Low and reduced carbohydrate diets – challenges and opportunities for type 2 diabetes management and prevention

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Abstract

Low-carbohydrate diets (LCD) have been promoted for weight control and type 2 diabetes (T2D) management, based on an emerging body of evidence, including meta-analyses with indication of publication bias. Proposed definitions vary between 50 to 130 g/d, or <10% to <40% of energy from carbohydrate, with no consensus on LCD compositional criteria. LCDs are usually followed with limited consideration for other macronutrients in the overall diet composition, introducing variance in the constituent foods, and in metabolic responses. For weight management, extensive evidence supports LCDs as a valid weight loss treatment, up to 1-2 years. Solely lowering carbohydrate intake does not, in the medium/long term, reduce HbA1c for T2D prevention or treatment, as many mechanisms interplay. Under controlled feeding conditions, LCDs are not physiologically or clinically superior to diets with higher carbohydrates for weight-loss, fat loss, energy expenditure or glycaemic outcomes; indeed, all metabolic improvements require weight loss. Long-term evidence also links LCD pattern to increased cardiovascular disease risks and mortality. LCDs can lead to micronutrient deficiencies and increased LDL-cholesterol, depending on food selection to replace carbohydrates. Evidence is limited but promising regarding food choices/sources to replace high-carbohydrate foods that may alleviate the negative effects of LCDs, demanding further insight in the dietary practice of medium to long term LCD followers. Long-term, high-quality studies of LCDs with different food sources (animal and/or plant origins) are needed, aiming for clinical endpoints (T2D incidence and remission, cardiovascular events, mortality). Ensuring micronutrient adequacy by food selection or supplementation should be considered for people who wish to pursue long-term LCDs.

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Introduction

Low-carbohydrate diets (LCD) have been heavily promoted for weight management, and as a possible strategy for type 2 diabetes (T2D) management and prevention [1-3]. Current and emerging evidence from randomised trials remains inconclusive regarding the effectiveness of LCDs for health benefits (via weight control or metabolic control) [4]. As with any restrictive diet, the long-term sustainability of LCDs has been questioned, with additional concerns over safety, by comparison with current usual western diets or with alternative dietary recommendations [5-7]. This review explores the current evidence and debates which supports or challenges the use of LCDs for T2D management and prevention.

Type 2 diabetes: a disease process of obesity

T2D is primarily a nutritional disease, which used to be rare in pre-industrial societies, but is now emerging as one of the most common and damaging chronic diseases. Its global prevalence has approximately doubled from 1980 to 2014, in line with rising overweight and obesity [8]. It causes 1.6 million premature deaths annually, and shortened lives often end with years of pain and multiple disabilities [9].

The extraordinary association between T2D and elevated body mass index (BMI; not simply BMI >30 kg/m^2) was shown graphically in the prospective Nurses Health Study. Compared to BMI <22 kg/m^2, women with a BMI 23-23.9 kg/m^2 had a 3.6-time higher relative risk of incident T2D, rising to ~60 times higher risk in women with a BMI ≥35 kg/m^2, levels strongly indicative of a causal relationship [10, 11]. Excessive body fat accumulation is the critical, but reversable factor underlying T2D and metabolic syndrome development. In people who are predisposed (for genetic and other reasons), fat accumulates in ectopic sites including liver and pancreas, which damages organ functions [12], (Figure 1). Reversing that process by weight loss of at least 3-7% is a key mechanism to prevent or delay onset of T2D [13-16], and remission of established T2D can be achieved by greater loss, >15% for greatest success, with an intensive weight management program [17].

Lifestyle modification, through dietary change and increasing physical activity, to halt or delay the disease-process which is driven by weight gain and excess body fat in susceptible individuals, is

fundamental for T2D prevention and management [13]. Advice and support for affected individuals can be very effective [17, 18] but is strongly undermined by effective social marketing driving greater energy intake, while physical activity continues to fall in the post-industrial environment [19]. Self-reported food consumption by individuals with overweight and obesity can also be misleading, with notable underreported food energy intake (~100 kcal/day) in adults with BMI >30 kg/m^2 [20, 21]. Meanwhile, food disappearance data show consistent positive relationships between rising obesity, increasing energy intake and consumptions of all food groups and all macronutrients [22-25].

Role of carbohydrate in the diet

A primary role of carbohydrates is to serve as main and preferable source of body energy, contributing toward approximately half of energy intake per day at population level [26, 27]. Carbohydrate-rich foods, consumed regularly everyday as part of our main diets, are considered staple foods, including potatoes, rice and wholegrains, breads, pasta. Carbohydrates are also found in fruits, milk, beans and some starchy vegetables [28]. After consumption, foods containing carbohydrates are digested by the enzymes in the small intestine and absorbed in the form of glucose molecules. Glucose absorbed into the blood stream is transported into cells with the help of insulin, then directly converted to energy or stored as glycogen [28]. Not all carbohydrates are digested in the small intestine, with undigested constituents passing to the large intestine (colon); these are classified as dietary fibre [28]. Dietary fibre can be fermented by the resident bacteria in the large intestine, forming short-chain fatty acids, and also carry out a functional role through water absorption and bulking of stools [28]. Carbohydrate-rich foods are also a good source of vitamins and minerals, as they come from plant-sources. In the UK, cereals and cereal products, vegetables and potatoes, and fruits are the major food groups contributing to vitamins and minerals intakes, either naturally presented or fortified, (Table 1) [26].

Not all carbohydrates are the same, and types and quality matter. Eating carbohydrate-rich foods like wholegrain, whole-wheat pasta, brown rice, potatoes with skin, fruits and vegetables is associated with chronic disease risk reduction, which is partly explained by dietary fibre, found in plant cell walls [29]. Fibre can help with body weight maintenance through regulation of energy balance and satiety [30, 31]. Fibre also impacts on bowel health, with decreased risk of constipation [29]. In contrast, consumption of free sugars (table sugar, fruit juice, honey, sugar-sweetened beverages, or sugary snacks) could result in excess energy intake leading to overweight and obesity [32].

National nutrition surveys in the UK and USA found that ultra-processed foods (NOVA classification) accounted for 65-90% of energy intakes from sugars, and approximately 50% of total energy intake [33, 34]. Ultra-processed foods often have high fat and salt contents, and include highly processed refined carbohydrates which are low in fibre (e.g. white flour) [35]. A controlled in-patient metabolic ward RCT of ad libitum intake showed that more calories were consumed with a diet offering of ultra-processed foods, compared to unprocessed foods, resulting in 1 kg weight gain over 2 weeks [36].

What are low-carbohydrate diets?

Prominent media coverage has promoted the idea that obesity and metabolic diseases derive almost entirely from consumption of sugar, and because all carbohydrates are digested as sugars, from any dietary carbohydrate. The promotion of very low-carbohydrate diets, with unlimited fat (including saturated fats) and protein stems from this paradigm; for example, the Atkins Diet, which limits intakes of bread, pasta, and rice, allows unlimited consumption of animal foods such as red meat and processed meat, high in saturated fatty acids [37]. While calories from sugar (free sugar, added sugar) are largely unnecessary, total carbohydrate restriction could also entail avoiding health-promoting constituents of high-carbohydrate foods such as wholegrains.

Definitions of 'low-carbohydrate diets' in the scientific literature vary, and may reflect either diets low in carbohydrate as percentage of energy intake, or low absolute daily consumption (grams) of carbohydrate. Commonly used definitions for humans range from intakes below 20% to below 45% of energy, and from below 60 g to below 120 g of carbohydrate daily [38-42]. Some authors propose referring to '*low-carbohydrate diet*' as carbohydrate below 40%[43] or 26%[1] of energy, and to '*very low-carbohydrate diet*' when carbohydrate is under 20%[43] or under 10%[1] of energy, with no consensus to date (Table 2). The term '*low-carbohydrate diet'* is commonly applied regardless of other macronutrient contents in the overall diet composition, which introduces variance in the constituent foods being used, and in metabolic responses. For example, a low-carbohydrate, high saturated fat diet increased LDL-cholesterol [44], whereas a low-carbohydrate, low saturated fat, high unsaturated fat diets showed no change in LDL-cholesterol [45]. Another study of plant-based LCD with low saturated/high unsaturated fat contents also reported a reduction in LDL-cholesterol [46].

