British Journal of Nutrition (2023), 129, 1677–1692 doi:10.1017/S0007114522001854

When and what to eat? A scoping review of health outcomes of fasting in conjunction with a low-carbohydrate diet

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(Submitted 24 September 2021 – Final revision received 27 May 2022 – Accepted 8 June 2022 – First published online 29 June 2022)

Abstract

Over the last several decades, there has been an increase in chronic diseases such as neurodegenerative, inflammatory, cardiovascular disease (CVD) and cancer. Two eating patterns, a low-carbohydrate diet (LCD) and fasting, have been researched independently over this period and found to be beneficial in reducing many of these chronic diseases' detrimental effects. However, there have been limited studies about the synergy of these eating patterns. This current scoping review aims to explore the evidence of the health outcomes of using a LCD in conjunction with fasting. Four databases were searched, and fifteen articles were found that fit the inclusion criteria. The articles reported positive effects of combining the two eating patterns for type 2 diabetes, CVD, inflammatory conditions and weight reduction and maintenance. LCD and fasting together provide synergy in decreasing metabolic syndrome (as the key causes of chronic illnesses), such as insulin levels, fasting glucose, blood pressure, TAG and regulating lipid profile. Due to the paucity of research, further high-quality studies are needed to substantiate this evidence.

Keywords: Low-carbohydrate diet: Fasting: Low glycaemic: Intermittent energy restriction: energetic restriction

Chronic diseases are rising despite societal preoccupations with dieting and image consciousness[1]. Low-carbohydrate diet (LCD), energetic restriction over extended periods and fasting practices, for health benefits, have been an emerging research focus in nutritional epidemiology, health intervention and health promotion[2,3]. There has been an increasing number of systematic reviews (including a diverse range of meta-analyses of randomised control studies) with a key focus on either LCD or fasting[4–8]. However, there have not been any review papers investigating fasting in conjunction with LCD to assess the integrated impact.

Fasting has been practiced and studied for religious, socio-economic, experimental and therapeutic purposes for centuries[9]. Various forms of fasting have recently become popularised, including alternate-day fasting (ADF) (1-d energetic restriction then at liberty energetic intake the next)[6,8], 24-h fasting several times per week, daily 16-h fasts[5,10,11], the Michael Mosley 5:2 (2-d energy restriction and 5 d at liberty) and fasting-mimicking diet[12] and intermittent fasting/time-restricted feeding (abstaining from food for periods of 16–18 h alternating with normal eating for 6–8 h)[13]. Some of the fasting methods can be more adjustable to enhance adherence (e.g. intermittent fasting)[14]. Fasting research has substantially focused on improving cellular health for longevity[15], lifespan and healthspan[3]. Other significant areas of research into fasting include its impact on different types of cancer[16], inflammatory diseases, neurodegenerative diseases[13,17], weight control[5,6,8,10], reversing type 2 diabetes[6,9], decreasing cardio-metabolic disease risk factors[5,8,10], improving lipid profiles or dyslipidaemia parameters[8,10,11] and decreasing fasting plasma glucose and insulin resistance[5,8].

There is also a long history of how humans eat that involves restricted, selective or LCD. The popular Palaeolithic diet, based on the pre-agricultural period of eating with a focus on higher protein, fat and selective carbohydrate composition, has seen a re-emergence in the past two decades, from its first introduction in the 1970s[18]. The Atkins, Zone, South Beach and ketogenic diets are also common LCD that are gaining popularity[2], each focusing on different percentages of carbohydrates, proteins and fats. According to the American Diabetes Association, LCD are defined as having below 130 g/d or 26 % of total energy intake from carbohydrates. Studies on LCD classify carbohydrates into moderate (< 45–40 % energy intake), low (< 40–30 % energy intake) and very LCD (< 30–33 % energy intake)[19]. Systematic review papers on LCD report similar findings to review papers on fasting, indicating a decrease in metabolic syndrome – as a group of risk factors (e.g., blood glucose, blood pressure, TAG, insulin levels, weight gain and an improvement in lipid profiles)[7,19]. Decreasing these risk factors

Abbreviations: ADF, alternate-day fasting; LCD, low-carbohydrate diet.

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improved chronic lifestyle diseases such as cardiovascular risk factors[4], type 2 diabetes[20], obesity[14] and cardiovascular/cardiometabolic disorders[21].

An LCD is typically considered low in digestible carbohydrates, high in fat and moderate in protein[14,20,22]. This review considers the term 'low-carb diet' as low in starch[18] and includes indigestible or slowly digested carbohydrates[23] or low glycaemic index and includes thresholds of carbohydrate intake below 45 % energy intake. The general term 'low-carb' is used in this study, including ketogenic diets as a low-carb diet. Ketogenic diets include a very minimum carbohydrate (< 20 g/d) and exclude foods with a high glycaemic index, such as simple sugars, highly processed foods, fruits and starches[14]. Other LCD may have more flexibility than a ketogenic diet regarding the range of carbohydrate percentages and type of carbohydrate inclusion (fruit, for example is not included in a ketogenic diet, but may be included in a more moderate low carb diet) based on an individual's health status and physical activity levels[22]. However, the foundation of all types of LCD is relatively similar – to decrease the number of carbohydrates consumed and use fat as the body's preferred energy source. This scoping review aims to explore the evidence on the health outcomes of using an LCD in conjunction with fasting due to the scarcity of reviews around this topic.

Materials and methods

Scoping review design

This study is a scoping review using PRISMA-ScR, which is the Preferred Reporting Items for Systematic Review and Meta-analysis Extension for Scoping Reviews checklist[24]. This review was performed to explore and systematically map the existing literature to identify concepts, theories and types of evidence and ascertain gaps in research around fasting and LCD in combination[25].

The review has been conducted by applying the steps outlined by Arksey and O'Malley[26]: (a) identifying and articulating the research question, (b) identifying and implementing the search strategy, (c) selecting relevant studies, (d) extracting and charting data and (e) analysing, summarising and reporting on results.

Identifying the research question

Two independent reviewers (NS, MW) searched for and read articles on fasting and LCD patterns. A consensus was reached for the research question: *What are the health-related outcomes of LCD in conjunction with fasting?*

Search strategy

Two independent reviewers (NS, MW) conducted a literature search across four databases, Medline, PubMed, CINAHL and Scopus, from inception to the end of 2021. These were chosen as they contain an extensive range of articles from the medical and nutrition field. Searching title and abstracts for the following keywords: 'low carb*' OR 'low-carb*' OR 'low glycaemic' OR 'low glycemic' OR 'low GI' OR keto* OR paleo* OR Atkins OR zone AND fasting OR 'intermittent energy restriction' OR '5:2 diet*' OR '16:8 diet*' OR 'meal frequency' OR '800 calorie diet*' OR 'warrior diet*' OR 'eat stop eat' OR 'spontaneous meal skipping' OR 'caloric restriction'. We limited our searching to the English language and human studies only. There were no limitations on the publication date or age of participants. Figure 1 provides a summary of the search, inclusion and exclusion strategies in the PRISMA flow diagram.

Study selection

Papers were screened by title and abstract by all reviewers independently (NS, MW). Results that met the following inclusion criteria were included (1) both fasting and LCD intervention, (2) any health outcome (e.g. treatment and/or prevention of physical, psychological and social aspects of health), (3) quantitative, qualitative and mixed methods research and (4) scholarly peer-reviewed sources in English. Further publications were sourced through snowball searching, including Google Scholar, and scanning reference lists of included papers. A total of fifteen papers were included in the scoping review that met all inclusion criteria.

