X-PERT Health Position Statement: Low Carbohydrate Dietary Approaches and Type 2 Diabetes

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Executive Summary

- There is a strong physiological rationale supporting the role of carbohydrate restriction for the management of Type 2 diabetes
- Available evidence shows that low carbohydrate dietary approaches are as good as, or superior to, other dietary approaches for the management of Type 2 diabetes
- Low carbohydrate dietary approaches are consistently superior to higher carbohydrate dietary approaches in relation to reducing medication requirements, and as such their benefits may be underestimated by many studies and reviews
- Concerns about the safety of low carbohydrate dietary approaches, including in relation to cardiovascular disease risk, are not supported by the available evidence
- The absence of longer-term evidence should not be used to suggest low carbohydrate dietary approaches are inferior to other approaches as no dietary approach has high quality long-term evidence of safety or efficacy, at least in part due to the nature of nutritional research
- A growing number of important organisations support the use of low carbohydrate approaches
- Low carbohydrate dietary approaches should be promoted as a suitable choice, as part of a menu of options, for individuals with Type 2 diabetes
- Although one size does not fit all, and individuals should be supported in adopting any approach that is safe and suitable for them, some degree of carbohydrate restriction may be the most effective method for improving health for many people with Type 2 diabetes

Introduction

Although carbohydrate restriction is not a new approach for the management of Type 2 diabetes, interest in its safety and efficacy has increased significantly in recent years. The purpose of the current position statement is to summarise the key relevant research in this area and to clearly set out the position of X-PERT Health on the use of low carbohydrate dietary approaches (LCDs) in this population. This document supersedes the May 2015 X-PERT position statement on low carbohydrate dietary approaches, to reflect the large number of studies, reviews, policy statements and guidelines that have been published or updated since then.

What are low carbohydrate dietary approaches?

Although there is no universally agreed definition of what constitutes a LCD the most commonly used definitions, and those applied by X-PERT Health, are those outlined by Feinman and colleagues[1]. These definitions state that:

- any way of eating where less than 130g carbohydrate is consumed each day, or less than 26% total energy comes from carbohydrates, is classified as a low carbohydrate dietary approach
- any way of eating where less than 50g carbohydrate is consumed each day, or less than 10% total energy comes from carbohydrates, is defined as a very low carbohydrate dietary approach (VLCD). This degree of carbohydrate restriction is sometimes referred to as “ketogenic”, as it allows the body to

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enter a state called nutritional ketosis. It is important to note that this is NOT the same as diabetic ketoacidosis, and is not an inherently dangerous state[2]

For simplicity, the abbreviation "LCD" will be used throughout this document to include both low and very low carbohydrate dietary approaches. Where evidence pertains to VLCDs specifically this will be noted.

Physiological rationale for, and possible benefits of, carbohydrate restriction

There are a number of mechanisms through which LCDs may be beneficial for people with Type 2 diabetes, including that they can:

- **improve blood glucose control -** Most people with type 2 diabetes have a reduced ability to remove carbohydrate from their blood efficiently, as a result of insulin resistance[3, 4]. They also often have an impaired ability to moderate the delivery of new glucose into the blood, as the body is less able to control gluconeogenesis (the production and release of glucose within the body)[5]. The absence of the first phase insulin response, a pathology that is typical of Type 2 diabetes[6, 7], further exacerbates this latter issue, because this impairs the body's ability to prevent glucose being released from the liver when glucose is entering the circulation from dietary sources[8]. Reducing the intake of dietary carbohydrate, the nutrient that has the biggest impact on glycaemic control[9], can mitigate for these issues, leading to rapid improvements in blood glucose control even before any reduction in body weight is seen[10]. This acute effect is further demonstrated by the fact glucose lowering agents need to be reduced at the onset of a LCD[11]. Beyond this, LCDs may also help to address the underlying issues noted above more chronically. These factors are discussed below.
- **improve weight management –** Although some of the benefits of LCDs may be independent of weight loss[12, 13], many of the possible longer-term positive effects are likely influenced or caused by a reduction in body fat[14]. There are a number of mechanisms through which LCDs may improve weight management, the most important of which is perhaps the consistently seen reduction in *ad libitum* energy intake in individuals following a LCD[15-18]. Supporting the presence of this effect, some studies allow *ad libitum* energy intake in LCD groups whilst imposing an explicit calorie restriction on the control groups when comparing diets[(e.g. 19, 20)]. A second potential contributor is that LCDs naturally result in a reduced intake of ultra-processed foods. This is significant in relation to weight management, as consumption of these energy-dense, nutrient poor foods has been shown to result in increased energy intake and, consequently, weight gain[21]. Reduced hunger is discussed more below.

  A further point that is pertinent to the issue of weight management is that LCDs are effective for reducing insulin levels and insulin resistance[15, 22-25]. Insulin's most sensitive effect is the inhibition of lipolysis (the breakdown of fat), whilst it also increases lipogenesis (the creation of fat) significantly[26]. Insulin interacts with other regulatory factors too – including other hormones, neuronal activity and gut function – and so may influence weight management through multiple means[26]. Reducing insulin levels in Type 2 diabetes, which is a hyperinsulinaemic condition[27, 28], should therefore be considered a priority[10]. Further, weight gain is consistently seen in those on insulin therapy too[29]. The impact of insulin on weight management in this population may be even more important than in those who are not on insulin therapy. This is because 50-80% of insulin produced in the pancreas is taken up by the liver cells and thus doesn't enter the peripheral circulation, whereas a greater proportion of injected insulin is circulated around the body, increasing the storage of fat[26]. Therefore, the ability of LCDs to reduce insulin requirements in those who use exogenous insulin[11, 30, 31] can have important benefits in terms of weight management.
- **reduce hunger –** In individuals who follow a LCD reduced hunger is often reported[32]. Possible reasons for this include an increase in energy availability in the late post-prandial period[33] and/or changes in

hunger hormones, such as a reduction in ghrelin[34]. It may also in part be due to the improvement in the quality of the foods people tend to eat when adopting this way of eating. This is not a trait that is necessarily unique to carbohydrate restriction, but, as noted above, omitting carbohydrate-rich foods naturally involves cutting out many of the highly processed foods some people regularly consume (for example cakes and crisps). These foods are often energy dense and hyper-palatable, causing people to crave more of them[35, 36]; an issue that is avoided when higher quality foods are consumed in preference. Adopting a LCD may also lead to an increased intake of protein, which has been consistently shown to be the macronutrient that has the greatest influence on satiety[37, 38].