In addition, there are many different commercial versions of the LCD, such as the Atkins Diet, Zone diet, or the South Beach Diet [47, 48]. The most popular have been based on the Atkins Diet, with 17 million copies of '*Dr Atkins New Diet Revolution'* sold, and heavy promotion in the media and on

the internet [37, 49, 50]. This diet suggests 2 phases. The induction phase limits intake of carbohydrate to no more than 20 g, with liberal intake of fat and protein including red meat, butter and vegetable oils, and exclusion of bread, pasta, grains, fruits, other starchy vegetables and dairy products except cheese, cream and butter. Supplementary multivitamins and fibre are recommended. In the second phase, once a desirable weight has been achieved, daily carbohydrate intake can be increased to the level that can maintain weight [37].

Hypothesis about low-carbohydrate diets and obesity and type 2 diabetes

Common features among obesity, T2D and metabolic syndrome are hyperinsulinemia and insulin resistance. Instead of excessive total energy intake causing weight gain, insulin resistance and hyperinsulinemia, a carbohydrate-insulin model of obesity (CIM) hypothesises that carbohydrate intake, including refined starchy foods and sugars causes postprandial hyperinsulinemia, promotes lipogenesis leading to decreased level of metabolic fuels (glucose and lipids), and leads to weight gain through increased hunger and less energy expenditure [51]. By this CIM, LCDs could reduce postprandial insulin secretion, promote fat loss, and decrease risks of chronic diseases [51].

Weight loss with either LCD or low-fat diet (LFD) showed an improvement in insulin resistance, measured by intravenous glucose tolerance test (IVGTT) or euglycaemic hyperinsulinemic clamp [52, 53]. In contrast, non-weight loss, controlled feeding, short-term studies of very-low carbohydrate, high fat (high saturated fat) diets in healthy young men showed worsened insulin sensitivity, measured by oral glucose tolerance [54], IVGTT [55] and euglycaemic-hyperinsulinemic clamps [56, 57]. On the other hand, short-term studies in healthy overweight and obese postmenopausal women [58], and men with T2D [59] showed no difference in insulin sensitivity by euglycaemic-hyperinsulinemic clamp between LCD and LFD, this might be explained by the unsaturated fatty acids used to replace carbohydrate [60].

The evidence of LCDs on beta-cell function is limited. One short term crossover RCT of LCD vs. normal diet showed a reduction in first-phase insulin response after 3-day of very low-carbohydrate, high-fat diet in healthy young men [54]. In animal studies, long-term ketogenic diets in mice showed an increased insulin resistance, did not prevent beta-cell mass decline [61], and even showed a reduction in beta-cell mass, including smaller size of islets [62]. Although LCDs could reduce postprandial glucose and postprandial insulin response, without weight loss, the limited evidence fails to support that LCDs could reverse pathophysiology of hyperglycaemia in obesity and T2D.

Opportunities for the use of low-carbohydrate diets for diabetes prevention in individuals with overweight and obesity, who are at high risk of type 2 diabetes

Weight management, either weight loss or weight maintenance, plays the biggest role in T2D prevention in individuals with overweight and obesity. Several large 'diabetes prevention' trials have shown a clear benefit on T2D risk reduction principally by modest weight loss mainly by lowering fat intake (<30%E). Other lifestyle modifications have more modest value [13-16]. While weight loss by LFD has been largely incorporated in 'diabetes prevention' trials, the randomised controlled trials (RCT) of LCDs for weight loss do not have long enough follow-up to evaluate incident T2D and were not designed to study incident T2D as a primary outcome. As weight loss is an essential mechanism for T2D risk reduction, this section also discusses the role of LCDs in weight loss.

The idea of LCDs for weight loss first attracted public interest with the letter of William Banting published in 1863 describing his successful personal weight loss of 46 lbs (~20 kg), from 202 lbs to 156 lbs over a 12-month period, by cutting bread, potato, pastry, milk, sugar, and a majority of fruits [63]. Several anecdotal reports of similar success have been discussed in the media [64-66], highlighting that the successful weight loss stories with LCDs could be subject to survival bias, with the experience of those who tried and failed not being reported. LCDs can achieve a mean weight loss of 7 kg approximately over 6-24 months, up to 10% of baseline body weight in non-controlled studies [67-70]. LCDs, however, certainly work for some, as highlighted in the DIETFITS study that participants who assigned to LCD group lost a maximum of 30 kg body weight, while some participants gained up to 10 kg body weight [42].

Randomised controlled trials and meta-analyses evidence of low-carbohydrate diets for weight loss

Several RCTs and meta-analyses have been conducted to examine the effects of LCDs for weight loss, compared to LFDs [71-73]. The conclusion has repeatedly been that there may be marginally greater weight loss in the short term (approximately the 2 kg expected from depletion of glycogen and its associated water), but no consistent superiority of LCDs over the longer term [4]. At 6 months (Figure 2A), meta-analyses reported that weight loss from LCDs was greater than LFDs by 0.7 to 4 kg, but this difference dropped to 0.5 to 1 kg at 12 months, Figure 2B [4, 40, 41, 47, 71, 74].

Factors contributing to inconsistent findings among published meta-analyses of low-carbohydrate diets and low-fat diets for weight loss

Our recent systematic review of published meta-analyses [4] explores these inconsistent findings regarding the effectiveness of LCDs and LFDs for weight loss, partly explained by large differences in methodology. Definitions of what constitutes LCDs varied among meta-analyses, ranging from 20 g/d to <45% energy from carbohydrate. The more extreme carbohydrate restriction (20-60 g/d or 10-20%E) resulted in greater weight loss compared to LFDs [4]. With unrestricted energy LCDs, participants typically consumed 30% less total energy than baseline, resulting in a greater weight loss over 3-6 months [72, 73, 75]. The weight loss is then attenuated over time (12 months or more), probably via loss of adherence, as commonly occurs in weight loss trials in free-living participants who tend to return to their previous diet and lifestyle in the obesogenic environment [76, 77].

Quality and bias among published meta-analyses of low-carbohydrate diets and low-fat diets for weight loss

We also assessed quality of each published meta-analyses using AMSTAR 2 criteria [78]. Contrasting with the wide popularisation and mediatisation of LCDs, only two meta-analyses were *'high quality'* (n=2/10) and they reported no weight loss difference compared to LFD, while half (n=5/10) were of '*critically low quality'* but reported LCD superiority over LFD for weight loss, up to 4 kg difference [4]. Of particular interest, meta-analyses favoring LCDs but of low-quality also had higher citations (rho = -0.9, p=0.037), suggesting that public and scientific communities might be responding most to findings generated through poor methodology [4]. Despite featuring at the top of the evidence hierarchy, meta-analyses remain open to biases.