The main reasons for excluding papers after reading the full text are the key focus on either fasting, or LCD intervention, in isolation. In some studies although both fasting and LCD were used, they were not combined. Furthermore, there were hypothetical studies without any specific intervention and data set. Some examples of the papers excluded are provided below:

Study conducted by Aoki, T. (1981), on '*Metabolic adaptations to starvation, semistarvation, and carbohydrate restriction*', which focussed mainly on fasting intervention[27],

Study conducted by Kirk, E. (2009), on '*Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction'*, which focussed mainly on LCD intervention[28],

Study conducted by Ramakrishnan, T. (1985), on '*Beneficial effects of fasting and low carbohydrate diet in D-lactic acidosis associated with short-bowel syndrome'* and also study conducted by Nuttall, F.Q. (2015) on '*Comparison of a carbohydrate-free diet v. fasting on plasma glucose, insulin and glucagon in type 2 diabetes*', which both focussed on either fasting or LCD, and not combining the two[29,30],

The study conducted by Brown, A.J. (2007) on '*Low-carb diets, fasting and euphoria: Is there a link between ketosis and γ-hydroxybutyrate (GHB)',* with no specific intervention (a hypothetical work).[31]

Data extraction, charting and analysing the data

Data extraction was conducted by two independent reviewers (NS, MW) using a predefined format[32]. Data extraction was done based on (1) author, year, country, (2) research aim, (3) research design, (4) types of fasting and LCD, (5) health outcomes (including health promotion and treatment) and (6) quality appraisal (Table 1). Critical Appraisal Skills Programme (CASP - 2018) checklists were used to assess the quality of the papers based on their designs. No scoring system was provided by CASP. These included various designs, such as observational, longitudinal/cohort (both retrospective and prospective), case study, clinical trial and randomised crossover trial.

https://doi.org/10.1017/S0007114522001854 Published online by Cambridge University Press

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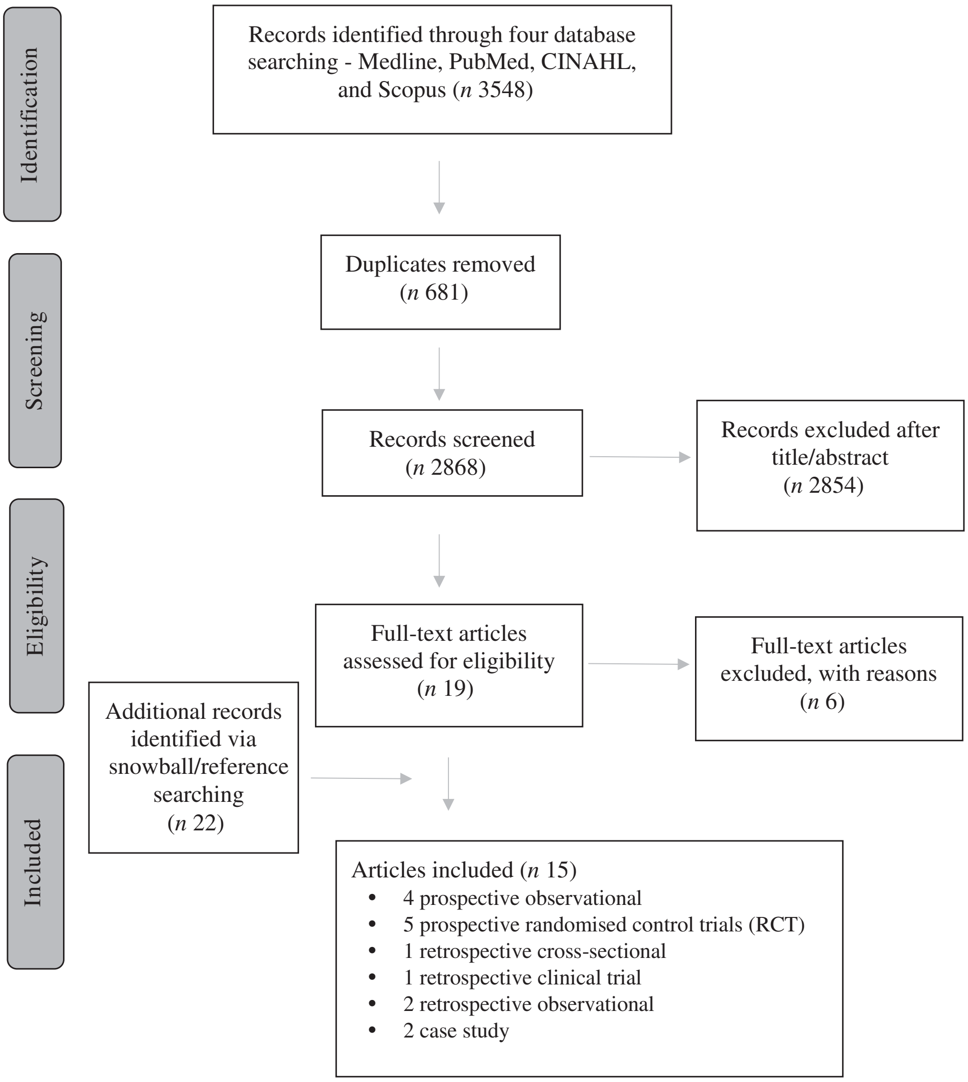

Fig. 1. PRISMA flow figure.

Content analysis was used to create codes, followed by categories and themes. Both authors were engaged in the thematic analysis of the findings separately, and the consensus was achieved via multiple meetings. This resulted in categorising the health-related outcomes of LCD and fasting based on population (children *v.* adults). The two key themes and subsequent categories were health outcomes of fasting in conjunction with LCD in children (Neurological Conditions – Epilepsy) and health outcomes of fasting in conjunction with LCD in adults (Type 2 diabetes, CVD, inflammatory diseases, weight loss/maintenance and sleep quality).

Results

Study characteristics

The fifteen articles were reviewed with various research designs, including four prospective observational studies, five prospective randomised control trials, one retrospective cross-sectional survey, one retrospective clinical trial, two retrospectives observational and two case study reports. The oldest study was published in 1992, and the more recent studies were published between 2013 and 2021. Studies were conducted in the USA (*n* 11), Canada (*n* 1), Japan (*n* 1), Korea (*n* 1) and Australia (*n* 1). Five studies[33–37] were conducted among children aged 2·5–14 years, while the remainder of the studies focussed on adults in the age range of 22–76 years. There was a low number of papers found for this scoping review, particularly control trial studies.

Although a quality appraisal is not necessary for a scoping review, we have assessed the quality of papers for a more thorough analysis of the final included papers. The majority of papers were moderate to high quality (*n* 10) – this included six high-quality and four moderate-quality papers. There were overall four low-quality papers, including two case studies and two retrospective studies.

The results across the fifteen articles were divided into health outcomes of fasting in conjunction with LCD in children and adults, as these two populations can be different in terms of their response to LCD and fasting, due to their metabolic responses.

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Table 1. Quality appraisal table