In those following a VLCD, hunger may be further reduced due to the onset of nutritional ketosis[15-17, 39, 40]. Supporting the significance of this effect, the influence of ketosis on appetite suppression is believed to play an important role in the efficacy of very low energy diets too[41]. It is important to note, elevated ketone levels are only dangerous if insulin levels are insufficient – which can lead to diabetic ketoacidosis (DKA). This is only usually an issue in people with Type 1 diabetes though, and DKA is a very different condition to the nutritional ketosis experienced by individuals restricting carbohydrate intake when insulin levels are not insufficient[2].

- **reduce insulin resistance –** Insulin resistance is the central issue with Type 2 diabetes in most cases[3, 4]. The primary means by which this can be addressed appears to be through fat loss, particularly from the central organs[42], which can be facilitated by a LCD. Fat loss from the liver, discussed subsequently, reduces its resistance to insulin[42]. This leads to a reduction in gluconeogenesis[8], which has important benefits for overall blood glucose control. A second pathway through which a LCD can help to address insulin resistance is through reducing the body's exposure to insulin[43, 44]; thus this dietary approach can help to address this key issue through multiple means.

- **reduce hepatic (liver) fat –** Elevated hepatic fat is a key driver of Type 2 diabetes[45], with hyperinsulinaemia and excess energy intake thought to be key drivers of hepatic fat accumulation[46, 47]. Although weight loss can be effective for reducing liver fat content there is some evidence that the benefits of LCDs may be, at least in part, independent of this[48, 49]; and that greater improvements may be achieved through carbohydrate restriction than calorie restriction[46]. Research has also shown that improvements in response to LCDs can occur rapidly[50]. Overconsumption of carbohydrate may be especially detrimental to the liver[46, 47], with excess being converted to fat through *de novo lipogenesis*[51]. Further still, sugary carbohydrates may be particularly harmful because the majority of fructose that enters the body has to be processed within the liver before it can be stored or utilised by other body cells[52]. Based on this, the ability of LCDs to address liver fat is perhaps not surprising as they address both of the primary mechanisms of hepatic fat accumulation; i.e. elevated insulin levels and excess energy intake (particularly from carbohydrates).

- **reduce pancreatic fat -** A reduction in hepatic fat also helps to facilitate a reduction of fat in the pancreas. Triglyceride rich lipoproteins expelled from the liver have a direct impact on the pancreas, as outlined in Professor Roy Taylor's twin-cycle hypothesis[45]. A reduction in hepatic fat therefore reduces the downstream influence on the pancreas, increasing the ability of the body to reduce pancreatic fat storage. Reduced pancreatic fat is a key outcome in relation to blood glucose control, as it enables the specialised function of the beta-cells to return for many individuals[53]. It is worth noting however that these specialist functions, such as stimulating the first phase insulin response, may be less important in individuals who have reduced their carbohydrate intake anyway; as the inability of the body to effectively deal with dietary carbohydrates is not as relevant to blood glucose control if there is less dietary carbohydrate to be processed.

- **allow the pancreatic beta-cells to rest -** Lowering dietary carbohydrate intake reduces the need to shuttle glucose into the cells, thus there is a decreased requirement for insulin. As a result, the workload of the pancreas is not as high when an individual adopts a LCD. This period of rest may contribute to the return of beta-cell function[48, 54], though further research is required to confirm this.

- **reduce glucotoxicity -** Insulin production and secretion are negatively affected by glucotoxicity[54, 55], defined as when supraphysiological exposure to glucose over an extended time period causes beta-cell damage[56]. Reducing the exposure of the beta-cells to glucose by limiting the intake of dietary carbohydrate may therefore be beneficial[48].
- **improve blood pressure –** Weight loss is one means through which a LCD may help to reduce blood pressure, though a recent paper assessing the impact of carbohydrate restriction concluded that weight loss alone would could not explain the drop in blood pressure that was observed[57]. It is possible, as suggested by the authors of the before mentioned paper, that a reduction in insulin levels may play a role. This is because, in addition to controlling the usage and storage of energy, insulin causes sodium to be retained in the body[58, 59]; which can lead to an increase in blood pressure[60]. A LCD also typically results in a reduced intake of highly processed foods, which tend to have a high salt content. As a result, LCDs often lead to both a reduced intake and a reduced retention of sodium; and it can in fact be necessary for individuals following this approach to add salt to their food to prevent sodium levels, and blood pressure, dropping too low[61, 62]. As with glucose lowering medications, it is often necessary for hypertensive medications to be adjusted at the onset of a LCD[61, 62], further supporting the assertion that LCDs can reduce blood pressure rapidly and at least in part independent of weight loss.
- **reduce triglyceride (fat) levels –** LCDs consistently lead to a reduction in triglyceride levels[63], an effect that is likely linked to the ability of this approach to reduce hepatic fat (see above). This is because when hepatic fat is elevated excess triglycerides are shunted into the blood[1]. Reducing triglyceride levels can lead to additional benefits too, as the amount of triglyceride in the blood has an impact on the size, structure and number of circulating lipoproteins (e.g. high-density lipoprotein, HDL, and low-density lipoprotein, LDL)[63]. Improvements in these markers result in an overall reduction in cardiovascular disease risk[64].

These possible benefits are not necessarily exclusive to LCDs, but nevertheless are means by which dietary approaches of this nature may improve the health of individuals with Type 2 diabetes.

Available evidence: systematic reviews and meta-analyses

There are a number of published systematic reviews considering the effect of LCDs on weight loss and other markers of health in people with Type 2 diabetes. All identified reviews which included meta-analyses of randomised controlled trial (RCTS), considered to be the gold-standard of evidence, are outlined in Appendix 1 (n=11[30, 65-74]). The general conclusion of many of these is that LCDs perform better for weight loss and improving diabetes control in the short-term, but over the longer-term (more than six months) there is often little difference between LCDs and control arms (which are usually based on low fat diets). The apparently diminishing differences may be as a result of reduced adherence to LCDs over time, or indeed they may be a true reflection of the physiological impacts of such diets. The outcomes may also be influenced by other limitations with the methods of these reviews or of the studies included within them, a topic revisited below. Regardless of the reasons, these reviews provide clear and consistent evidence that LCDs can be at least as effective as other dietary approaches. They therefore support the use of LCDs as a suitable option in this population. Notably, where there are differences between groups they consistently favour LCDs. This assertion holds true in relation to body weight, blood glucose control, blood pressure, triglycerides, and HDL.