Predictors of weight loss: macronutrients and/or diet adherence - findings from controlled feeding studies and free-living participants

LCDs have been promoted on the basis that they theoretically reduce more body fat than LFDs, via lessened stimulation of postprandial insulin secretion, leading to lessened inhibition of lipolysis. This hypothesis is, to date, not supported by a meta-analysis of controlled feeding studies comparing the effect of isoenergetic LCDs vs. LFDs, with equal protein [79]. A strength of the controlled feeding studies is of the by-passing of adherence as a confounder. The pooled results showed that LFDs yielded a 26 kcal/d greater difference in energy expenditure, and a 16 g/d greater loss in body fat change, compared to LCDs with equal protein [79]. However, these differences are small and could not infer clinical impact of the effect of dietary fat and carbohydrate on body weight loss, when energy intake is equally held between the two diets. Consistent findings were also seen in weight loss trials in free-living participants. A meta-analysis of LCDs vs isoenergetic LFDs [74] reported little

difference in body weight loss between the two diets at 3-6 months (mean difference -0.74 kg; 95%CI -1.49 to 0.01) and 1-2 years (mean difference -0.48 kg; 95%CI -1.44 to 0.49). This highlights that caloric restriction and adherence to the program are superior for weight loss than macronutrients composition.

Macronutrients, appetite and weight control

Given that controlled metabolic studies find no difference in weight loss with low or high carbohydrate diets [79], the small short-term weight-loss advantage of LCDs over high-carbohydrate energy-restricted diets in free-living people may be due to greater ease, willingness or enthusiasm to restrict high-carbohydrate foods. High carbohydrate foods are also somewhat easier to identify [80, 81], as much fat in foods is hidden (e.g. in cakes, biscuits, muffin, pizza, cereal bars) [82], and this approach is currently heavily promoted via the mainstream and social media. In principle, restricting fat (9 kcal/g) should be more effective than restricting carbohydrate (4 kcal/g). It is however possible that the higher protein intake from Atkins-style LCDs could suppress appetite [83-86].

A further oft-cited possibility is that the ketosis that develops with more extreme carbohydrate restriction, suppresses appetite [86, 87]. When body fat or dietary fat is oxidised, with weight loss or with a very high fat diet, the fat oxidation products 'ketone bodies' accumulate in the blood stream (e.g. β-hydroxybutyrate, 0.3-0.8 mmol/L on LCDs vs ~0.1 mmol/L on typical diets with 50%E carbohydrate) [88, 89]. Ketone body production is a biochemically necessary accompaniment of weight loss, and appetite usually increases with energy restriction and starvation [90, 91], as a powerful survival mechanism. Very limited evidence has examined the specific effect of raising ketone bodies to be able to confirm or refute this theory, which is highly relevant to sustainability of carbohydrate restriction and appetite control. Stubbs et al. [92] recently published a crossover RCT of exogenous ketone (via a ketone ester drink) compared to a dextrose drink. Ketone ester ingestion markedly increased blood β-hydroxybutyrate level from 0.2 to 3.3 mM after 60 minutes, and suppressed reported hunger and desire to eat (both measured by visual analogue scales) by 50% compared to a dextrose drink, 1.5 to 4 hours postprandially [92].

There is current interest in the evidence that some carbohydrates, functioning as dietary fibre, can suppress appetite and weight gain by releasing short-chain fatty acids, which stimulate GLP-1 release from the large intestine, through the action of gut microbes [93]. Dietary inulin-propionate ester is metabolised by gut microbes to deliver propionate to the large intestine [94, 95]. Propionate acutely stimulates GLP-1 production resulting in appetite suppression and decreased energy intake [93]. However, the effect on GLP-1 release is not well sustained over time, while the effect on appetite

suppression is maintained [93], suggesting that other mechanisms unrelated to GLP-1 may operate (96). Other physical effects of dietary fibre (e.g. viscosity, gel formation) could also play a role in appetite suppression [97]. Although the underlying mechanism of dietary fibre and appetite suppression is not fully confirmed, the collective evidence would support the use of high fibre diets for weight control [93-95, 97, 98]. Figure 3 illustrates the levels of ketones, propionate and satiety in relation to carbohydrate and dietary fibre intakes.

Opportunities for the use of low-carbohydrate diets as a treatment strategy for patients with type 2 diabetes

Controlling blood glucose within a desirable range, evaluated via measurement of HbA1c, is a primary aim for T2D management [99, 100]. LCDs have been postulated to have physiological benefits over higher carbohydrate diets for HbA1c reduction. A lower postprandial glucose excursion would be expected after LCDs, compared to higher carbohydrate diets if they present greater glycaemic index or glycaemic loads [66, 101]. A reduced postprandial excursion should lead to a better overall glucose control and lower HbA1c. Recent clinical guidelines recommend individualised nutrition therapy for people with T2D, and allow flexibility of carbohydrate intake to suit personal preferences and metabolic goals [99, 100]. However, the role of LCDs in T2D remain unclear and often yield mixed results [102-104]. This is likely to be influenced by level of energy restriction, and protein/fat composition of the diets.

Randomised controlled trials and meta-analyses evidence of low-carbohydrate diets for blood glucose control

Meta-analyses of LCDs in patients with T2D have showed little greater reductions in HbA1c compared to higher-carbohydrate diets, by 0.17% to 0.34% over short term period up to 6 months with evidence grades ranging from very-low to moderate certainty [102-104]. Notably, results from RCTs with <6 months duration showed that a lower carbohydrate intake was associated with a greater extent HbA1c reduction ($r = -0.8$, $p<0.01$) [104], this could be explained by a greater weight loss following LCDs within 6 months duration[4, 102, 103]. However, there is no difference in HbA1c reduction between the two diets at 12 months or longer [102-104]. The definitions of LCDs in those meta-analyses were <45%E from carbohydrates, which departs from more conservative definitions. More importantly, the difference in HbA1c reduction between the two diets is of unclear clinical importance, with a majority of RCTs included in those meta-analyses with high risk of bias [102, 103].

Randomised controlled trials evidence for type 2 diabetes remission

There have been debates on the definitions of remission of T2D [105, 106]. While there is no consensus on the remission criteria, it is obvious that blood sugar, both HbA1c and fasting blood glucose, should be below the diagnostic threshold for diagnosis of T2D. To date, there is no RCT to study the effect of LCDs on T2D remission, and clinical trials aiming at T2D remission outcome were also limited with unclear report on remission rate and criteria [69, 88]. A single-arm longitudinal study of a Low-Carb Program in patients with T2D reported a 1-year result that 26% of patients (n=195/743) had HbA1c below 6.5%, with either metformin or no prescribed diabetes medication [69]. Another non-RCT (Virta Health study) also reported that 25.5% (n=52/204) participants in the LCD group (carbohydrate <30 g/d, with behavioral therapy and frequent follow-up) had HbA1c below 6.5% without prescribed diabetes medication at 1 year of intervention [88].

Weight loss masking the effect of low-carbohydrate diets on blood glucose improvement and type 2 diabetes remission

HbA1c reduction and T2D remission following LCDs have been largely confounded by weight loss [69, 88, 102-104, 107], leaving considerable doubt over the benefit for HbA1c which can be attributed to carbohydrate quantity *per se*. Most evidence featuring in meta-analyses comparing the impact of LCDs and LFDs on HbA1c was weight loss trials [69, 88, 102-104]. Similarly, the Virta Health study showed a reduction in HbA1c, from 7.6% to 6.3%, along with a mean weight loss of 14 kg in patients with T2D [88].

Evidence of LCDs in non-weight loss trials is limited. A crossover RCT of a low-carbohydrate, high-protein diet (LCHP; 30%E carbohydrate, 30%E protein) vs. an isoenergetic conventional diabetes diet (CD; 50%E carbohydrate, 17%E protein) reported a greater reduction in HbA1c in the LCHP group (-0.6 ± 0.1%) compared to the CD group (-0.1 ± 0.1%; $p<0.001$) [108]. This study, however, is limited by a small sample size (n=28), short duration (6 weeks for each diet), and no washout period - which could not exclude carryover effect. More importantly, greater weight loss was reported in the LCHP group (-1.4 kg) than the CD group (-0.8 kg; $p=0.07$) [108]. Another crossover RCT of LCHP diet vs. LFD (n=8; 5 weeks) also showed a greater reduction in HbA1c following LCHP, but it is noted that there was a 2 kg weight loss during the 5-week study duration regardless of diet [109]. The greater HbA1c reduction following LCHP could be attributed to the insulinotropic effect of high protein intake [110-113]. The results, therefore, needs to be confirmed by larger and longer duration RCTs.