Author (year) country	Study design	Quality	Appraisal
O'Driscoll et al. (2021) Canada	Observational Study	Moderate	The study had a focussed research aim – could a low carb and fasting intervention be utilised for weight loss in a rural setting. Recruitment methods were appropriate, but a small sample size was noted. Self-selection bias was also noted. The outcomes were accurately measured, however high attrition was noted due to lack of rigorous follow-up. Confounding factors were considered. Follow-up was sufficient to see results (12 months). The results of the study are precise. The results seem generalisable to the population from which the sample is drawn.
Kalam et al. (2021) USA	Longitudinal study (Secondary Analysis)	High	The study had a focussed research aim. Recruitment methods were appropriate, but a small sample size was noted. The intervention was accurately measured to minimise bias except they did not include a control group, each participant was used as their own control. The outcome was accurately measured, however high attrition was noted due to the nature of the meal replacement intervention and the extended period necessary to undertake the intervention. Confounding factors were considered. Follow-up was sufficient. The results of the study are precise but report that self-report bias could skew results. The results seem generalisable to the population from which the sample is drawn. Research and clinical implications were sufficiently addressed.
Kalam et al. (2021) USA	Longitudinal study (Secondary Analysis)	High	The study had a very focussed research aim. Recruitment methods were appropriate, but small sample size was noted. The intervention was accurately measured to minimise bias except they did not include a control group, each participant was used as their control. The outcome was accurately measured, however high attrition was noted due to the nature of the meal replacement intervention and the extended period necessary to undertake the intervention. Confounding factors were considered. Follow-up was sufficient. The results of the study are precise but report that self-report bias could skew results. The results seem generalisable to the population from which the sample is drawn. Research and clinical implications were sufficiently addressed.
Lichtash et al. (2020) USA	Case Study	Low	The study reported on a case (*n* 1) rather than a research question. The research method was appropriate for answering the study design. The setting and the participant were not generalisable to the general population of patients with type 2 diabetes. Methods and quality control are clearly described. It was not mentioned whether the case study analysis was completed in duplicate. Results may not be transferrable to clinical applications or other settings.
Jacobi et al. (2019) USA	Observational Retrospective Study	Moderate	The study focussed on a clear question – the long-term effects of a VLC diet with IF on metabolic profile. Lack of generalisability to the general population as convenience samples recruited from one very specific Facebook group which focuses on the scientific evidence of lifestyle disease due to food choices. A retrospective study across two-time points. Relied on self-report online survey questionnaires but did include voluntary laboratory reports (pre and post-intervention) where available. Confounding variables such as other lifestyle factors, medications and comorbidities are accounted for. No mention of subsequent follow-up periods. Results were clinically significant and precise.
Blanco et al. (2019) USA	Case study	Low	The study focussed on reporting a case rather than answering a research question (*n* 1). The study's focus was unclear. The research method was appropriate to answer the study design however both the setting and the subject were not representative of the general population. The methods were clearly described in a narrative of what had occurred. No quality control measures are described in evaluating results. It is not mentioned whether the analysis of the case study was complete in duplicate. The results may not be credible or relatable to clinical practice outcomes and may not be transferable to other settings
Kalam et al. (2019) USA	Longitudinal study	High	The study had a very focussed research aim. Recruitment methods were appropriate, but small sample size was noted. The intervention was accurately measured to minimise bias except they did not include a control group, each participant was used as their control. The outcome was accurately measured, however high attrition was noted due to the nature of the meal replacement intervention and the extended period necessary to undertake the intervention. Confounding factors were considered. Follow-up was sufficient. The results of the study are precise but report that self-report bias could skew results. The results seem generalisable to the population from which the sample is drawn. Research and clinical implications were sufficiently addressed.
Bowen et al. (2018) Australia	Randomised Control Trial	High	The aim was clear and focussed. Participants were randomised to treatment sufficiently. All participants were accounted for after the trial. Blinding of participants and researchers was not conducted. Groups were similar at the start of the trial and treated equally. All clinically appropriate outcomes were considered. The results seem generalisable to the population from which the study was drawn. The benefits of the trial outweigh the risks and costs. Sufficient reporting of limitations of the study.
Manabe et al. (2016) Japan	Clinical trial	High	The study had a clear and focussed aim. Recruitment methods were appropriate, but small sample size was reported. The intervention was well-considered but differing measurement tools (PET systems) may have affected the results. The outcome was addressed, and effect estimates were precise. Confounding factors were addressed. A sufficient time for follow-up was reported. The results are generalisable for clinical outcomes and could be transferrable to other settings.

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Table 1. *(Continued)*

Author (year) country	Study design	Quality	Appraisal
Hartman et al. 2013 USA	Retrospective Analysis	Low	The study had a clear and focussed aim. Recruitment methods were appropriate, but a small sample size (*n* 6) was noted. The intervention was well considered. The outcomes were measured but based on self-reporting. Generalisable to child populations only. The benefits of the trial outweigh the risks and costs. Formal statistical analysis was not performed.
Freeman et al. 2009 USA	Randomised, double-blinded Crossover Trial	High	The aim was clear and focussed. Participants were randomised to treatment sufficiently. All participants were accounted for after the trial. Blinding of participants and researchers was conducted. Groups were similar at the start of the trial and treated equally. Large effect sizes noted. A precise estimate of effects. All clinically appropriate outcomes were considered. Generalisable to child populations only. The benefits of the trial outweigh the risks and costs. Sufficient reporting of limitations of the study.
Kossoff et al. (2008) USA	Retrospective Analysis	Moderate	The study had a clear and focussed aim. Recruitment methods were appropriate. The outcomes were measured. Generalisable to child populations only. The benefits of the trial outweigh the risks and costs. Follow-up was sufficient.
Berqqvist et al. (2005) USA	Prospective randomised study	High	The aim was clear and focussed. Participants were randomised to treatment sufficiently. All participants were accounted for at the completion of trial. Blinding of participants and researchers was not conducted. Groups were similar at the start of trial and treated equally. Large effect sizes were noted. Precise estimate of effects. All clinically appropriate outcomes considered. Generalisable to child populations only. Benefits of the trial outweigh the risks and costs. Insufficient reporting of limitations of the study.
Kim et al. (2004) Korea	Retrospective Study	Low	The aim of the paper was clear and focussed. Research team at a single institution has long-term research experience in protocol used. Cases were recruited in an appropriate fashion; retrospective nature of study was a limitation as the research team used historical subject records as a control group. This may have introduced bias into the measurement of the outcome and both groups may not have been treated equally. Confounding factors not sufficiently considered. CI not reported on effect sizes.
Klein et al. (1992) Texas	Randomised Crossover Trial	Moderate	The aim of the study was clear. Participants were randomly selected and served as their own control. Blinding of participants and researchers was not possible. Small sample size. Moderate effect sizes noted. Clinically appropriate outcomes considered. Generalisable across populations. Benefits of the trial outweigh the risks.

Notes: Critical Appraisal Skills Programme. (2018). *CASP checklists*. https://casp-UKnet/casp-tools-checklists/.

The only health outcome measured in children was related to epilepsy, as a neurological condition. Various health outcomes were assessed in adult populations, including type 2 diabetes, CVD, inflammatory disease, weight loss/maintenance, sleep quality, insomnia and sleep apnoea (Table 2).

Health outcomes of low-carbohydrate diet in conjunction with fasting in children

Neurological conditions – epilepsy. Five studies compared the impacts of a ketogenic diet on reducing epileptic seizures in children with and without an initial fasting period[33,35,36,38]. Although the studies were a combination of high-quality and low-quality designs, they had consistent results, confirming the significant benefits of fasting in conjunction with LCD on decreasing epileptic seizures in children. The studies suggested that although (short-term) fasting in conjunction with LCD provides the ideal results in epilepsy treatment, only focusing on the LCD (usually ketogenic) in this specific population can be more feasible and well-tolerated. A high-quality prospective randomised control trial found significant reductions in seizures after a 3-month follow-up in both the fasting (78 %) and non-fasting groups (67 %). They also reported that 21 % of both the non-fasting and fasting groups were seizure-free after 3 months. The non-fasting group lost less weight and experienced less hypoglycaemia, acidosis and dehydration than the fasting group[34]. The second study, a low-quality retrospective clinical trial, also reported significant reductions in seizures in both the fasting (41 %) and non-fasting groups (42 %). They also found that around 22 % of both the fasting and non-fasting groups were seizure-free at the 3-month follow-up. The non-fasting intervention was better tolerated with less dehydration and fewer hospitalisations.[33]. In the more recent studies (2008–2013), similar results were found – in the low-quality retrospective analysis by Hartman *et al.*, only three of the six participants were able to adhere to the IF/ketogenic protocol for 2 months or longer and seizure improvement ranging between 50 and 99 % seizure reduction was observed[37]. One participant's seizures only improved on fasting days. The two participants with the best seizure control reported no adverse effects, with other patients reporting hunger and one losing 1 kg during the regime. In the high quality, blinded crossover study by Freeman *et al.* which attempted to eliminate ketosis in the crossover group, a decrease in seizures was seen in both groups – 65 % of participants had a greater than 50 % decrease in seizures during the study period with 50 % of those still reporting more than 50 % reduction at 6 months follow-up. This protocol was well tolerated, despite two 36-h fasts within 12 d. There were some adverse effects, with six children reporting vomiting, three reporting fatigue and three reports of hypoglycaemia[36]. In the study by Kossoff *et al.*, 84 % of participants stated seizure reduction, in those who were fasted seizure reduction, the improvement was faster (median 5 d compared with 14 d without fasting initiation). No difference in fasting *v.* no fasting was seen at the 6-month follow-up. Over the 6