As alluded to above, there are some important limitations with many of these reviews and/or the studies they include. Consistent issues include:

- the grouping of papers based on target dietary intake rather than actual dietary intake, thus studies are often presented as assessments of low or very low carbohydrate diets despite actual carbohydrate intake exceeding stated thresholds. In some reviews, where the actual carbohydrate intake is not fully considered, there is as little as 8g difference in the carbohydrate consumption of the “high” and “low”

carbohydrate groups[75], whilst in one identified study the carbohydrate intake was actually lower in the control group than the low carb group at certain time points[76]

- failure to consider the quality of the foods consumed as part of the intervention and/or control diets
- a failure to measure or consider the pre-study dietary intake of the participants
- differences between studies in relation to baseline characteristics (such as duration of diabetes, baseline HbA1c, or insulin sensitivity)
- differences in the level of support provided to the intervention and control arms
- the dietary interventions in many studies are designed to provide an equal amount of energy (calories) in both the LCD and control groups. This precludes any difference being observed as a result of changes in hunger leading to changes in a*d libitum* food intake
- the methods of tracking and/or assessing the diets of the participants are often flawed, an issue that is largely unavoidable but provides a limitation for much of the body of nutrition research. The limitations of dietary assessment methods such as food frequency questionnaires and 24-hour dietary recall are well described elsewhere, whilst more robust methods such as weighing foods and completing food diaries are still not without flaws and are often not adhered to
- a failure to consider the influence of the intervention and control arms on medication requirements

The last limitation in the list above is a particularly important one, as studies consistently demonstrate greater reductions in diabetes medication requirements in the lower carbohydrate arms. Where an outcome such as HbA1c is similar between two groups, but one group has achieved this whilst significantly reducing the amount of medication they require, this demonstrates a superior performance from the intervention that allowed this. The ability to reduce medication needs is a strong motivator for many individuals too, and indeed the requirements for many diabetes medications is reduced or removed at the onset of a LCD (see Murdoch et al 2019[11], which provides a practical guide to support healthcare professionals in adjusting medications appropriately for individuals following LCDs, for more details). Therefore, the failure of many of the reviews to effectively consider this may penalise the low carbohydrate groups by failing to consider potentially important benefits. However, as studies do not report medication usage or changes in a uniform way it is often not possible to pool outcomes related to this. Where reviews have considered medication changes the outcomes are as follows:

- Snorgaard et al (2017)[69] found that, in the seven studies they included which reported relevant outcomes, medication was reduced at three and six months with lower carbohydrate dietary approaches compared to higher carbohydrate dietary approaches; and was “numerically lower” at 12 months. The authors acknowledged that “changes in glucose lowering medication have probably led to an underestimation of the effect of low carb diets on glycaemic control”
- Sainsbury et al (2018)[71] found that, in the 12 studies they included which reported relevant outcomes, there was a greater reduction in medication use for participants on carbohydrate-restricted dietary approaches compared with higher carbohydrate dietary approaches at every time point; with all studies that reported on such outcomes observing either reduced dosage of oral medications and/or insulin, or an elimination of medication altogether, in the lower carb groups
- van Zuuren et al (2018)[72] reported that “in all of the studies that included patients taking medication and that adequately reported eventual adaptations, with the exception of one, glucose lowering drug doses were reduced in participants who consumed low-carbohydrate food, but not in those consuming low-fat food.” It should be noted however that this was based on just four studies
- Korsmo-Haugen et al (2018)[30] concluded that the information available suggests that there was a greater reduction in the use of diabetes medication, particularly insulin, in the LCD groups – and that

this may have masked a more positive influence of LCDs on glycaemic control. They acknowledged that this conclusion was based on limited information however, with only four studies showing a significant difference in the change in medications between diets (it was unclear how many studies performed analyses to assess whether there was a significant difference for this)

- Huntriss et al (2018)[73] found that, in the 14 studies they included which reported relevant outcomes, every study reported a greater reduction in the requirement for diabetes medication in the low carbohydrate group than in the control group. Of the 11 studies that ran relevant analyses nine (82%) found this difference to be statistically significant

When appraising this evidence it should be considered that there is an overlap in the studies included within these reviews. They therefore should not each be considered to provide additional, independent evidence. Nevertheless, the findings of reviews and studies considering the impact of different dietary approaches on the need for diabetes medication are clear and consistent.

Of note, a joint review of the evidence pertaining to carbohydrate restriction for the management of Type 2 diabetes is currently being carried out jointly by the Scientific Advisory Committee on Nutrition (SACN), NHS England, and Diabetes UK. This review, which is expected to be published in 2020, is likely to be the most comprehensive and influential review of the subject to date, and may therefore have implications for the role of LCDs in nutritional recommendations/guidelines and practice going forward. Based on the publicly available minutes of meetings of this committee, it is clear that the panel have acknowledged that existing reviews fail to fully consider the important influence of changes in medication in their conclusions. It is therefore highly likely that this factor will be considered in their final report.

Available evidence: randomised controlled trials

As well as considering the conclusions of systematic reviews and meta-analyses it is beneficial to consider the outcomes of individual studies, as this allows the evidence to be appraised in a manner that takes into account the limitations identified with existing systematic reviews. In particular, it allows a focus on studies where the reported intake of carbohydrate was consistent with the definitions of LCDs stated earlier and it provides an opportunity to further consider the importance and influence of changes in medication requirements.

To inform the current position statement, all studies included within the meta-analyses listed in the previous section were considered. This list was then filtered using the criteria applied by the National Institute of Health and Care Excellence (NICE) in their development of the guidelines for the management of Type 2 diabetes in 2009 (subsequent updates to this guideline did not appraise the relevant evidence pertaining to the effect of different dietary approaches). These criteria were simply that research had to have a minimum of 50 participants and a follow up of at least three months.