Randomised controlled trials evidence for vascular and renal function in type 2 diabetes

Long-term RCT evidence on the safety of LCDs is limited. One RCT comparing very low-carbohydrate, low-saturated fat diet vs. low-fat, low-saturated fat diets in patients with T2D and no pre-existing kidney disease reported that no difference was found in vascular function determined by flow mediated dilatation that might be explained by these two diets had similar level of saturated fatty acids [114]. Regarding renal function, a meta-analysis of nine RCTs of LCDs and LFDs for weight loss showed that a mean change in an estimated glomerular filtration rate following LCDs was little greater than LFDs by 0.13 ml/min per 1.73m^2, with duration up to 1-2 years [115].

Dietary recommendations for patients with type 2 diabetes

While there is no ideal amount of carbohydrates for patients with T2D, a guideline emphasises reduction of refined carbohydrates and added sugars, and focus on carbohydrates from vegetables, legumes, fruits, dairy (milk and yogurt), and whole grains, in order to achieve healthful eating patterns with a variety of nutrient-dense foods [99]. If patients prefer LCDs, this approach should be only used for a short-term, up to 3-4 months, due to limited evidence on long-term benefits and harms of LCDs [99].

Challenges associated with the use of low-carbohydrate diets

Low-carbohydrate diets and micronutrients

While weight is often the main outcome, nutritional quality of all diets should be a key primary concern. As key characteristic of LCDs, avoidance of wholegrains, fruits and starchy vegetables could reduce vitamins, minerals, as well as plant bioactives (which play a role in the modulation of glycative stress [116, 117], relevant to T2D pathophysiology). The negative impact of LCDs on micronutrients has often been neglected. Our systematic review [118] found 7 RCTs [73, 119-124], 2 non-controlled trials [125, 126], and 1 cross-sectional study [127] reporting rather consistent reductions in thiamine (vitamin B1), folate, vitamin C, magnesium, calcium, iron, and iodine intakes [118]. Although there is no definitive guidance for supplementation during LCDs, only one study provided supplementation to participants [126]. Most of the studies included did not report on supplements used in their studies [118]. It is therefore difficult to assess whether inadequate micronutrient intakes have been topped-up by supplementation [118].

This could have clinical consequences. For example, severe thiamine deficiency and beriberi are well-recognized with prolonged extreme LCDs [128, 129]. Inadequate intakes of folate and iodine in women of child-bearing age could increase risk of poor foetal outcomes [130]. Gardner and colleagues showed that individuals on the Atkins Diet had lower intake of thiamine and magnesium over 8 weeks [120]. Unfortunately, there have been case reports of thiamine deficiency from following a LCD. Bilateral optic neuropathy was reported in two patients who followed a prolonged carbohydrate-restricted diet [128]. Another case of Wernicke's encephalopathy and cardiac beriberi was reported in a patient with obesity who restricted breads and pasta from his diet [129].

Low-carbohydrate diets and low-density lipoprotein cholesterol

Lipid disturbance is commonly seen in individuals with overweight and obesity, including those with T2D, who are at high risk of atherosclerotic cardiovascular diseases (ASCVD). High triglyceride (TG) and low high-density lipoprotein (HDL) cholesterol are risk factors of ASCVD, while high low-density lipoprotein (LDL) cholesterol is a main culprit of ASCVD, depositing in arterial wall, initiating plaque formation and progression of ASCVD [131, 132]. There has long been a concern about increasing LDL-cholesterol following LCDs, albeit balanced by decreasing TG level [4].

Evidence from weight loss trials showed that LCDs increased LDL-cholesterol to a greater extent compared to LFDs (by 0.1 to 0.4 mmol/L – or 4 to 16 mg/dL) over 6 to 24 months intervention [38-41, 71, 133]. The lower carbohydrate component in the diet may be associated with a greater increment in LDL-cholesterol level, as seen in a cohort of patients with T2D following ketogenic diets (<30 g/d of carbohydrate) that LDL-cholesterol increased by 10% after 1 year of the diet [88]. In non-weight loss studies [44, 89, 134], low-carbohydrate, high fat, high saturated fat diets (18-25%E saturated fat) for 3-4 weeks, showed 17-21% increment in LDL-cholesterol from baseline, including increments in small and medium LDL particles [44, 89].

Most importantly, there were two case reports of acute coronary syndrome in patients following the Atkins Diet. A 51-year-old man, healthy, physically active, no previous heart disease, diabetes, hypertension or dyslipidaemia developed marked change in LDL-cholesterol, from 2.2 mmol/L (85 mg/dL) at 6 months prior to the Atkins Diet to 4 mmol/L (154 mg/dL) at 1 month after the diet, BMI 21.8 kg/m^2, despite a 3 kg weight loss. The patient remained on this diet until 29 months later when he experienced exertional chest pain, and his cardiac catheterisation demonstrated a severe stenosis of the left anterior descending artery [135]. Another case report was a 41-year-old man, who had no ASCVD risks and no family history of premature coronary artery disease. His BMI was 19.5 kg/m^2.

The patient adhered to the Atkins Diet for 6 years with repeated cycles each year. His blood lipids, apoliprotein A and homocysteine levels were within normal limits. He presented with acute chest pain in which the investigation showed an acute myocardial infarction [136].

Low-carbohydrate diets and ketoacidosis

Ketosis is associated with, and largely causes, dangerous acidosis (ketoacidosis) in poorly treated insulin-deficient type 1 diabetes. Apart from micronutrient inadequacies and increased LDL-cholesterol, ketosis usually develops in individuals following LCDs [88]. Although there is no severe ketacidosis reported in clinical trials, there is a case report of ketoacidosis in a non-diabetic lactating woman following a ketogenic diet with <20 g/day of carbohydrate. The patient developed nausea and vomiting after 10 days of the diet. Serum pH was 7.2 indicating acidosis, with blood ketones of 7.1 mmol/L (reference <0.5 mmol/L). The authors hypothesised that lactation could aggravate or trigger ketoacidosis: during lactation, women require increased energy intake to meet the high demand of substrate to produce milk. Fat, whether stored or dietary, is the primary resource of energy during a ketogenic diet, and thus responsible for ketoacidosis [137].

Long-term epidemiological evidence on low-carbohydrate diets, type 2 diabetes, cardiovascular risks and mortality

Intervention studies comparing LCDs and LFD have shown little or no difference on weight change over 1-2 years, but do not have long enough follow-up to study the clinical outcomes such as incident T2D, cardiovascular diseases, and mortality, or long-term safety.

Low-carbohydrate diets, HbA1c level and incident type 2 diabetes

Our cross-sectional analysis in people without known diabetes in the National Diet and Nutrition Survey (NDNS, UK) showed that, although few people (n=8, or 0.24% of the overall sample) met the conservative definition of LCD (<26%E), both lower carbohydrate intake (per 5%E band) and LCD pattern (according to LCD adherence score), were associated with higher HbA1c (+0.16 mmol/mol, p=0.012, per 5%E decrease in carbohydrate; +0.10 mmol/mol, p=0.001, per 2-point increase in LCD adherence score) [138]. The NDNS used food diaries for estimation of dietary intakes, which are more accurate and less reliant on memories compared to the food frequency questionnaires (FFQ). While the study design does not inform cause and effect, the findings are to some extent in line with longitudinal studies [139, 140]. This evidence indicates that it is unlikely that consuming lower carbohydrate content *per se* could lower HbA1c level. Other mechanisms (e.g.

oxidative stress, peripheral insulin resistance) could contribute to HbA1c elevation, as high oxidative stress can enhance protein glycation without hyperglycaemia [141].