Table 2. Data extraction of the included papers

Author (year), country	Research aim	Research design	Fasting protocol	Dietary intervention	Health outcomes	Follow-up
O'Driscoll et al. (2021) Canada[46]	Effectiveness of a primary care initiative combining fasting and LCD – The NOT-FED study	1 year prospective observational Study Ninety-four initial participants Thirty-six completed 1 year	Intermittent fasting (a daily 16 h fast) is recommended. Participants reported an average of 15-h daily fasts.	– *Ad libitum* LCD – no macronutrient breakdown provided, but the education provided to lower carbohydrates to less than 40 % of TEI.	– 12-month participants lost an average of 8·2 kg (9 % decrease) and an 8·6% decrease in BMI and waist circumference – 3-month participants lost an average of 4·9 kg and 6-month participants lost an average of 6·7 kg	No follow-up
Kalam et al. (2021) USA[48]	Changes in subjective measure of appetite during 6 months of alternate day fasting with a low carbohydrate diet	A prospective longitudinal study (6-month intervention – 3-month weight loss and 3-month weight maintenance) Secondary analysis of Kalam et al. (2019) Adults (18–65 years) in obese BMI category (*n* 31). Nutritional counselling is provided once a fortnight	Alternate day fasting (2510 kJ fast day alternated with a non-fast day)	– Low-carbohydrate background diet (30 % carbohydrates, 35 % protein, 35 % fat). – Meal replacements provided (carbohydrate 10 g, protein 26 g, fat 6 g, 200 kcal total) – Weight loss period. Fast days – three meal replacements (600 kcal), no other food or beverage. 'Feast' days- five meal replacements (1000 kcal) – *Ad libitum* consumption of LC food above meal replacements on 'feast' days. – Weight maintenance period. Fast and non-fast days – three meal replacements (600 kcal).	– Subjective fullness and hunger did not change throughout the study. Appetite neither increased nor decreased.	No follow up
Kalam et al. (2021) USA[47]	Effectiveness of alternate day fasting (ADF) combined with an LCD on sleep quality, duration, insomnia, sleep apnoea in adults with obesity	A prospective longitudinal study (6-month intervention - 3-month weight loss and 3-month weight maintenance) Secondary analysis of Kalam et al. (2019) Adults (18–65 years) in obese BMI category (*n* 31). Nutritional counselling is provided once a fortnight	Alternate-day fasting (2510 kJ fast day alternated with a 'feast day' – food consumed *ad libitum*)	– Low-carbohydrate background diet (30 % carbohydrates, 35 % protein, 35 % fat). – Meal replacements provided (carbohydrate 10 g, Protein 26 g, fat 6 g, 200 kcal total) – Weight loss period. Fast days – three meal replacements (600 kcal), no other food or beverage. 'Feast' days- five meal replacements (1000 kcal) – *Ad libitum* consumption of LC food above meal replacements on 'feast' days. – Weight maintenance period. – Fast and non-fast days (three meal replacements – 600 kcal)	– Bodyweight decreased during the weight loss period and stabilised during the weight maintenance. – Net weight loss at 3 months was 5·5 % and at 6 months was 6·3 %. Fat mass was reduced. Lean mass and visceral fat mass remained unchanged. – There was no effect of the conjunction of a low-carbohydrate diet and fasting on sleep quality or duration, insomnia or risk of sleep apnoea from baseline to 3 or 6 months follow-up	No follow-up

Table 2. (*Continued*)

Author (year), country	Research aim	Research design	Fasting protocol	Dietary intervention	Health outcomes	Follow-up
Lichtash et al. (2020) USA[42]	Effectiveness and sustainability of intermittent fasting and ketogenic diet in a patient with type 2 diabetes	Case study (*n* 1) Normal weight participants (57 years) with type 2 diabetes than standard care had no improved glycaemic control	Intermittent fasting - 24 h, 3 times per week for the first fortnight – 42 h, 3 times per week for 4 months Follow-up fasting – 42 h Monday and Wednesday, 16 h Fridays for 4 months Maintenance – 16 h per day and 24 h three times per month for 6 months	– Ketogenic diet (5 % carbohydrate, 15 % protein, 80 % fat, 1500 kcal)	– HbA1c levels reduced from 9·3 % to 5·8 % – Loss of 4·3 kg over 14 months – Able to reduce medication for diabetes significantly	14-month total follow-up
Jacobi et al. (2019) USA[40]	Impact of a very-low-carbohydrate diet and intermittent fasting on metabolic parameters	A retrospective cross-sectional survey including metabolic data pre and post-lifestyle change. Participants with type 2 diabetes (*n* 63) voluntarily adhere to a very-low-carbohydrate diet and intermittent fasting.	Intermittent fasting (16–18 h/d)	– Very-low carbohydrate (mean 10 % carbohydrates, 50·1 % fat, 38·8 % protein) for 35·8 months.	– Mean weight loss = 16·1 kg. – Glucose – 40 % of participants decreased – HbA1c – 54 % participants decreased – Insulin - 14 % participants decreased – TAG – 56 % of participants improved – HDL – increased in 52 % of participants – Diabetes – 23 % reversed diabetes and 21 % pre-diabetes. 8·8 % from diabetes to pre-diabetes. – 58 % stopped diabetes medication. 17 % reduced the number of medications; 33 % on antihypertensives, stopped completely, 25 % reduced antihypertensives. – Lipids – 71 % stopped lipid-lowering drugs – Insomnia – 32 % documented insomnia at the start of the regimen, 8 % after – Inflammatory 51 % had joint pain at baseline, 7 % still had joint pain after	No follow up

https://doi.org/10.1017/S0007114522001854 Published online by Cambridge University Press

Table 2. (*Continued*)

Author (year), country	Research aim	Research design	Fasting protocol	Dietary intervention	Health outcomes	Follow-up
Blanco et al. (2019) the USA[43]	The case study reports starvation ketoacidosis following a ketogenic diet and prolonged fasting.	Case study (*n* 1) 60-year-old male on the self-administered vegetarian ketogenic diet and intermittent fasting for 1 year. History of type 2 diabetes	Intermittent fasting followed by 5-d prolonged fasting	– Low-carbohydrate (% not clear), high-fat vegetarian ketogenic diet.	– Weight loss – 20 pounds in the first year – HbA1c – reduction 11·5 % to 7·0 % – Adverse effects – dizziness, syncope, nausea, vomiting, suspected clinically significant ketoacidosis, presentation to the emergency department	No follow-up
Kalam et al. (2019) USA[41]	Effectiveness of alternate day fasting combined with a low carbohydrate diet on body weight and metabolic disease	A prospective longitudinal study (3-month weight loss and 3-month weight maintenance) Adults (18–65 years) in obese BMI category (*n* 31). Nutritional counselling is provided once a fortnight	Alternate day fasting (2510 kJ fast day alternated with a non-fast day)	– Low-carbohydrate background diet (30 % carbohydrates, 35 % protein, 35 % fat). – Meal replacements provided (carbohydrate 10 g, protein 26 g, fat 6 g, 200 kcal total) – Weight loss period. Fast days – three meal replacements (600 kcal), no other food or beverage. Non-fast days – five meal replacements (1000 kcal) – Eat at will over and above meal replacements on non-fast days. – Weight maintenance period. – Fast and non-fast days (three meal replacements – 600 kcal)	– Body weight decreased during the weight-loss period and stabilised during weight maintenance. – Net weight loss at 3 months was 5·5 % and at 6 months was 6·3 %. Fat mass was reduced. Lean mass and visceral fat mass remained unchanged. – Total and LDL cholesterol decreased by 8 %. Blood pressure was reduced by –7 mm Hg. Fasting insulin decreased by 24 %. No changes were seen to HDL-C, TAG, diastolic blood pressure, heart rate, fasting glucose, homeostatic model assessment of insulin resistance and HbA1c	No follow-up
Bowen et al. (2018) Australia[44]	To compare daily energy restriction (DER) protocol with a DER + ADF protocol	Randomised control trial of adults with overweight and obesity (25 – 60 years) 16-week intervention *n* 164 Randomised into DER or DER + ADF	ADF (Tuesday, Thursday, Sunday) with *ad libitum* Saturday	Planned energy and macronutrient composition of the DER protocol: 31 % carbohydrate, 38 % protein, and 28 % fat. Energy - 5000 kJ Planned energy and macronutrient composition of the modified fasting days was 40 % carbohydrate, 34 % protein, and 22 % fat. Energy – 2400 kJ *Ad libitum* day – not tracked – approx. energy - 10 000 kJ.	No significant difference between the DER and the ADF groups were found. Retention –82 % for ADF and 83 % DER retention at 16 weeks Weight loss – 10·7 +/–0·5 kg for the ADF group and _11·2 +/1 0·6 for the DER group Significant increases in transferrin saturation, ferritin, folate, vitamin B_{12} and zinc across both groups and significant decreases in Vit D, thiamine and transferrin across both groups. Significant reductions in total cholesterol, LDL-C, HDL-C, TAG, fasting glucose, fasting insulin, blood pressure, CRP were seen with no significant differences between the groups	24-week follow-up