Of the 61 studies included within the 11 identified meta-analyses (studies classified as “moderate” carbohydrate were excluded) only 21 had a stated target for carbohydrate intake in the low carbohydrate arm that was less than the definitions set out at the start of this position statement. Of these:

- eight studies had less than 50 participants[77-84]
- one study was not truly a study of LCDs, as it used protein shakes as meal replacements[85]
- in one study the reported carbohydrate intake was higher in the LCD arm than in the control group of the study at multiple time points, with the paper also stating that “macronutrient intake did not differ significantly between groups at any point”[76]
- two studies had a reported carbohydrate intake above the threshold to be defined as a LCD, despite the target carbohydrate intake meeting the applied criteria[86, 87]

Of the remaining nine publications[88-96] there were three occasions where two papers were based on the same trial; reporting different outcomes[93, 94] and/or different lengths of follow up[88, 89, and 95, 96]. An additional paper from one of these trials was also identified which had not been included in any of the reviews[97] (despite having been published before the stated cut-point for inclusion in the most recent review[74]). In all cases where multiple papers representing the same trial were identified, the paper with the longest follow up was included here. No papers which met the stated criteria were identified that had been published since the most recent review. The representative papers of each of the six identified eligible studies are summarised are summarised in Appendix 2.

Although a simplistic means of outlining the findings of these studies, it is of note that the HbA1c reduction was greater in the low carbohydrate arm of all six of these trials; though the difference between groups was only statistically significant in one. For other health markers most studies demonstrated comparable improvements for LCD and control arms, though where there were statistically significant improvements they were consistently in favour of the LCD arm. Importantly, all five studies that reported relevant outcomes demonstrate a greater reduction in diabetes medication requirements in participants randomised to follow a LCD than those in the control arms. As noted before, this results in an underestimation of the benefits of LCDs. These findings, based only on studies where reported carbohydrate intake was below the threshold used to define a LCD, clearly show that LCDs can be at least as effective as the low fat dietary approaches which have generally been recommended for the management of Type 2 diabetes.

When considering the evidence pertaining to carbohydrate restriction it is sometimes argued that very low energy diets should be included, as such interventions often meet the stated criteria in relation to absolute carbohydrate intake (i.e. they contain less than 130g carbohydrate). Indeed it is possible that at least part of the benefit seen from interventions of this nature, for example the DiRECT study[53, 98], could be attributable to carbohydrate restriction rather than being solely due to low energy intake or weight loss. One mechanism through which this may be the case is by allowing the beta-cells time to rest and recover, which energy (calorie) restriction in the absence of carbohydrate restriction would not allow to the same degree. This could conceivably contribute to the re-differentiation of the beta-cells (the return of the cells to their specialised function), a key feature in the remission of Type 2 diabetes[53]. However, these approaches are not designed to be long-term and do not represent LCDs in a form congruent to that which would usually be promoted. Therefore evidence of this nature will not be considered further in the current position statement.

Available evidence: other sources

RCTs and systematic reviews/meta-analyses of such trials are considered to be the highest quality of evidence, but important information can also be obtained from alternative sources. Although other forms of evidence may be considered inferior on some levels they can also have their own strengths, for example they are often more ecologically valid than RCTs (i.e. they often reflect a real world setting more closely than controlled trials do). This type of evidence can therefore help to bridge the gap between research and practice. Relevant evidence pertaining to carbohydrate restriction from sources other than RCTs includes:

- Virta Health have demonstrated excellent outcomes that further support the safety and efficacy of carbohydrate restriction for the management, and possible remission, of Type 2 diabetes[31, 99]. Most of the participants in this study were consuming less than 30g carbohydrate per day (a VLCD). After two years of the trial 55% of those following the VLCD had an HbA1c below the cut-point used to define diabetes, 67% of all diabetes medications were no longer required, mean insulin dose was reduced by 81% (from 81.9 units/day to 15.5), and over 60% of those using insulin at the start of the trial were able to omit it altogether[31]. Virta have also demonstrated meaningful reductions in cardiovascular disease risk in participants of their programme, with a mean reduction in 10-year atherosclerotic cardiovascular

disease risk score of 11.9%[64]. Their two year results also showed an average reduction in triglycerides (-22%), CRP (-37%), and the resolution of metabolic syndrome in 29% of participants[31].

- The Diabetes.co.uk Low Carb Programme has had over 400,000 users, demonstrating the popularity of LCDs. Outcomes from a sample of 1,000 participants of the programme have been published in a peer reviewed journal[100]. The participants in this study were randomly selected from a larger convenience sample for whom baseline data was available, but the results were self-reported and there was no control group. Despite these limitations, the results support the efficacy of this programme. Of the 743 participants with an HbA1c above the threshold for Type 2 diabetes diagnosis, 195 (26.2%) saw a reduction in HbA1c that took them below this threshold. Of the 714 participants who were taking at least one medication to manage their diabetes, 289 (40.4%) reduced one or more of these medications; and 46.4% of participants lost at least 5% of their initial body weight.

  It is of note that this programme is included in the NHS App Library (https://www.nhs.uk/apps-library/low-carb-program/) and is part of an NHS innovation accelerator, a programme designed to speed up the uptake of high influence interventions. These facts provide evidence that this programme, and by extension LCDs, are deemed acceptable by the NHS. The programme has also received approval from the British Dietetic Association (BDA)[101], who concluded that "following the program will support individuals to improve the quality of their diet, lose weight, and likely improve their diabetes control."

- Evidence of the safety and effectiveness of LCDs for the management of Type 2 diabetes has been shown within primary care in the UK, for example in Dr David Unwin's GP practice in Southport[57, 102, 103]. Complete remission of Type 2 diabetes has now been recorded in 53% (71/135) of the patients who have adopted a LCD within this practice (unpublished data). The LCD intervention delivered by Dr Unwin has also demonstrated considerable financial benefits, with the overall diabetes drug spend approximately £45,000 less per year than the regional average[104].