When looking at incident T2D and LCDs, the most recent cohort study in Australian women showed a 27% higher risk of T2D with LCD (comparing extreme quartiles, with absolute risk increase of ~3%), although the relative risk (RR) was attenuated to 10% after adjustment for BMI [142]. A meta-analysis of 11 prospective cohort studies showed that different regions had different outcomes [143]. In Europe [144-147], LCDs increased the T2D risk by 12% (pooled RR 1.12; 95% CI 1.04-1.20), whereas in Japan [148] and China [149], LCDs decreased the T2D risk by 20% (pooled RR 0.80; 95%CI 0.70-0.90) [143]. The pooled result in Asian countries was explained by white rice as a key food source of (refined) carbohydrate, a major component in Japanese and Chinese diets [148, 149]. A study showed that substituting white rice with brown rice or wholegrain could result in T2D risk reduction by 16% and 36% respectively [150].

Sources of protein and fat in replacing for carbohydrate also contributed to T2D risk. LCD with high animal protein and fat was associated with a 37% increase in T2D risk in men (95% CI 1.2 – 1.58; p-trend <0.01) [139], and a 40% increase in T2D risk in women with history of gestational diabetes (95% CI 1.06 – 1.84; p-trend = 0.004) [151]. On the other hand, LCD with vegetable protein and fat was associated with a 18% T2D risk reduction in women (95%CI 0.71 – 0.94; p-trend = 0.001) [152]. Contrary findings between men and women could be explained by sex differences in T2D susceptibility [153]. Pre-menopausal women are less susceptible to T2D than men, partly explained by difference in sex steroid hormones [153]. Endogenous oestrogen plays a protective role in various metabolic regulations including insulin secretion and sensitivity, although the underlying mechanism has yet to be explored [153]. Women have higher capability for lipid utilisation, favouring subcutaneous adipose tissue as an energy storage, preventing them from ectopic fat accumulation [153].

Low-carbohydrate diets and cardiovascular diseases

In the prospective cohort Nurses Health Study of 82,802 women, diets were assessed by a validated FFQ and a calculated 'LCD score' (higher scores representing higher intakes of fat and protein, and lower intake of carbohydrate). During the 20 years follow-up, a higher LCD score (10th decile vs. 1st decile) was associated with a 29% increased risk of coronary heart disease (CHD) (age-adjusted RR 1.29; 95% CI 1.04-1.60). After adjustment for body mass index, smoking status, physical activity, history of diabetes and hypertension, the adjusted RR for CHD was attenuated to 0.94 (95%CI 0.76-

1.18, p for trend 0.19). Interestingly, when analysing the LCD score based on vegetable protein and vegetable fat, the adjusted RR of CHD was 0.70 (95% CI 0.56-0.88; p for trend 0.002) whereas when animal protein and animal fat were chosen, the adjusted RR was 0.94 (95% CI 0.74-1.19; p for trend 0.52) [154]. When using a composite outcome of cardiovascular events (ischemic heart disease, ischemic stroke, haemorrhagic stroke, subarachnoid haemorrhage and peripheral arterial disease), a large cohort study of 43,396 Swedish women reported that every 2 units greater in the low-carbohydrate, high-protein diet score was associated with a 5% increase in the incidence of cardiovascular events (incidence rate ratio 1.05; 95%CI 1.02-1.08) [155].

LCDs are also associated with increased risk of incident atrial fibrillation [156]. Findings from a large prospective community-based cohort study (Atherosclerosis Risk in Communities, ARIC Study) showed that every 9.4% higher in carbohydrate intake as percentage of energy (1-standard deviation) was associated with reduced risk of incident atrial fibrillation by 18% (adjusted hazard ratio (HR) 0.82; 95% CI 0.72 – 0.94), while there was no association found between animal and plant sources of protein and fat and incident atrial fibrillation [156]. These contrasting findings highlight the need to pay greater attention to the foods (and nutrients) replacing carbohydrates in LCDs.

Low-carbohydrate diets and mortality

Several prospective cohort studies and their meta-analyses showed consistent findings that LCD pattern was associated with increased risk of all-cause mortality and cardiovascular mortality [157-163]. The ARIC Study found a U-shape association between carbohydrate intake (%E) and all-cause mortality, with the lowest mortality risk at 50-55%E carbohydrate. The authors also conducted the meta-analysis for carbohydrate and mortality [162-164]. Compared to moderate carbohydrate intake (~50%E), low carbohydrate intake (<40%E) was associated with a 20% increased risk of all-cause mortality (pooled HR 1.2; 95%CI 1.09-1.32; p<0.0001), and high carbohydrate intake (>70%E) was also associated with a 23% increased risk of all-cause mortality (pooled HR 1.23; 95%CI 1.11-1.36; p<0.0001) [163]. The meta-analysis also showed that mortality increased by 18% when replacing carbohydrate with animal-sourced fat and protein, and decreased by 18% when replacing carbohydrate with plant-sourced fat and protein [163]. Another population-based cohort study also showed a 22% increased risk of all-cause mortality, a 13% increased risk of ASCVD mortality, and an 8% increased risk of cancer death in associations with LCD pattern (comparing between extreme quartiles, adjusted for BMI) [5].

Analysis of the combined databases of the Nurses Health Study and the Health Professional Follow-Up Study was performed in the population of post-myocardial infarction survivors [165]. Those in the highest quintile of the LCD score from animal-sourced protein and fat had a 33% higher risk of all-cause mortality (95%CI 1.06-1.65) and a 51% increased risk of cardiovascular mortality (95%CI 1.09-2.07) than those in the lowest quintile [165]. Interestingly, individuals who changed their diet from pre- to post-myocardial infarction towards LCD pattern was also associated with higher all-cause and cardiovascular morality by 30% and 53% respectively.[165]

Real world data on the use of low-carbohydrate diets

Evidence documenting the use of LCDs outside clinical trials remains scarce. In the UK, an estimated three-million people have tried LCDs, accounting for 7-10% of respondents in a media poll [49], similar to a finding of 7% from a population-based survey in Finland [166], while it was up to 17% in a nationally representative samples from the Health Information National Trends Survey in the USA [3]. A survey of individuals following LCDs (in the Active Low-Carber Forum, an online support group for LCDs in the USA) reported that Atkins-style diets ranked top of LCDs used, accounting for 74% of reports [167]. Two-third of respondents had lost 30 lbs in weight, or more [167]. Avoiding sugar (94%) and avoiding starch (84%) were important factors for weight loss plan, while only 12% of respondents thought that 'decreasing fat' was an important factor [167].

There is limited evidence for the use of LCDs in clinical practice. Dr Unwin et al. reported a case series of 19 patients with T2D and pre-diabetes who participated in a LCD program from one general practice [70]. The LCD advice was to reduce all starchy carbohydrate foods (e.g. breads, pasta, rice), tropical fruits and vegetable oils, while promoting consumptions of green vegetables, berries, meat, eggs, fish, olive oil, coconut oil and butter. Patients were also advised to consume processed meat like sausages, bacon, ham, in moderation. One patient withdrew at the initial stage for personal reason. Of 18 patients, mean weight loss was 8.6 ± 4.2 kg ($p<0.0001$), and HbA1c dropped significantly from 51 ± 14 to 40 ± 4 mmol/mol ($p<0.001$) over 8 months period [70]. Although this report was of small sample size with no control diet, it emphasised that LCDs can be effective for weight loss and glucose control, and can be implemented in clinical practice. Long-term data of LCDs in patients with T2D in primary care has the potential to depict both benefits and risks on hard clinical outcomes especially CVD events, renal adverse effects, and even mortality. The role of the healthcare practitioner as a source of support is also an important consideration in the context of this work.