https://doi.org/10.1017/S0007114522001854 Published online by Cambridge University Press

Table 2. (*Continued*)

Author (year), country	Research aim	Research design	Fasting protocol	Dietary intervention	Health outcomes	Follow-up
Manabe et al. (2016) Japan[45]	Low-carbohydrate diet and fasting on diffuse left ventricle fluorodeoxyglucose uptake and free fatty acid levels in patients with suspected cardiac involvement sarcoidosis.	Prospective randomised clinical trial Adults (22–76 years) with cardiac involvement sarcoidosis (*n* 82)	Participants were randomised into two groups – 6 h fasting without a low-carbohydrate diet (*n* 58) and 18 h fasting with a low-carbohydrate diet (*n* 24).	Low carbohydrate diet (less than 5 g of carbohydrate per meal)	– Fasting alone group – a higher percentage of diffuse left ventricle uptake than fasting and low-carbohydrate diet group – Fasting and low-carbohydrate diet group – higher free fatty acid levels	No follow-up
Hartman et al. (2013) USA[37]	Intermittent fasting: A 'new' historical strategy for controlling seizures?	Retrospective analysis Children (2–7 years) with seizures not responding to KD	Intermittent fasting – skipping two consecutive meals on two non-consecutive days per week	KD started before the fasting regime – 4:1 ketogenic ratio (fat: carbohydrate and protein)	– Three patients adhered to the combined intermittent fasting/KD regimen for 2 months or longer (and four had transient improvements in seizure control. Some hunger-related adverse reactions were reported.	No follow up reported
Freeman et al. (2009) USA[36]	A blinded, crossover study of the efficacy of the ketogenic diet	Blinded, crossover study Children (1–10 years) with Lennox-Gastaut syndrome (LGS) (*n* 20)	36 h initial fast	– Classic KD 4:1 ketogenic ratio (fat: carbohydrate and protein) with child randomised to one of two study solutions –Saccharin sweetened or 60 g glucose sweetened – the glucose solution was intended to stop ketosis. – All children completed the 12-d protocol	– Both groups saw a highly significant decrease in seizures over the 12-d protocol – a median decrease of 34 seizures per day with the difference between the two arms NS. 65 % of patients experienced a > 50% reduction in seizures – The saccharin arm saw uniformly large ketones (80–160 mg/dl), however, even the glucose arm ketones were trace to moderate (15–60 mg/dL)	6 and 12-month follow-up
Kossoff et al. (2008) USA[35]	When do seizures usually improve with the ketogenic diet	Retrospective Children (0·3–15 years) with intractable epilepsy (*n* 118)	Either an initial 24 h fast or initial 48 h fast or no fasting initiation	KD diet (macronutrient composition not defined in article)	– 84 % reported some seizure reduction. 16 % reported no seizure reduction. – 5 % of those report first improvement within the first 14 d of treatment, 90 % within 23 d and 5 % had no reported improvement until 60–65 d after onset. The presence of initial fasting had a median time to the improvement of 5 d, compared to 14 d in those who did not fast. In those who improved the likelihood of seizure reduction within the first 5 d was twice as likely with fasting (60 %) *v.* 31 %. There was no statistical difference between the 24 h and 48 h fasts.	Follow-up at 3, 6 and 12 months

Table 2. (*Continued*)

Author (year), country	Research aim	Research design	Fasting protocol	Dietary intervention	Health outcomes	Follow-up
Berqqvist et al. (2005) USA[34]	Efficacy of ketogenic diet with and without initial fasting in epileptic seizure reduction in children	Prospective randomised control trial Children (1–14 years) who experience at least one epileptic seizure per 28 d and medication has failed to work at least three times (*n* 48) Randomised into a fasting (*n* 24) or non-fasting (*n* 24) ketogenic diet 6-d intervention; energy intake established by recommended energies, adjusted based on weight, height and physical activity Follow-up after 2 weeks and then 1, 2 and 3 months Nutritional education attended by families	Fasting group Days 1 and 2 – 48 h fast Day 3 – three meals with a third of daily energies Day 4 – three meals with two-thirds daily energies Day 5 and 6 – three meals with full energies (4:1 fat to carbohydrate ratio + protein)	Non-fasting group Day 1 – 1:1 ratio fat to carbohydrate + protein with full energies Day 2 – 2:1 ratio fat to carbohydrate + protein with full energies Day 3 – 3:1 ratio fat to carbohydrate + protein with full energies Day 4, 5 and 6 – 4:1 ratio fat to carbohydrate + protein with full energies	– Fasting group – 58 % had > 50 % reduction in seizure type at 3 months, and 21 % were seizure-free. Median seizure reduction 78 % – Non-fasting group – 67 % had a > 50 % reduction at 3 months, and 21 % were seizure-free. Median seizure reduction 94 %. – The non-fasting group lost less weight and had fewer and less severe episodes of hypoglycaemia, fewer treatments for acidosis and dehydration, but no difference in vomiting.	Follow-up at 0·5, 1, 2 and 3 months
Kim et al. (2004) Korea[33]	Efficacy and tolerability of a ketogenic diet with and without initial fasting in children with epilepsy	Retrospective clinical trial Children (2–7 years) with intractable epilepsy treated with a non-fasting ketogenic diet between 1999 and 2001 (*n* 41) compared with hospital records (1995–1999) of children (2–7 years) with refractory epilepsy who were treated with an initial fasting ketogenic diet (*n* 83). Three months follow-up Frequency of epileptic seizures recorded	Fasting group - fasting and fluid restriction until urinary ketosis, then 4:1 ratio diet (fat to protein and carb) increased until total energies met.	Non-fasting group - no fasting or fluid restriction. Day 1 – one-third of total energies Day 2 – two-thirds of total energies Day 3 – full energies	– Fasting group – 35 % seizure free, 18 % reduced seizures of > 90 %, 23 % reduced seizures 50 % to 90 %, and 48 % experienced nausea, vomiting, constipation or diarrhoea – Non-fasting group – 34 % seizure free, 20 % reduced seizures of > 90 %, 22 % reduced seizures 50 % to 90 %, 36 % experienced nausea, vomiting, constipation or diarrhoea – Dehydration was more frequent in the fasting group 62·7 % than non-fasting group 12·2 %	No follow up
Klein et al. (1992) USA[39]	Investigate the relationship between energy and carbohydrate intake and the metabolic response to fasting	Prospective randomised cross-over trial Two study protocols were separated by 3 weeks. Healthy male participants (*n* 5) Blood samples were taken before, during and after fasting protocols	Protocol one – 84-h fasting regime alone Protocol two –intravenous lipids are given during 84 h fast to meet resting energy requirements	After fasting participants consumed a free-choice diet for the 3-week interval between protocols	– Weight loss – .78 to .16 kg greater in the fasting-only protocol. – Nitrogen excretion – same in both studies – Changes in substrates and hormones – same in both studies – Fluid balance – more negative in fasting-only protocol, but not significantly • Plasma glucose and insulin – decreased in fasting-only protocol • Free fatty acids, ketone bodies and epinephrine increased in fasting-only protocol • Norepinephrine – no change in either protocol • TAG – increased in lipid protocol but not significantly	No follow-up

LCD: low-carb diets; VLCD: very low-carb diets.

https://doi.org/10.1017/S0007114522001854 Published online by Cambridge University Press

months, the majority either maintained (n 54) or improved (n 21) their seizure control. Twenty-four children saw a worsening in seizures after an initial improvement[35].