- We (X-PERT Health) ran a pilot project in partnership with Modality GP partnerships assessing the safety and efficacy of a "Modified Mediterranean Diet", supporting patients in reducing their carbohydrate intake to 20g per day using structured education[105]. Of the 35 participants who began the programme 27 (77%) completed it. Clinically meaningful improvements were seen at three months for body mass (mean change = -7kg), HbA1c (-15.6mmol/mol), systolic blood pressure (-7mmHg), diastolic blood pressure (-5mmHg) and triglycerides (-0.4mmol/l). 85% of participants who were taking medication at the onset of the pilot reduced their requirement, with 25% of them omitting their medication entirely. Half (3/6) of insulin users were able to omit it.

Position of other organisations

Arguably above and beyond the quantity and quality of available evidence for a particular approach or intervention, the position of bodies who produce relevant policy and guidelines is highly significant. This is because many healthcare professionals, particularly those who are not specialists within a given area, are not familiar with emerging evidence, and/or do not have the time or skills to fully appraise it. As a result they will defer to the position of relevant organisation to guide their practice, and will often not feel comfortable or confident with promoting and supporting an approach until they perceive it to be supported by such bodies. Importantly, a number of influential organisations, nationally and internationally, now support the use of LCDs for the management of Type 2 diabetes:

- Diabetes UK (DUK) guidance from 2011[106] and 2018[107] concluded that there is insufficient evidence to promote a specific dietary approach or to conclude what percentage of a person's energy intake should come from fat, protein, or carbohydrate. They state that adherence to a dietary approach is the best predictor of long-term success, that individualisation of approaches is important, and they support carbohydrate restriction as a suitable option. A 2017 Diabetes UK position statement also supports the use of LCDs[108]

- The BDA released a position statement in 2018 supporting carbohydrate restriction as a viable option for adults with Type 2 diabetes[109], with caveats around the need for more research to ascertain the ideal nutritional compositions and the long-term effects
- The Scottish Intercollegiate Guidelines Network (SIGN) updated their national clinical guidelines for the management of diabetes in 2017[110], and now recommend that people with Type 2 diabetes be given dietary choices for achieving weight loss that may also improve glycaemic control. The listed options for achieving this include restricting the total amount of carbohydrate
- A 2018 joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) reached conclusions similar to DUK (see above), promoting individualised dietary approaches, with LCDs being included as a suitable option, for all patients[111]
- A 2019 report from the Legislative Assembly of Western Australia's Education and Health Standing Committee reached conclusions supportive of LCDs for the management of Type 2 diabetes[112]
- A 2019 consensus report from the ADA concluded that "a variety of eating patterns are acceptable for the management of diabetes" supporting the need to individualise approaches[113]. In relation to carbohydrate restriction specifically, this report acknowledges:
    - Glucose requirements can be met by the body's metabolic processes, thus there is no lower limit of necessary carbohydrate intake
    - "Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycaemia and may be applied in a variety of eating patterns that meet individual needs and preferences"
    - "For select adults with type 2 diabetes not meeting glycaemic targets or where anti-glycemic medications is a priority, reducing overall carbohydrate intake with low- or very low-carbohydrate eating plans is a viable approach"
    - "…from the current evidence, this eating pattern does not appear to increase overall cardiovascular risk…", with the authors noting that this was the case even though most of the included trials did not restrict saturated fat

  The position set out in this consensus report was subsequently included in the 2020 update to the ADA Standards of Medical Care in Diabetes[114], which represent the ADA's current clinical practice recommendations.

However, the current guidance provided by the National Institute of Health and Care Excellence (NICE) is not fully consistent with the organisations referenced above[115]. Although elements of this guidance are aligned with these other bodies, for example it includes recommendations to favour lower glycaemic index carbohydrates and to individualise carbohydrate intake and meal timings, the overriding message is to promote the same way of eating that is recommended for the general population (i.e. The Eatwell Guide[116]). Disappointingly, when updating these guidelines in 2019 it was decided that the section on dietary approaches did not warrant review. This is despite multiple stakeholders, including DUK, the BDA and X-PERT Health, challenging this position during the consultancy phase (comments and responses are accessible here: https://www.nice.org.uk/guidance/ng28/evidence/appendix-b2-stakeholder-consultation-comments-table-ng28-pdf-6837997937). This inconsistency in guidance has the potential to cause confusion. This was therefore a missed opportunity to help healthcare professionals, who, in the UK, are more likely to defer to NICE guidance where there is any doubt over what constitutes best practice in an area they do not specialise in, feel comfortable with supporting LCDs.

Of note though, the overall response summarising decisions made pertaining to the update of this guideline did state "NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns, which could include low carbohydrate and low calorie diets." It is therefore clear that the promotion

and support of LCDs for people with Type 2 diabetes is not precluded. NICE also stated an intention to reconsider these guidelines based on the conclusions arrived at by the Scientific Advisory Committee on Nutrition (SACN), NHS England and Diabetes UK in their joint review of the subject.

Long-term effects of low carbohydrate dietary approaches

Although the positions outlined in the previous section acknowledge the potential utility of carbohydrate restriction for people with Type 2 diabetes, the position of X-PERT Health is that there are still unnecessary caveats regarding the longer-term effects of this approach in many of them. There are two principle justifications for this:

1. **There is an absence of high quality evidence regarding the long-term safety and efficacy of ANY dietary approach.** This is largely due to the limitations of nutritional research, including the high cost of carrying out long-term follow ups, an inability to continuously track all relevant variables and outcomes, difficulty in monitoring dietary intake, and difficulty in controlling for other variables which might affect the outcomes. These limitations are true in relation to the study of all dietary approaches, including low fat approaches which have been adopted widely by organisations worldwide. Where longer-term studies have been attempted, the outcomes in relation to low fat dietary approaches often do not support its superiority over other approaches. For example, in the Women's Health Initiative study glycaemic control was worse in the low fat arm than the control group after 6 years[117] and in the LookAHEAD trial there was no reduction in cardiovascular disease risk, with the study being stopped after 9.6 years as a result[118]. This raises questions as to why low fat approaches are widely promoted without qualification, yet other ways of eating have been promoted with caution due to a perceived absence of long-term evidence. It is inappropriate to hold LCDs to a level of evidence higher than that which other dietary approaches can meet.
2. **Evidence exists supporting the safety and efficacy of LCDs from studies of greater than 12 months, without an increase in cardiovascular disease risk.** In the absence of high quality, long-term evidence assessing differences in disease prevalence, cardiovascular mortality and/or total mortality between different dietary approaches, studies considering changes in relevant risk markers provide the best available evidence. Changes in cardiovascular markers for the LCD arms of such studies are comparable, or often superior, to those of the control groups, which are usually based around low fat dietary approaches. In support of this assertion, the ADA 2019 consensus statement on nutrition therapy for adults with Type 2 diabetes concluded that "…from the current evidence, this eating pattern does not appear to increase overall cardiovascular risk…" and, notably, they acknowledge that this appears to be true even within studies where the intake of saturated fat was increased[113].