Real-world data on dietary intakes in self-reported LCD followers are also limited [127, 168]. A recent cross-sectional study from Iceland with 54 self-reported LCD followers (80% overweight and 60% with elevated LDL-cholesterol level) demonstrated further insight into nutrient intakes [127]. Median intake of carbohydrate was very low (only 8%E) while median fat intake was very high at 68%E, with 25%E from saturated fatty acid. Consumption of whole grain was only 5 g/day and fibre only 11 g/day. Vegetable intake was of 170 g/day compared to 120 g/day of general population – this shows that vegetable intake is an important source of fibre in the context of LCD, requiring further emphasis (beyond the simple 5-a-day message) when carbohydrate-rich foods are limited or excluded. Red meat intake was 130 g/day, nearly double the intake of the general population in Iceland. Approximately half of participants had intakes of vitamin A, thiamine, folate, vitamin C, calcium, iron, and magnesium lower than recommendations. In contrast, 75% of participants consumed greater sodium than recommended (2400 mg per day) [127].

As such, healthfulness of LCDs is highly dependent on choices of the foods to restrict but also foods to include and promote. As practiced, LCDs may not be a healthful, nutritionally-replete dietary approach, unless great care is taken to balance intakes. In USA, LCD followers had a healthy eating index score lower than those with higher carbohydrate diets (58.2 vs. 70.4, p=0.012) [168]. Only half of LCD followers had support from their doctors, and two-thirds valued information from online supporting websites instead of government websites/publications [167]. Our own work is currently seeking to establish a clearer picture of such practice (Churuangsuk et al., in preparation). Figure 4 summarises the opportunities and challenges presented by LCDs in T2D management and prevention.

Limitations of current research

The well-known limitation of the RCTs of LCDs is the absence of evidence for long-term effectiveness on hard clinical outcomes like incident T2D, cardiovascular events, and mortality, instead of weight loss. Regarding T2D management, remission should be a primary aim for T2D treatment especially in early T2D, and high quality RCTs of LCDs aiming at T2D remission in comparison to other weight loss diets or routine care are needed.

RCTs and epidemiological evidence showed that selection of food choices/sources of protein and fat could have different effects on health, but limited RCTs on the effect of food choices/sources of protein and fat in replacing carbohydrate have been conducted [45, 46]. It is possible to design a healthful LCD with complete micronutrient profile and no detrimental effect on LDL-cholesterol [45,

[46, 169], but this may require close supervision by dietitians in collaboration with other health care professionals.

The ongoing debate on the usefulness of FFQ as a dietary assessment tool in epidemiological studies has highlighted the pitfalls associated with poorer accuracy of nutrient intake estimation and reliance on memory for recall. While FFQs are practical in the context of large sample sizes (e.g. population-based study) and to rank dietary data, carbohydrate intake reports generate via this method should be evaluated carefully. While the epidemiological evidence to date shows detrimental effects of LCDs on health, the amount of carbohydrate consumed are usually higher than intakes relevant to individuals following (very) low carbohydrate intake, <20-30%E. Real-world data in self-reported low-carbohydrate dieters may help better elucidate the relationship between LCDs, dietary habits and long-term health status.

Conclusions

RCTs clearly show the efficacy of LCDs for weight loss in people with obesity and/or T2D, leading to glycaemic improvement. Their efficacy, however, is little different to that of higher carbohydrate diets or other weight loss diets with less drastic restriction of whole food groups. Many studies show only short-term benefit when compared to higher carbohydrate diets. LCDs may be preferred by some people, and have value at least for short-term results, but may potentially lead to micronutrient deficiencies and increased LDL-cholesterol, and there are longer-term risks of T2D and cardiovascular diseases. Ensuring dietary micronutrient adequacy through food fortification or supplementation should be considered for all who wish to pursue or prescribe long-term LCDs. Food choices in replacement of carbohydrate source may alleviate the negative effects of LCDs, but evidence on this topic remains limited. Evidence is lacking over whether the main energy source during LCDs should be fat or protein. Long-term, high-quality RCTs of LCDs with different food sources between animal and plants, aiming for hard clinical endpoints instead of weight loss are difficult to conduct, but needed to generate reliable advice.

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AUTHORSHIP.

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List of Tables

Table 1 Percentage contribution of carbohydrate foods groups to average daily vitamins and minerals intakes in the UK adults 19-64 years (NDNS 2008-2014)

Food groups	Energy	CHO	Free sugars [a]	Fibre (NSP)	Vit A	Vit B1	Vit B2	Vit B3	Vit B6	Folate	Vit B12	Vit C	Vit D	Vit E	Iron	Ca	Mg	I	Se	Zn
Cereals and cereal products	31	45	21	39	8	35	22	25	17	27	7	4	13	19	39	31	28	11	27	25
Vegetables and potatoes	11	14	2	31	32	21	6	8	20	26	1	37	2	20	17	7	16	5	6	11
Fruit	3	6	1	9	1	3	2	1	6	4	0	19	0	5	2	2	5	2	1	2
Milk and milk products	9	5	6	1	14	6	28	7	8	7	33	6	5	4	1	36	10	33	6	15
Sugar, preserves and confectionary	5	7	26	1	1	1	2	1	0	1	1	1	0	2	2	2	2	2	1	1

CHO, carbohydrate; NSP, non-starch poly saccharides; Vit, vitamin; Ca, calcium; Mg, magnesium; I, iodine; Se, selenium; Zn, zinc;
[a] from non-milk extrinsic sugars
Colour code: in blue, macronutrients, energy and fibre; in green, micronutrients. Darker colours highlight a higher contribution of the good group to the UK adult intake for each specific nutrient, based on the UK NDNS data.

Table 2. Proposed definitions of low-carbohydrate diets

Categories	Frigolet 2011 [43]	Feinman 2015 [1]	Examples
Very low-carbohydrate (ketogenic) diet	<20%E or <20-50 g/d	<10% of the 2,000 kcal/d diet or 20-50 g/d	Atkins diet (Induction phase)
Low-carbohydrate diet	20-40%E	<26%E or <130 g/d	Zone diet
Moderate-carbohydrate diet	-	26-45%E	
High-carbohydrate diet	-	>45%E	

E, energy; g/d, grams/day; kcal/d, kilocalories/day

Figures legends:

Figure 1: Schematic diagram of weight gain and type 2 diabetes (T2D) development

Figure 2: Mean differences in weight loss between low-carbohydrate diets (LCD) vs. low-fat diets (LFD) at 6 months (A) and 12 months (B) of each meta-analysis (adapted from Churuangsuk et al. [4])

Horizontal axis indicates mean differences in weight loss in kilograms between LCD and LFD. The minus value indicates that LCD is more effective for weight loss than LFD.

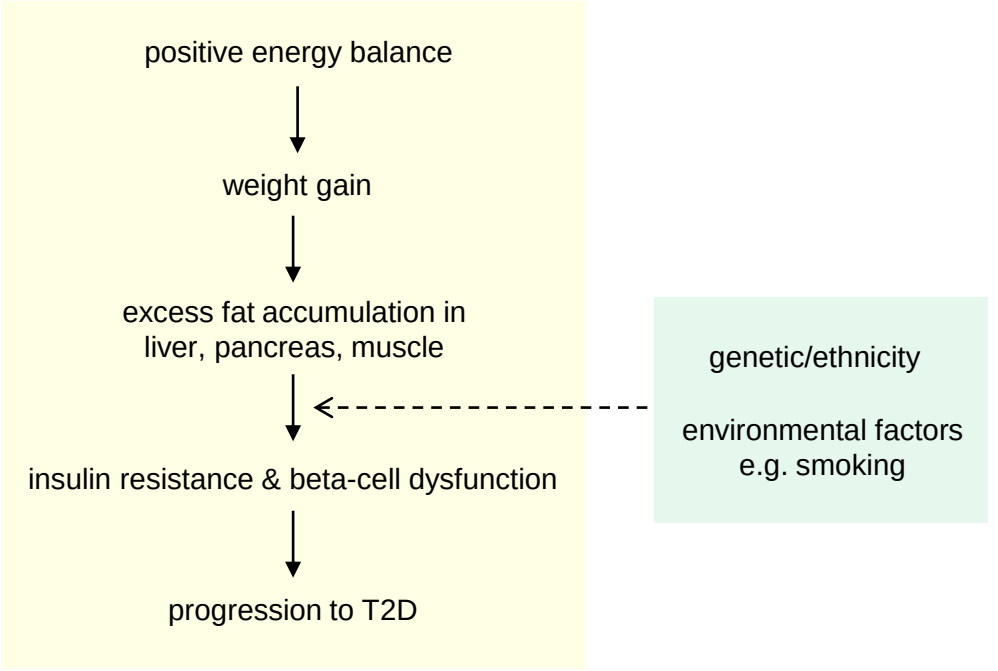
Figure 3: Proposed relationships between carbohydrates, dietary fibre, ketones and propionate levels, and satiety