Health outcomes of low-carbohydrate diet in conjunction with fasting in adults

Type 2 diabetes. Five studies explored the effect of LCD in conjunction with fasting on health outcomes related to type 2 diabetes[39–43]. The majority of these studies have moderate- to high-quality designs (except one case study), and all confirmed the significant results in improvement of the risk factors related to type 2 diabetes, using an LCD in conjunction with fasting. One moderate-quality retrospective cross-sectional study from a fasting and LCD social media group included metabolic data pre- and post-fasting/diet change[40]. They found that 23 % of participants reversed their type 2 diabetes and 21 % reversed their pre-diabetes[40]. In 58 % of participants, diabetes medications were reduced. The HbA1c levels decreased in 54 % of participants. They also reported significant reductions in diagnostic parameters of plasma glucose in 40 % of participants and fasting insulin in 14 % of participants[40]. A second study, a high-quality prospective longitudinal study, reported a reduction in fasting insulin by 24 % after 6 months of combining ADF and LCD but found no change in participants fasting glucose, insulin resistance or HbA1c levels[41]. A moderate-quality prospective randomised cross-over trial reported decreases in plasma glucose and insulin in the fasting-only protocol but not in the fasting protocol that included intravenous lipid injections[39]. Finally, the moderate-quality case study on a normal weight 57-year-old woman with diabetes found that combining LCD and intermittent fasting over 14 months decreased her HbA1c levels from 9·3 % to 5·8 %[42]. This was supported by findings from a low-quality case study of a 60-year-old man who self-administered a vegetarian ketogenic diet with intermittent fasting whose HbA1c decreased from 11·5 % to 7 %[43]

Cardiovascular diseases. Four studies with moderate- to high-quality designs focussed on the effect of an LCD and fasting on cardiovascular health and CVD[39–41,44]. All papers confirmed the benefits of LCD and fasting in improving the risk factors for CVD. The first study, a moderate-quality retrospective cross-sectional study, found that 56 % of participants' TAG levels improved and HDL-cholesterol increased for 52 % of participants[40]. They also reported that 71 % of participants were able to discontinue their lipid-lowering medications. The second study, a moderate-quality prospective randomised cross-over trial with two protocol arms separated by 3 weeks, reported a reduced carbohydrate intake was fundamental to the 'metabolic' response in short-term fasting rather than overall energetic or energy restriction[39]. The third study, a high-quality prospective longitudinal study, reported decreased total and LDL-cholesterol by 8 %, but there were not many changes in HDL-cholesterol, TAG or diastolic blood pressure[41]. The fourth study (Bowen et al 2018) reported a significant decrease in total cholesterol, LDL, HDL, TAG, C-reacitive protein (CRP) and blood pressure at week 16 in comparison with the baseline with no significant differences between fasting and non-fasting protocols[44].

Inflammatory diseases. Two studies, including one high quality and one moderate-quality design, focused on inflammatory conditions and a combination of fasting and LCD[40,45]. The first, a high-quality prospective randomised control trial, looked at the effects of 6-h fasting without an LCD compared with 18-h fasting and an LCD on patients with suspected cardiac involvement sarcoidosis[45]. According to the outcomes, higher levels of free fatty acids were detected in the longer fasting, LCD group compared with the shorter fasting group. The second study, a moderate-quality retrospective cross-sectional study, reported the benefits of intermittent fasting and an LCD for other inflammatory conditions[40]. They found that 51 % of participants reported joint pain at baseline, which reduced to 7 % after lifestyle change implementation[40].

Weight loss/maintenance. Obesity and weight gain, particularly around the waist, are considered the key indicators of metabolic disorders[7]. Nine papers reported the effect of an LCD and fasting on weight loss and maintenance[39–41,43,44,46–49]. The majority of these studies had moderate- to high-quality designs, and all confirmed the beneficial impact of an LCD and fasting on weight loss and weight maintenance. A mean weight loss of 16 kg over 3 years was reported by Jacobi *et al.*[40] in their moderate-quality retrospective cross-sectional study. Kalam *et al.*[41] and the secondary analyses by Kalam *et al.*[47,48]reported a net weight loss of 5·5 % of body mass at 3 months and 6·3 % after 6 months in their high-quality prospective longitudinal study. Klein and Wolfe[39] reported weight loss to be greater in the fasting group *v.* the lipid intervention group in their moderate-quality prospective randomised cross-over trial, although this was attributed to fluid loss. Lichtash *et al.*[42] reported a weight loss of 4·3 kg over 3 years in their case study of a healthy weight woman with type 2 diabetes. Blanco *et al.*[43] reported a 9-kg weight loss over 1 year in their low-quality case study. O'Driscoll *et al.* reported a 9 % weight loss and 8·6 % decrease in BMI and waist circumference[46]. Bowen *et al.* reported a 10·7 kg weight loss for the fasting (ADF) group and 11·2 kg for the non-fasting group. This result was unexpected, as with energy calculations the fasting group was expected to ingest less energy, leading to a greater weight loss. This result could have been confounded by the inclusion of an eating *ad libitum* day once per week[44].

Sleep quality. Two studies reported that combining the two dietary patterns did not adversely affect sleep factors[47]. A moderate cross-sectional study by Jacobi *et al.*[40] found a 24 % reduction in participants reporting insomnia at the end of the intervention. A moderate-quality longitudinal study by Kalam *et al.*[47] found no difference from baseline, 3 months and 6 months in sleep quality, duration, insomnia or the risk of apnoea. That is, sleep quality was not worsened, and sleep duration was not shortened.

Discussion

To our knowledge, this scoping review is the only one to date that has examined the potential health outcomes of LCD in conjunction with fasting. The reason for conducting a scoping

https://doi.org/10.1017/S0007114522001854 Published online by Cambridge University Press

British Journal of Nutrition

review was the paucity of literature and to allow the inclusion of all possible papers on the topic. Overall, the quantity of final included papers is not an issue as far as the review follows a systematic approach[50,51]. The limited number of papers (particularly control trial studies) indicates the importance of further studies on the topic.

We have categorised our argument on the unique position of fasting in conjunction with LCD into six key sections: (a) the possible advantage of shifting the body fuel from glucose to fat as a more sustainable fuel; (b) improving metabolic syndrome (as the root cause of the most of chronic illnesses); (c) the necessity of individualised approach to the incorporation of fasting in conjunction with LCD; (d) interpretation of blood test markers, particularly lipid package for individuals with LCD; (e) healthy *v.* unhealthy LCD (well-planned LCD can meet all the Nutrient Reference Values) and finally (f) recommendations for further studies.

LCD in conjunction with fasting (Fig. 2) changes body fuel from glucose to fat, as a more sustainable fuel due to the creation of ketone bodies. This may contribute to glycaemic control (less glucose fluctuation) and hence reduce hunger, which ultimately results in a more viable weight loss and maintenance[40,43]. According to 'The carbohydrate-insulin Model of obesity' (CIM), diets high in carbohydrates (particularly ultra-processed foods) can cause postprandial hyperinsulinaemia, leading to the deposition of energies in fat cells rather than being used as energy in muscle cells. This ultimately results in weight gain due to frequency of eating, reducing metabolic rate or both[52]. Kalam *et al.*[41] discussed the benefits of alternative day fasting and LCD as the most clinically significant results to date with a weight loss of 5·5 % of body weight after 3 months[53,54], specifically due to carbohydrate restriction to 20–35 %. In addition, combining the two patterns does not impact sleep quality, duration, insomnia or risk factors for obstructive sleep apnoea[33].