Based on these points, our position is that caveats in the position of other organisations pertaining to the long-term effects of LCDs are not justified; though, as with anything else (or with any other dietary approach), it is essential that this topic continues to be assessed to increase our understanding and to ensure that no long-term harm is caused.

Adherence

Another criticism in relation to carbohydrate restriction is regarding its sustainability. Evidence suggests that the approach which is most likely to result in long-term health improvements is whichever one the individual is able to continue following, so this is an important issue. However, the available evidence does not support the assertion that LCDs are more difficult to follow than other approaches.

In the Virta trial, for example, where participants were highly motivated and self-selected the diet, adherence was 83% at one year[99] and 75% at two years[31]. These values were for a VLCD (most individuals were required

to consume less than 30g carbohydrate per day), which may be more difficult for many people to stick to than a more moderate carbohydrate restriction. In RCTs, where individuals may be randomised to an approach that is not consistent with their own preferences, completion rates are in fact very similar for LCD and control arms. Indeed, in the six trials summarised in Appendix 2 the average completion rates at the most recent time points for which data are available were 73% and 72% in the intervention and control arms respectively. Although completion rates are not a perfect marker of adherence they do provide an indication of this, particularly within studies where reported carbohydrate intake is consistent with the standard definition of a LCD. It is possible that adherence rates in these studies may be higher than in a general population however. Some studies provide high levels of support, or even provide the participants with the food they are required to consume, both factors which would make sticking to a dietary approach easier than it would be in the real world. Further, many studies are of a short duration, which might help motivate individuals to stick to a LCD even if they are not finding it enjoyable. It is also possible that individuals volunteer for such studies as they have an interest in a LCD, which may result in favourable adherence rates for the LCD arms when compared to the control arms. Supporting this, in one study all of the participants who withdrew from the control group did so because they were disappointed at not being randomised to the low carbohydrate arm[79]. Despite these possibilities, there is still an absence of evidence that LCDs are more difficult to follow than other ways of eating.

In the "real world" there are still practical barriers to adopting LCDs. These barriers include, in the UK, that:

- the reference intakes and traffic light colour coding on food labels are designed to support a low fat dietary approach
- many people are not supportive of their friends or family members if they try to follow a LCD, in part because a general "fat-phobia" still exists through much of society
- most readily available food in shops and eateries is geared towards a low fat way of eating; for example, sandwiches are still the most abundant lunch option in most places

These factors may therefore make it more difficult for someone to adopt a LCD, but that does not mean that it is not possible. Indeed, anecdotal evidence supports that many people are able to sustain a LCD long-term; and in a survey of dietitians in the UK the majority responded that they felt a LCD was achievable for the "right individuals" as long as they received appropriate support[119]. Ensuring individuals are well informed regarding what barriers they may face and what their options include, and are provided with appropriate support where possible, is important. Practical advice is available through a number of channels, including:

- structured education programmes - such as the X-PERT Diabetes and X-PERT Insulin Programmes
- mobile Apps - such as the diabetes.co.uk Low Carb Programme and X-PERT Diabetes Digital
- websites – such as Diet Doctor
- books – such as the X-PERT Eat Fat Handbook

Support for healthcare professionals, to help them learn about LCDs and how they can support their patients in adopting them, is also available. For example:

- a clinicians guide to inpatient LCDs was recently published In *Diabetes Management*[61]. This guide includes practical guidance at all stages of care and additional advice regarding common side effects and concerns
- comprehensive guidelines, covering the assessment of participants' health status, different ways of adopting a LCD, medication adjustment, and information on maintenance and adherence of LCDs, are available at Guideline Central (http://eguideline.guidelinecentral.com/i/1183584-low-carb-nutrition-queens-units/0)[62]

- the Royal College of General Practitioners provide an online course, titled "Type 2 diabetes and the low GI diet", which is free for their members to access through their e-learning module (https://elearning.rcgp.org.uk/)

As alternative dietary approaches become more widely accepted some of the limitations outlined above may dissipate. However, changes in the food environment, which are necessary, are unfortunately tied more closely to economic priorities than health-related ones. It is therefore crucial that people wishing to adopt a LCD are provided with the education and support necessary to help them make informed decisions about their food choices.

Additional concerns

Beyond those discussed above, there are a number of other objections to LCDs that are often raised. The most common are briefly covered here:

- **LCDs cause hypoglycaemia (low blood glucose levels):** although minor hypoglycaemia can be experienced by anyone, severe hypoglycaemia is only a danger for individuals taking certain medications, particularly insulin or sulphonylureas. This is because these medications continue to remove glucose from the blood even if blood glucose levels are already low. At the onset of a LCD these medications are reduced or omitted, thus there is actually a reduced risk of hypoglycaemia in individuals following a LCD **as long as they have a medication review before they begin** (see Murdoch et al 2019[11] for details of appropriate medication adjustments). Of note, there were no serious adverse events reported in the RCTs identified for inclusion in the current document (see Appendix 2) and where reported in the identified systematic reviews (see Appendix 1) there was no difference in adverse events, including hypoglycaemia, between diets[30, 69]
- **LCDs are nutrient deficient:** any dietary approach can result in individuals not obtaining all of the dietary components that the body requires to function optimally if they are not well planned or if they are based on highly processed foods. In relation to LCDs concerns are often raised in relation to fibre in particular. However, there are a wide variety of foods that can provide fibre without contributing large quantities of carbohydrate to the diet, e.g. nuts, seeds and dark chocolate (over 80% cocoa solids); whilst the staple components recommended when individuals adopt LCDs are invariably nutrient dense foods, such as non-starchy vegetables, eggs and oily fish. This is further discussed by Zinn, Rush and Johnson (2018)[120], who provide a hypothetical case study demonstrating that LCDs need not be deplete of any important nutrients
- **LCDs are more expensive:** health inequalities are a major issue, with any intervention which is not suitable for individuals with a lower socio-economic status exacerbating the problem. It has been posited that LCDs are not suitable for lower income households, but that is based on false assumptions regarding the types of food an individual may regularly consume when following this approach. As with any dietary approach there are more expensive options which may not be suitable for everyone, but there are also multiple ways this way of eating can be adapted to be more cost-effective. For example, staple ingredients such as eggs or tinned oily fish need not be expensive; whilst purchasing frozen vegetables, for example, can reduce waste and help save money. An analysis of the cost of food for a family of four switching from a low fat diet to a LCD supports that this approach does not need to be significantly more costly[121]. It should also be considered, as discussed previously, that LCDs have been demonstrated to reduce hunger for many people. This naturally reduces food intake, often leading to less snacking and/or a lower eating frequency, and thus less money is required to be spent on food. It is important that socio-economic factors are not disregarded though, and people should be supported to adopt the best quality diet that they can afford, regardless of which dietary approach they wish to follow

