setting/ population, mean age ± standard deviation (range)	Trial type	**Carbohydrate****	Diet length	**Ketogenic arm *n* = start/ finish**	KD/LCD energy intake	KD/LCD weight loss (range)	Reported inflammatory outcome (overall summary)
NEURODEGENERATIVE (*n* = 2)									
Randomised controlled trials									
Bock[61]	2018	Uni clinic, MS, 43 years	RCT, three arms (KD, 1 week fast, then MED, control)	<50 g	~2 weeks (genetic analysis timepoint) (6 months)	20/18 (90%)	*Ad libitum*	BL BMI: 25·9 kg/m^2, loss −0·78 ± 0·3 kg/m^2	(KD combined with fasting group at 2 weeks to analyse groups in ketosis compared with control). Significant decrease of pro-inflammatory enzymes implicated in demyelination. Decreased ALOX5, COX1 and COX 2. (positive)
Non-randomised or non-controlled trials									
Brenton[62]	2019	Community, MS, median 38 (15–50) years	Prospective, single-arm KD	<20 g	6 months	20/18 (90%)	*Ad libitum*	BL BMI: 34·1 ± 6·9 kg/m^2, loss −3·0 ± 2·2 kg/m^2	No significant increase in adiponectin. (equivocal)
AUTO-IMMUNE (*n* = 1)									
Randomised controlled trials									
Schmidt[140]	2019	Diabetes clinic, T1D, 44 ± 12 years	RCT crossover (LCD or HC 250 g)	<100 g	12 weeks arms 12 weeks washout	14/10 (71%)	*Ad libitum*	BL: 77·4 ± 10·6 kg to 75·5 ± 0·9 kg	No significant changes to concentrations of IL-1β, IL-6, IL-10 or TNFα for either diet. (equivocal)
MUSCULOSKELETAL (*n* = 1)									
Randomised controlled trials									
Strath[78]	2019	Community, knee OA/ pain, 72 ± 2 years	RCT three arms (KD, low fat or habitual)	20–40 g	12 weeks	8/8 (100%)	*Ad libitum*	BL: 98·5 ± 18·5 kg to 89·6 ± 17·9 kg	Significant decrease in KD oxidative stress (TBARS) and leptin. IL6 and CRP not significant, TNFα borderline significant for KD. (positive)
PERFORMANCE (*n* = 1)									
Randomised controlled trials									
Paoli[141]	2021	Male body builders, muscle biomarkers, 27 ± 1 years	RCT (KD or HC 55%)	<50 g	2 months	9/9 (100%)	Body building regimen	BL 86·4 ± 15·4 kg to 85·5 ± 13·62 kg	Significant decrease in inflammatory cytokines with KD (IL6, IL1β, TNFα); significant increase in BDNF with KD. (positive)
SPINAL CORD INJURY (*n* = 1)									
Randomised controlled trials									
Yarar-Fisher[83]	2018	Spinal rehab ward, acute SCI, 32 ± 15 years	RCT (KD or 44% HC)	3–8%	5 weeks	4/4 (100%)	*Ad libitum*	NR	Increased lysophospholipid 16:0 and fibrinogen (AI) in KD. (positive)

ADA, American Diabetes Association diet; AI, anti-inflammatory; ALOX5, arachidonate 5-lipoxygenase; BDNF, brain-derived neurotrophic factor; BL, baseline; BMI, body mass index; COX, cyclooxygenase; CRP, C-reactive protein; CVD, cardiovascular disease; DG, dietary guidelines; DHA, docosahexaenoic acid; EE, energy expenditure; F, female; FGF21, fibroblast growth factor 21; HC, high-carbohydrate; hsCRP, high sensitivity C-reactive protein; HF, high fat; HUF, high unsaturated fat; ICAM-1, intracellular cellular adhesion molecule-1; IFN-γ, interferon gamma; IL, interleukin; kcal, kilocalorie; KD, ketogenic diet; kJ, kilojoule; LF, low-fat; M, male; MC, moderate-carbohydrate; MCP-1, monocyte chemotactic protein-1; MCT, medium-chain triacylglycerol; MD, Mediterranean diet; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NR, not reported; O3, omega-3; PAI-1, plasminogen-activator inhibitor-1; ROS, reactive oxygen species; SF, saturated fat; T1D, type 1 diabetes; T2D, type 2 diabetes; TBARS, thiobarbituric acid reactive substances; TNF-α, tumour necrosis factor alpha; USF, unsaturated fat; VLCKD, very-low-calorie ketogenic diet; VLCnKD, very-low-calorie non-ketogenic diet.

** Carbohydrate presented as either (a) ratio of fat: protein + carbohydrate, (b) grams per day or (c) a daily percentage.

Comparator diet showed significant positive outcome.

sensitivity[148], nutritional strategies to address chronic pain are potential treatment options. A diet that potentially reduces inflammation is also an option.