LCD and fasting together provide synergy in reversing metabolic syndrome, as the root cause of chronic diseases (e.g., CVD, type 2 diabetes and inflammation). It will decrease fasting glucose, insulin level and blood pressure, as well as regulate cholesterol by decreasing small dense LDL, decreasing TAG and increasing HDL[40,43,45]. However, it is unclear if improving metabolic syndrome is due to the LCD, fasting or both. One argument is that it is likely that carbohydrate restriction, not the absence of energy, is significant in health outcomes[39]. It is argued that the satiating effects of higher concentrations of fat and protein in LCD suppress the appetite, and hence contribute to less fluctuation in glucose and positive health outcomes[19]. It is also argued that although there was a weight reduction, the participants did not report any changes in appetite[48].

LCD in conjunction with fasting may not be applicable for some specific populations or demographics (e.g. children, pregnant women, people with anorexia or those with kidney complications). Kim[33] concluded that the fasting initiation to the LCD for decreasing seizures in children with epilepsy was not therapeutically superior to the non-fasting initiation and was deemed unnecessary as it resulted in more discomfort and distress. The authors discussed that their results were similar to previous case series studies[55,56] in both groups in terms of achieving an appropriate level of urinary ketosis and time to onset of reduction of seizures/being seizure-free. Overall, the benefit of initial fasting on the ketogenic diet is the possibility of screening for metabolic syndrome[36]. Kossoff states that although fasting is not necessary as long-term outcomes remain similar, fasting can lead to a more rapid reduction in seizures (an average of 5 d with fasting or 14 d without)[35]. However, this type of initiation may increase the frequency of hypoglycaemia and gastrointestinal problems[34]. It is emphasised that children with epilepsy better tolerate a low-carb diet initiation *v.* a fasting initiation to the LCD (in which fewer adverse events were reported, such as hypoglycaemia and acidosis). This can be achieved by gradually and briefly increasing the ratio of fat to carbohydrate Kim[33].

Overall, as childhood is a time of rapid growth and development, any dietary intervention needs to be approached with caution, and in any intervention, care needs to be taken to ingest sufficient energies and protein for continued growth. Children undertaking LCD for epilepsy treatment should be closely medically monitored, particularly in case of utilising any form of fasting[38]. Possible adverse effects associated with LCD (either alone or combined with fasting) in children are hypoglycaemia, lethargy, dehydration, metabolic acidosis, gastrointestinal symptoms and weight loss (the most common side effect). For precautionary reasons, multivitamin and mineral supplements can be used if required[38].

It is important to highlight that adherence to LCD and fasting lifestyle patterns can be decided on a personal level, based on health status and weight loss goals, as it may not be achieved easily for everybody[40]. Overall, one diet does not fit all, and optimal nutrition should emphasise high-nutrient density while managing energy balance. Although these two dietary interventions are gaining in popularity, there may not always be significant additional benefits to be gained from fasting[44] or LCD. For many people improving diets by reducing ultra-processed foods (increasing consumption of high-quality protein and fresh fruits and vegetables) can improve inflammation and pain independent of carbohydrate levels[1,57]. For example, a positive correlation was found between the risk of metabolic syndrome and higher consumption of carbohydrates, particularly ultra-processed foods in Asian and less developed nations *v.* non-Asian and more developed countries[7]. This may be linked to biological and socio-economic status in the study areas and the health literacy around eating patterns.

Individuals need to receive personalised dietary advice, based on their specific situation, which can provide a more sustainable approach, to adhering to the diet. However, there is an argument that the incorporation of more minimally processed foods needs to be considered as a foundation across different dietary patterns. In addition, individual adjustment to the diet may be different based on the health background and socio-demographic status. For example, someone with type 2 diabetes may require more time to adapt in comparison with a healthy individual, due to differences in their levels of insulin resistance. Those with a specific illness require consultation with their health professionals before commencing lifestyle changes. A narrative interpretation of a case study (included in our review) showed that a man with type 2 diabetes self-administered an LCD and fasting regime without professional monitoring. This ultimately resulted in admission to the emergency department

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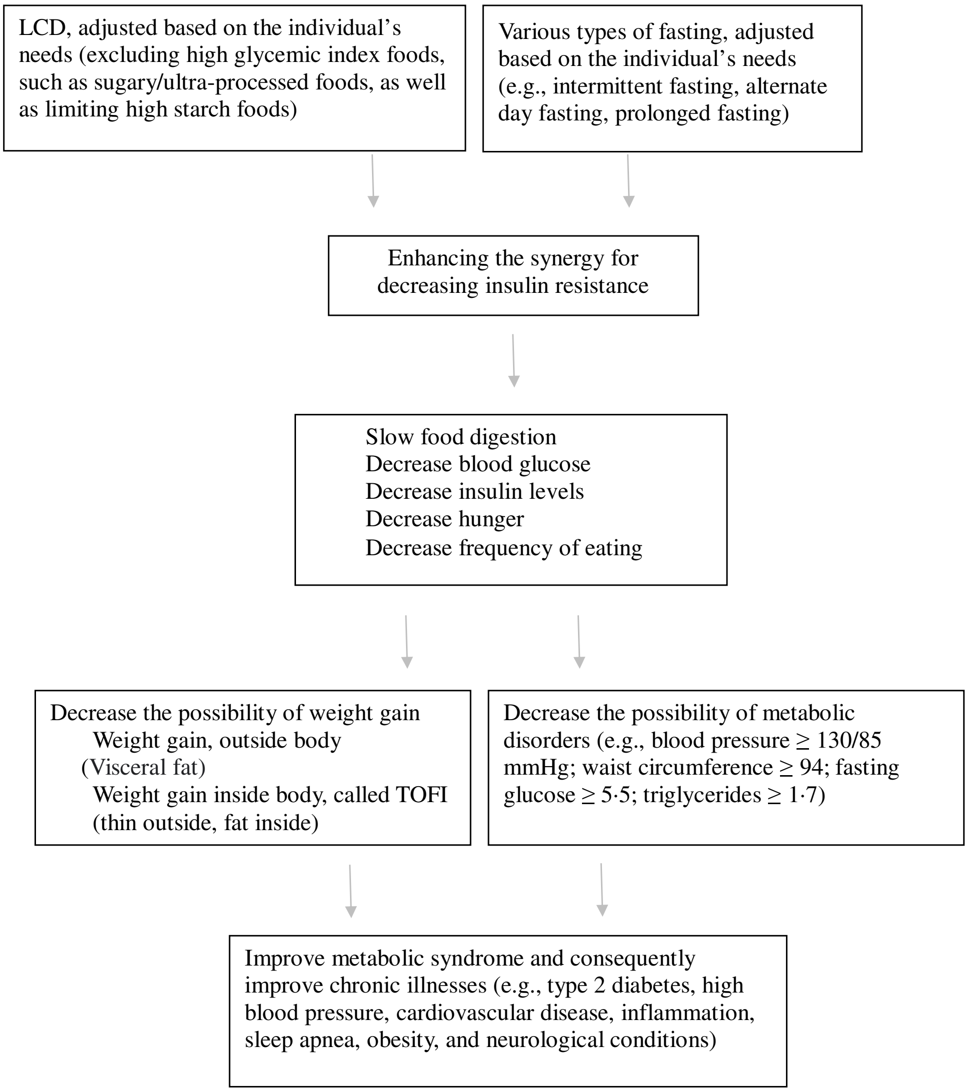

Fig. 2. Fasting and Low-Carbohydrate Diet Synergy Flow Chart.

with suspected starvation ketoacidosis due to prolonged fasting (5 d of only water)[43]. This study concluded that if the fasting period is too long or the energy intake is too low, there is a possibility of ketoacidosis, especially in patients with comorbid illnesses such as type 1 or type 2 diabetes[43]. However, how the diet was administered was not reported in this study, and there were no quality control measures, indicating the lack of credibility and relatability of clinical implications which can result in a high level of bias. To our knowledge, there is only limited human research on the dangers of ketoacidosis from low-carbohydrate, low-energetic dietary patterns to date. Overall, we recommend an informed, personalised approach to the prevention, treatment and recovery of each individual (not one size fits all approach). We also suggest providing training in updating healthcare providers' nutrition literacy (particularly general physicians) based on the most recent and reliable evidence-based research on emerging dietary patterns, including LCD and fasting. Enhancing the nutrition literacy of healthcare providers will impact the way they guide consumers, and subsequently enhance the health and nutrition literacy of consumers to make an informed decision, based on their specific situation.