CHO, carbohydrates; E, energy

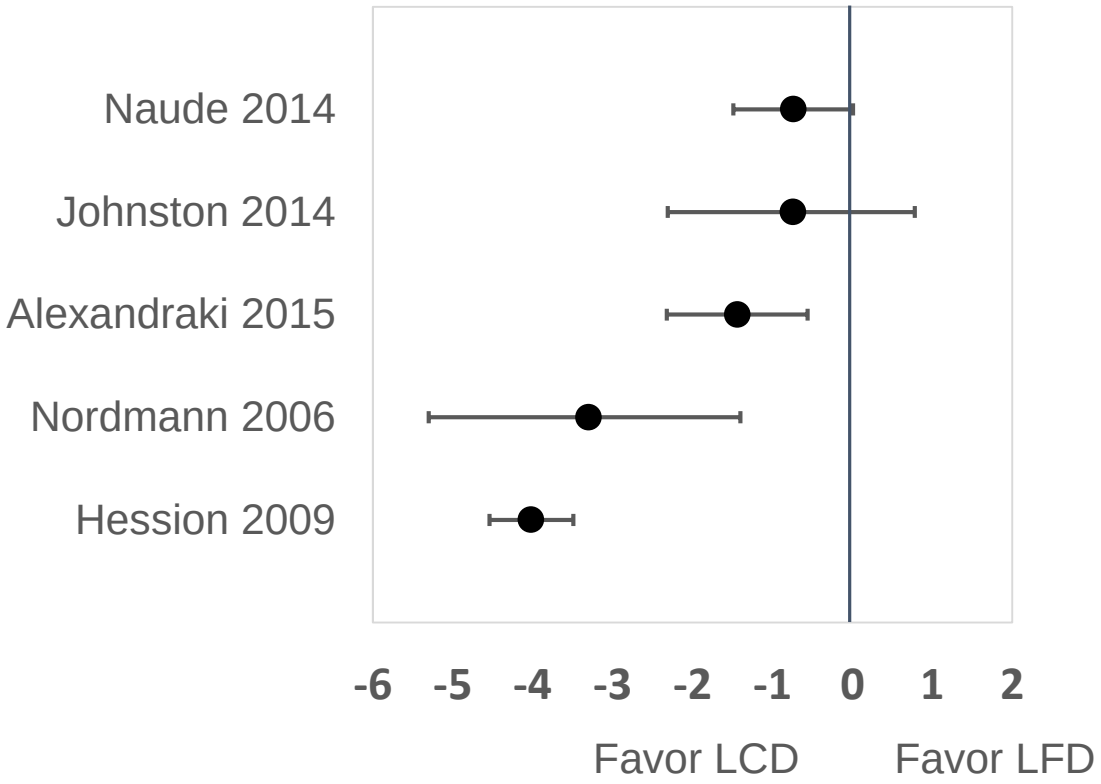
Figure 4: Opportunities and challenges for low-carbohydrate diets in type 2 diabetes management and prevention

Solid line indicates extensive and strong evidence. Dashed line indicates limited evidence. (+) indicates positive effect. (-) indicates negative effect. (?) indicates no sufficient evidence.

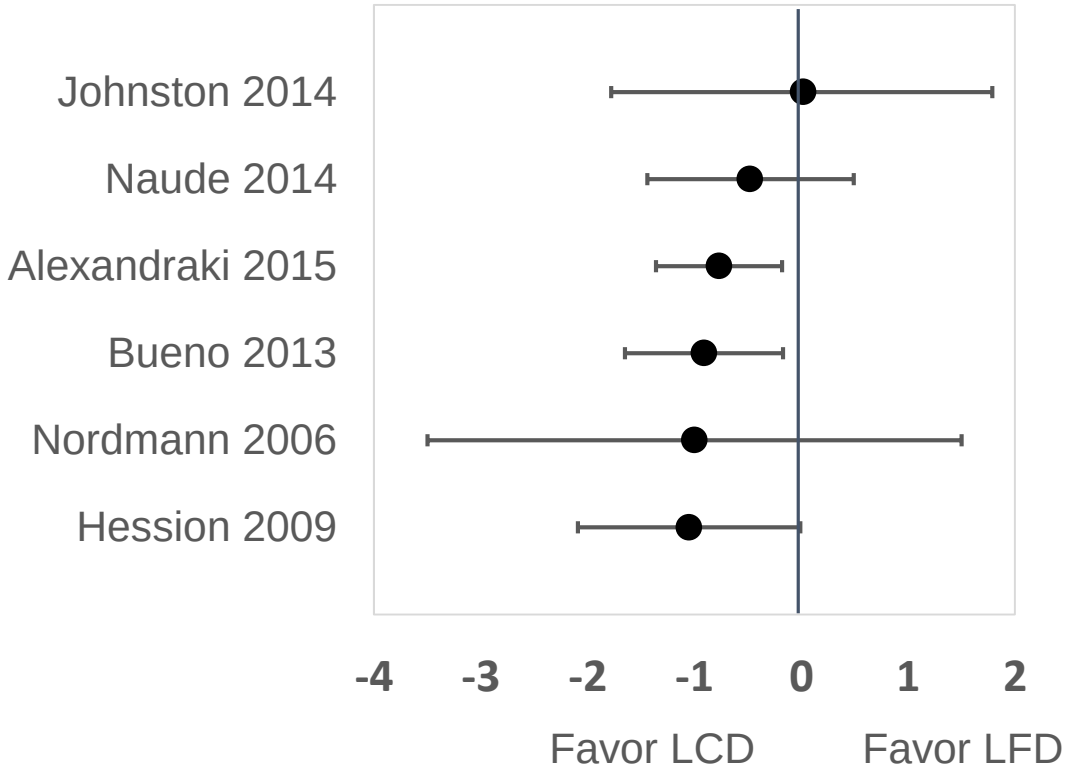
LCD, low-carbohydrate diet; MUFA, mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; LDL, low-density lipoprotein; T2D, type 2 diabetes; CVD, cardiovascular disease.