KD has also been reported to reduce inflammatory loading, which is supported by the results from this review. Increased levels of inflammatory cytokines (such as CRP, TNF-α and ILs 1, 6 and 8) have been demonstrated in chronic pain presentations, with a potential link between an increase in low-grade inflammation and the development of persisting pain[12,149,150]. Within the nervous system, pro-inflammatory mediators can activate the microglia, increasing their number and size, altering morphology and increasing receptor expression. This results in further up-regulation of neuroinflammation leading to maladaptive synaptic plasticity and central sensitisation[151–154]. In contrast, the presence of ketones and/or the suppression of glycolysis positively influence the microglia, shifting them towards anti-inflammatory phenotypes[155]. In addition, ketone bodies acting as signalling molecules can mitigate NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome activity in the microglia and central nervous system, and act as a ligand for G-protein receptors becoming class 1 and 2 histone deacetylase (HDAC) inhibitors within the brain up-regulating anti-inflammatory and antioxidant pathways[6,155]. Inducing ketosis via a KD to mitigate inflammatory processes can be supported mechanistically[7,156] as well as clinically from the human studies retrieved (Table 3).

All seven migraine studies utilised a KD and reported positive outcomes. There are several mechanisms relevant to migraine development that are influenced by a KD. In addition to cortical excitability and inflammation already discussed, an energy deficit from impaired glucose metabolism/transport, mitochondrial dysfunction and oxidative stress are also implicated in migraine as well as other neurodegenerative disorders[157,158]. In the context of glucose restriction, ketones are supplied to the neuron for fuel from the periphery through the blood–brain barrier, but also by fatty acid oxidation occurring in within the astrocyte[158]. Ketones can meet the energy shortfall and provide bioenergetic stability. They also reduce oxidative stress by up-regulating antioxidant defence and improved mitochondrial respiration[4,159]. Whilst the presence of ketones on a KD provides a plausible mechanistic explanation for pain reduction, the absence of ketones on an LCD does not necessarily remove the potential benefit.

An LCD which does not achieve significant levels of blood ketones may also improve chronic pain through mechanisms related to lower blood glucose levels rather than ketone-mediated actions. Chronic hyperglycaemia results in the production of advanced glycation end products which activate receptors on the neuron, potentially damaging it and promoting inflammation (such as in diabetic neuropathy)[10]. It also results in hyper-insulinaemia where some cells fail to respond correctly to insulin signalling (insulin resistance) linked to the development of chronic pain such as fibromyalgia[160]. A reduction in glucose also reduces the NADH:NAD^+ ratio, which signals a reduction in the transcription of pro-inflammatory genes in the microglia[11]. Interestingly, cross-sectional studies investigating the effect of glucose-lowering medication such as metformin report reduced musculoskeletal pain[161]. Overall, the beneficial outcomes on pain from an LCD or a KD may be a synergistic action of lowered blood glucose and increased blood ketones.

Defining the most beneficial diet for chronic pain has been the target of recent systematic reviews[162–164]; however no clear diet stands out[162]. Only two studies using a low-carbohydrate approach specifically for pain were found during this review[77,78]. Both demonstrated improvements in pain outcomes, one using a KD[78] and the other an LCD[77]; however, neither presented ketone levels or measured dietary carbohydrate data. A third study[14] published after the scoping review date also reported significant improvements in pain outcomes using a KD protocol with a significant but small rise in ketone levels and measured daily carbohydrate intake reduced to 70 g per day in the intervention group. The human trials presented support the use of a KD for a reduction in nervous system sensitivity; however, an LCD also reports benefits. It is unclear from the current research what level of carbohydrate restriction is required, whether the effect increases proportionately with carbohydrate reduction, or what diet duration length is required for favourable impacts on nervous system sensitisation. Further research using larger participant numbers is required to help answer these questions which are relevant for clinical application.

A limitation of this review is the confounding variable of weight loss. A large portion of included studies reported significant weight loss, which is also reduces inflammatory cytokines and may be also responsible for positive outcomes. A further limitation was the exclusion of extensive paediatric studies that may have provided further mechanistic evidence (such as Napolitano and colleagues[165] who were the first to show an increase in the antioxidant glutathione in human rather than animal models) (Supplementary Appendix 1). Despite this, an LCD or a KD is supported by mechanistic animal research as well as the human data presented here to provide plausible rationale as to how physiology might be influenced in a way to reduce pain perception.

Conclusion

This scoping review of LCD and KD research identified a large body of prospective adult human dietary intervention trials that reduced carbohydrate intake to below 130 g per day and exceeded 2 weeks in length. From these, there were sixty-four studies reporting neurological outcomes of which 83% showed improvement, and sixty-three studies reporting inflammatory biomarkers of which 71% improved. Both nervous system sensitisation and inflammation occur in chronic pain and as such may be improved by low-carbohydrate nutritional therapy. More clinical trials within this population are required to build on the few human trials that have been done.

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Supplementary material

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