The other ongoing debate on LCD is related to the lipid profile. It is suggested to interpret lipid profiles differently in LCD, as it can increase the level of both LDL- and HDL-cholesterol but lower TAG (triacylglycerol or triacylglyceride)[19,58], which is not necessarily a negative point. The preservation of HDL-cholesterol could be described by the decrease in postprandial lipaemia (defined as the rise of TAG-rich lipoproteins following food consumption). In addition, elevated LDL in isolation is not a strong indicator of cardiovascular risk[59–61]. Increased LDL-cholesterol can be explained by increased levels of larger sized LDL, that are less atherogenic in comparison to small dense LDL[58]. Overall, LDL can be detrimental when joined with fructose and glucose (from high glycaemic index foods), as well as when it is accompanied by a high level of n-6[59]. This can result in the accumulation of glycation/glycated LDL (small dense LDL), and subsequent oxidation, which may not be recognised by the body to be eliminated, and therefore become a risk factor for CVD[59].

Overall, it is suggested to interpret cholesterol measurements based on the TAG:HDL ratio ≤ 0·8 (TAG ≤ 0·5 (mmol/l); HDL ≥ 1·5 (mmol/l)). Further testing can be done to clarify cardiovascular risk for patients concerned with cholesterol levels such as a Coronary Artery Calcification score, as well as testing subfractions to check for small dense LDL particles[62]. LCD improves the lipoprotein profile by improving postabsorptive and postprandial TAG, HDL and distribution of LDL subfractions[63]. Furthermore, contrary to earlier short-term reports on adverse impacts of LCD, a 10-year prospective longitudinal study shows no cardiovascular risks[64]. Interestingly, a 2020 meta-analysis of LCD showed an improvement in cardiovascular risk factors[65]. The hypothesis that elevated TC or LDL-cholesterol is the cause of atherosclerosis and CVD has been disproved by numerous studies. Higher levels of LDL-cholesterol have even been shown to be protective in older populations[66].

It is also paramount to highlight the health benefits of good fat, as a carrier for the fat-soluble vitamins, such as vitamins A, D, E and K. These vitamin deficiencies can result in adverse effects, such as rickets, blindness and haematological disorders. In addition, low consumption of these vitamins can be associated with calcification of the arteries osteoporosis, CVD, type 2 diabetes, depression and some other neurological disorders[67]. Animal-based protein, in particular, organ meats such as the liver, as well as dairy products are valuable sources of these fat-soluble vitamins. When following a well-planned LCD most of the fat consumed will be from animal sources – such as that found in meat, eggs and dairy as well as some sources of plant-based oils such as extra virgin olive oil and nuts[67].

It is worth noting that just because a diet is low in carbohydrates does not mean it is a healthy diet, as it may still contain many ultra-processed foods. As LCD have grown in popularity, manufacturers have begun to target this market with a variety of low carb or keto foods, which vary widely in quality. LCD increases satiety and decreases libitum energy intake, by increasing the absorption of nutrient-dense foods and replacing ultra-processed foods with more natural and fresh foods[68]. In addition, LCD improves weight loss/maintenance by improving metabolic changes through enhancing glycaemic control, TAG, HDL-cholesterol and reducing small dense LDL particles that are considered atherogenic[68].

One argument often used against LCD is that they differ greatly from the dietary guidelines of many countries and therefore may not enable followers to meet their recommended daily intake of essential nutrients. However, a recent study by Zinn *et al.* has effectively shown that a well-planned LCD can meet all the Nutrient Reference Values without the inclusion of unusual ingredients such as offal[69]. As with all diets, some planning to meet the Nutrient Reference Values is required, but as the LCD does not exclude any food groups specifically it means a wide variety of nutritious foods can be consumed while following an LCD.

In the end, we have three key recommendations for future studies. First, further high-quality studies (with longitudinal, randomised control trial designs, including higher sample size and longer follow-up) are required regarding the combination of fasting and LCD to enhance the reliability and generalisability of the information. Some of the limitations of the current studies included a small sample size[39,43]; were self-reported (rather than focusing on active metabolic parameters)[40,41,45]; and had large attrition rates[41,46], making them susceptible to social desirability bias and underreporting of food intake. There is a need for a design that enhances adherence and compliance, considering this programme as a lifestyle change rather than an unsustainable/short-term diet. Second, there has been a lack of consistency concerning the definition and criteria provided for LCD (different percentages), making the comparison between studies difficult. Macronutrient composition, particularly carbohydrate limits should be clearly defined. In addition, more regular and longer-term follow-ups are required to maintain compliance with the criteria and achieve a more reliable result. We may need to use diverse ranges of classifications of LCD, based on the literature, as different individuals may respond differently to LCD interventions. We recommend classifications of LCD according to Feinman *et al.* (2015), comprising very-low-carb diet (< 10 % total energy intake or < 50 g/d); low-carb diet (10–26 % total energy intake or 50–130 g/d), and moderate-low carb diet (< 45 % to > 26 % total energy intake or 130–225g/d). We suggest excluding any diet with more than >45% carbohydrate, irrespective of whether it is given a name or not, in the research on the LCD category[70]. Third, we suggest taking into consideration a personalised approach to fasting in conjunction with LCD. These can include individual demographics such as age, illnesses and metabolic conditions.

Conclusion

Two popular dietary lifestyle movements, LCD and fasting, have emerged as a result of common chronic lifestyle diseases, and self-educating, autonomous populations have naturally, or for health reasons, gravitated towards, either/or both patterns of eating. Although this is an emerging field of research, combining the two shows promise of improving and even reversing chronic diseases, possibly unburdening the public health system and enhancing the health span of a large percentage of the world's population. These eating methods may provide holistic benefits to health and global health economics and the environmental sustainability of eating less often, eating nutrient dense and focusing on functional food choices[41].

Our paper has highlighted the multiple benefits of combining an LCD with various fasting protocols. The benefits are multifaceted at three different levels, including prevention (e.g. disease prevention, maintaining or achieving a healthy weight, enhancing sleep quality); diagnosis (e.g. diagnosis of cardiac-related sarcoidosis) and treatment (e.g., improving and reversing type 2 diabetes and prediabetes, CVD, inflammation-reducing joint pain, epilepsy in children). Overall, the combination of LCD and fasting assists in improving the root causes of many diseases, which can be metabolic syndrome.

Although the combination of LCD and fasting can result in synergy, it is still unclear from our work what is the more potent driver of these benefits – is it the fasting or the LCD, or do they have equal importance in improving the disease? There is plenty of literature supporting the use of either fasting or LCD for the same benefits; however, it is not very clear how the combination of both will enhance the synergy. As the first known review of LCD and fasting, we have highlighted the scarcity/paucity of research in an area that is of growing interest and popularity and indicated an area for potential research opportunities. Interestingly, what has been seen in practice is that the two often occur naturally – as patients often report reductions in appetite when following an LCD and will naturally begin to incorporate elements of fasting into their day – in contrast to the need to eat at regular intervals driven by blood sugar fluctuations. Further randomised control trials to confirm the combined benefit are required.

Acknowledgements

This research received no external funding

Both authors contributed significantly to all aspects of the scoping review. N. S. contributed specifically to initiating the research idea, conceptual framework, writing, data analysis and critical argument of the paper. M. W. contributed to searching, data extraction, writing, editing and critical argument of the paper.

The authors declare no conflict of interest.

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