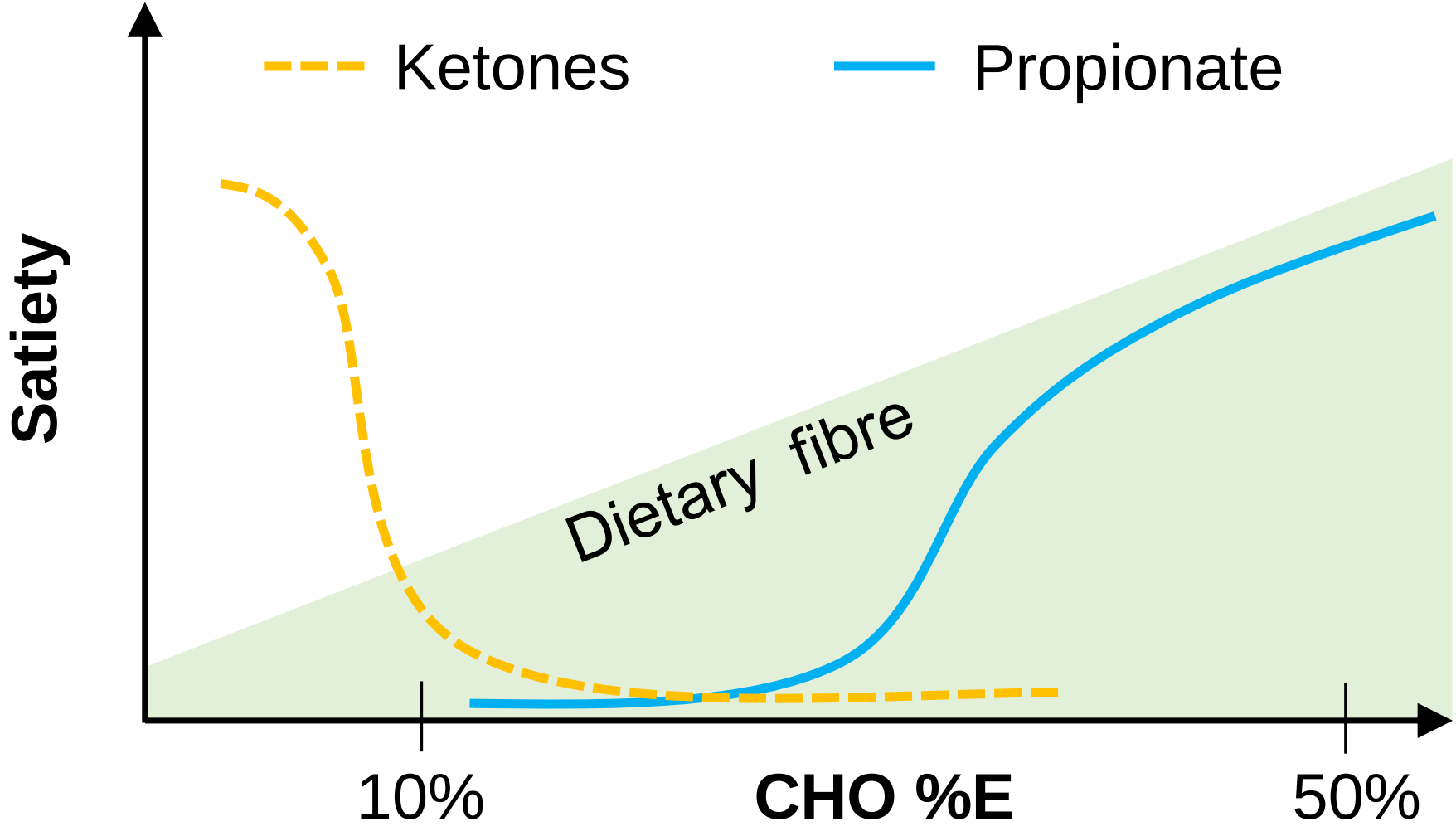

positive energy balance
weight gain
excess fat accumulation in liver, pancreas, muscle
insulin resistance & beta-cell dysfunction
progression to T2D
genetic/ethnicity
environmental factors e.g. smoking

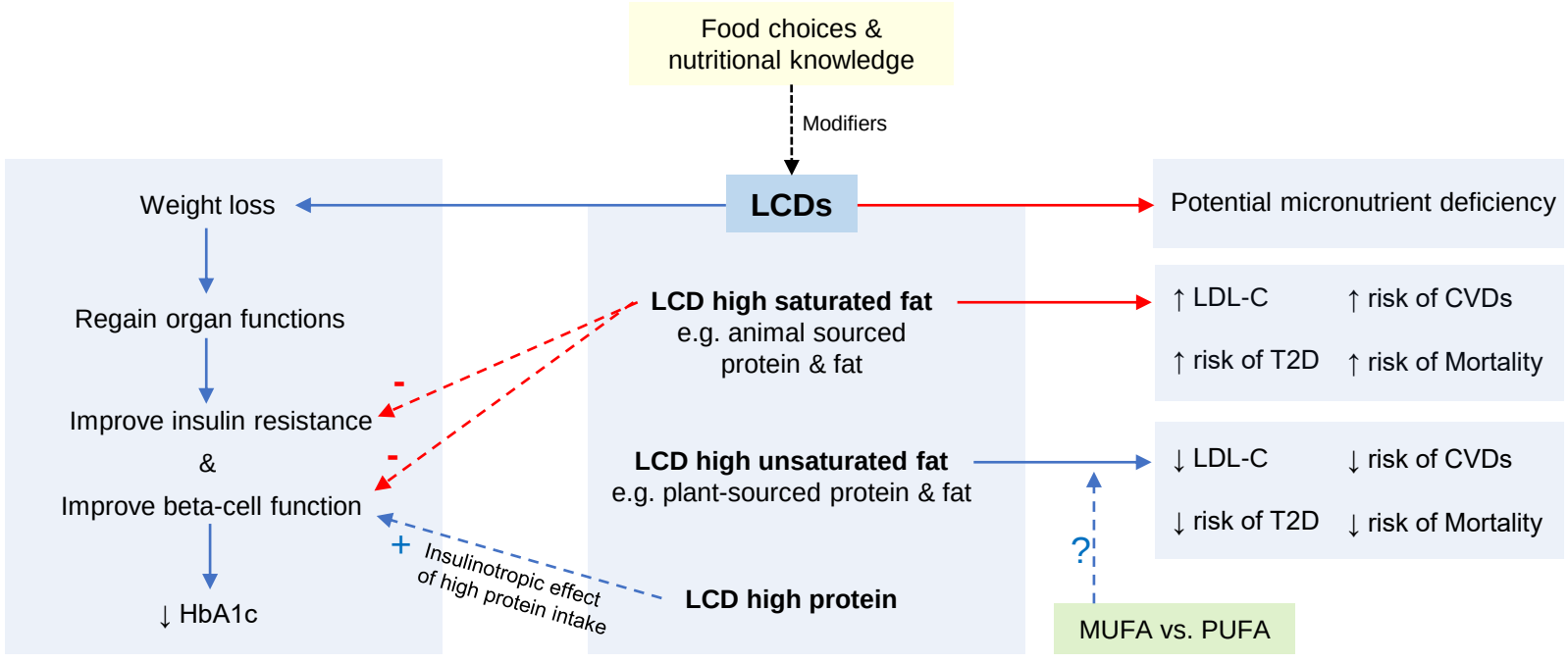
A


Naude 2014
Johnston 2014
Alexandraki 2015
Nordmann 2006
Hession 2009
-6 -5 -4 -3 -2 -1 0 1 2
Favor LCD
Favor LFD

B


Johnston 2014
Naude 2014
Alexandraki 2015
Bueno 2013
Nordmann 2006
Hession 2009
-4 -3 -2 -1 0 1 2
Favor LCD
Favor LFD


Ketones
Propionate
Satiety
Dietary fibre
10%
CHO %E
50%


Food choices &
nutritional knowledge
Modifiers
LCDs
Weight loss
Regain organ functions
Improve insulin resistance
&
Improve beta-cell function
↓ HbA1c
Potential micronutrient deficiency
LCD high saturated fat
e.g. animal sourced
protein & fat
↑ LDL-C
↑ risk of CVDs
↑ risk of T2D
↑ risk of Mortality
LCD high unsaturated fat
e.g. plant-sourced protein & fat
↓ LDL-C
↓ risk of CVDs
↓ risk of T2D
↓ risk of Mortality
?
MUFA vs. PUFA
-
-
+
Insulinotropic effect
of high protein intake
LCD high protein