Should all people with Type 2 diabetes restrict carbohydrates?

The overall ethos of X-PERT Health is that "one size doesn't fit all", as there is evidence that a number of different dietary approaches can be effective for facilitating improvements in health in people with or without Type 2 diabetes. Essentially, there is no value in a person trying to adopt a dietary approach that they cannot sustain, and/or in trying to adopt a different dietary approach if they find their current way of eating is allowing them to meet their health goals. However, as Type 2 diabetes is a condition of carbohydrate intolerance[1], there may be an upper limit of carbohydrate intake that an individual with Type 2 diabetes can tolerate before they have difficulties managing their blood glucose levels and other markers of health. An element of carbohydrate restriction may therefore be necessary, though that does not necessarily mean individuals will be required to follow a "low carb" diet to meet their goals. This is supported by a recent survey of dietitians, with the majority of respondents believing that the Public Health England guidance of a 50% energy intake from carbohydrates was inappropriate for this patient group[119].

Further, the evidence pertaining to Type 2 diabetes remission suggests that LCDs may have an advantage over other dietary approaches. Until recently it was not known or accepted that Type 2 diabetes remission was possible at all[122], suggesting that standard dietary management approaches are not effective for achieving this. Although there is now evidence that Type 2 diabetes remission is possible with a number of approaches (including Mediterranean[123] and low fat diets[124-126]), the evidence is strongest for very low energy diets[98, 127] and VLCDs[31, 99]. The former of these methods, very low energy diets, is different in nature to a VLCD however as it is only a short-term approach; thus a long-term, sustainable dietary approach still needs to be adopted after the weight loss phase. Additionally, the success of a very low energy diet in relation to Type 2 diabetes remission is dependent on the ability of the pancreatic beta cells to regain their specialist function[53]. Evidence suggests however that some people, particularly those who have had Type 2 diabetes for a longer duration[128], may not be able to achieve this. In these cases individuals may not see their ability to effectively metabolise carbohydrates return, and so reducing the amount of dietary carbohydrate they are required to process is likely a better strategy to help them improve their blood glucose control than targeting weight loss alone.

Are low carbohydrate dietary approaches suitable for people who do not have diagnosed Type 2 diabetes?

Although it is beyond the scope of this document to explore this in detail, it is worthwhile briefly considering the safety and efficacy of LCDs for people without diagnosed Type 2 diabetes. For individuals with prediabetes it could be argued that much of the evidence discussed thus far is still relevant, as prediabetes and Type 2 diabetes are typically as a result of the same underlying mechanisms (insulin resistance in particular)[6, 129-131]. There are clear rationales for why a LCD may help to prevent Type 2 diabetes[48], and it is logical that any approach that can be suitable for the management of Type 2 diabetes is suitable for those with impaired glucose tolerance but who have not yet reached the arbitrary threshold applied to diagnose Type 2 diabetes. Beyond this, most attempts to prevent prediabetes developing into Type 2 diabetes are based on weight loss[113]. As LCDs can be effective for achieving this[132-134] they should be considered a suitable option.

Extended to the general population, a high proportion of people who are overweight or obese have some element of insulin resistance[135, 136]. Indeed, research has shown that insulin levels and the pattern of insulin release is altered before the clinical appearance of impaired glucose control[137-141]. Thus it is possible that many people who are overweight may benefit from a LCD, for the same reasons this approach can be effective for those with Type 2 diabetes. Further, as with the management of Type 2 diabetes, weight maintenance (or the maintenance of weight loss) is heavily influenced by how well an individual can adhere to a particular diet[142, 143]. Therefore, the "one size doesn't fit all message" applies here too. Evidence shows that a LCD can be safe and effective for individuals without diagnosed chronic health conditions, with LCDs resulting in similar, and potentially superior, weight loss compared to control diets[132-134]. Based on this, there appears to be no reason that individuals should not be supported in adopting a LCD if it is the approach that they think is best for them.

Lastly, there is also evidence that a LCD is safe and can be effective for individuals with Type 1 diabetes[144-147]. This is again logical as the primary pathology (i.e. beta-cell dysfunction) is in relation to the metabolism of carbohydrates, so reducing the quantity of carbohydrate that needs to be metabolised can help reduce the impact of the underlying cause. Reducing carbohydrate intake reduces the requirement for insulin which, as long as appropriate adjustments are made, reduces the risk of hypoglycaemia, can improve weight management, and can have a positive effect on an individual's quality of life.

Summary

Available evidence supports the safety and efficacy of LCDs for the management of Type 2 diabetes. In particular, they appear to be superior to other dietary approaches for reducing the requirement for diabetic medications and for placing Type 2 diabetes into remission. LCDs should therefore be promoted as a possible option for the management of this condition. Despite claims to the contrary, adherence to LCDs is possible if an individual adopts, and adapts, it in a way that suits their preferences and lifestyle. Sufficient education and support may be necessary to facilitate this. There are also other dietary and lifestyle approaches that can be safe and effective, so individuals should be supported to identify the approach that is right for them. However, as Type 2 diabetes is a condition of carbohydrate intolerance, some level of carbohydrate restriction may be the most effective method for achieving significant health improvements in this population.

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Appendix 1. Systematic reviews with meta-analyses assessing low carbohydrate dietary approaches for the management of Type 2 diabetes

Article Reference*	Inclusion Criteria	Number of Studies/Participants	Assessment of Included Studies' Quality	Key Outcomes	Limitations
Kodama et al 2009 Diab Care, 32(5), 959-965	Studies published in English up to 2007 RCTs comparing low fat high carbohydrate and high carbohydrate low fat with no difference in energy and protein, in people with Type 2 diabetes	19 publications, which included 22 trials as some had multiple trials reported within a single publication, included in meta-analyses (n = 306)	10 described drop-out rates and 9 didn't; drop-outs ranged from 0 to 25% None of the articles described methods of randomisation, so all had low quality scores There was a relatively strong suspicion of publication bias for HDL cholesterol (Egger's test, P = 0.08 for HDL cholesterol; recommended level of significance, P 0.10)	There were no significant differences in HbA1c change between diets Two-hour glucose and insulin values were higher in the LF group than in the LC group by 10.3% (P <0.001) and 12.8% (P<0.001), respectively The LF diet also resulted in significant increases in triglyceride levels and a significant reduction in HDL cholesterol compared with that associated with the LC diet	Limited details of methods presented and the definitions of diets is vague Carbohydrate intake ranged from 30 to 42% total energy, so none were low carbohydrate by definitions applied here Requirement for protein and energy intake to be comparable between groups limits scope for natural effects of diets to be assessed Very short-term, studies ranged from 10 days to 6 weeks No heterogeneity data presented All studies were deemed to be low quality Of the 17 studies with a crossover design, 9 (covering 10 trials) did not include a washout period, which could lead to an underestimation due to a carryover effect

Ajala et al 2013 Am J Clin Nutr, 97, 505-516	Studies up to July 2011 No explicit mention of whether there were any language restrictions RCTs in adults with an intervention that lasted ≥ 6 months that compared low- and high-carb, high-protein, vegetarian and vegan, low-glycaemic, high-fiber, or Mediterranean diets with any control diet in people with T2DM	20 studies included in qualitative analyses (n = 3460). 9 studies compared a low carbohydrate diet to control, 8 of which were included in the relevant meta-analyses	No reported differences in baseline characteristics between intervention and control groups; 3/16 studies didn't report method of randomisation; 10/16 didn't report method of allocation concealment; 6/16 were analysed on ITT basis	LC diets significantly decreased HbA1c compared with other diets (WMD -0.12%, 95% CI -0.24 to 0.00, P = 0.04, I^2 = 75%) There was no difference in weight loss for LC diets compared with control diets (P = 0.21; though the number of studies or participants was not reported, no forest plot was included, and I^2 was not reported) LC diets appeared to be beneficial in increasing HDL (WMD 0.08 mmol/L, 95%CI 0.05 to 0.11, P<0.00001) with no significant difference in LDL (P = 0.57) or triglycerides (P = 0.47); though, again, the number of studies or participants was not reported, no forest plot was included, and I^2 was not reported	There is a lack of detail, making it difficult to appraise the results, and doesn't define "low carb" in inclusion criteria (discussion says low carbohydrate diets restrict carbohydrate intake to 20-60 g/d but this is not how it was defined in included studies, which included target carbohydrate intakes of up to 45%) One study was included in the MA despite not having separate data "for the diabetic group" because ">80% of the study population had diabetes" High heterogeneity for low carbohydrate glycaemic control meta-analysis, and I^2- not reported for weight and lipid analyses Study durations ranging from 6 months to 4 years, but no attempt to consider effect of this Includes Iqbal et al 2010 (Obesity, 18(9), 1733-8), where there was no difference in dietary intake between groups (and carbohydrate intake was actually higher in the control arm at multiple time points)

Naude et al 2014 PLoS ONE, 9(7), e100652	Studies published in English up to 19th March 2014 RCTs with more than 10 participants in each group, adults only Review not specific to diabetes but analysis limited to T2DM presented Compared low carbohydrate diets (defined as ≤45% total energy from carbs, with high fat or high protein) with control Prescribed energy content had to be similar in intervention and control groups	5 studies in people with T2DM were included in meta-analyses (n=660; 61 in 1 study assessing low carb, high fat and 599 in 4 studies assessing low carb, high protein)	For random sequence generation 4 studies were low risk and 1 was unclear For allocation concealment 2 were low and 3 unclear For performance bias all had unclear risk For detection bias 1 was low risk and 4 were unclear For attrition bias 3 were high risk, 1 was low and 1 was unclear For reporting bias 2 were high and 3 were low For "other" sources of bias 3 were high risk, 1 was low and 1 was unclear	There were no significant differences in HbA1c change between diets at 3-6 months (0.19%, 95%CI 20.0 to 0.39; 5 trials) or 1-2 years (0.01%, 95%CI 20.28 to 0.30, 4 trials) No differences between diets for fasting blood glucose were noted either, but few studies assessed this (two at 3-6 months, one at 15 months) There were no significant differences in body weight change between diets at 3-6 months (0.82 kg, 95%CI 21.25 to 2.90; 5 trials) or 1-2 years (0.91 kg, 95%CI 22.08 to 3.89; 4 trials) There were no differences in changes in SBP or DBP at 3-6 months (SBP: 95%CI 23.14 to 4.36 mmHg; 4 trials. DBP: 95%CI 21.77 to 3.30 mmHg; 4 trials) or 1-2 years (SBP: 95%CI 23.10 to 3.72 mmHg; 4 trials. DBP: 95%CI 21.95 to 2.13 mmHg, 4 trials) At 3–6 months, changes from baseline in blood lipids (TC, LDL, HDL and TG) were inconsistent and the changes on meta-analysis were small, suggesting little or no difference in effect between the two diets In 3 of the 4 studies with relevant data, adherence was better for LC than LF	Only isoenergetic studies included which, precludes the assessment of the real world effects of diets High threshold for classifying low carbohydrate and no sensitivity analysis Only 5 studies (< 600 participants for all meta-analyses at 3-6 months, < 500 for all at 1-2 years) Quality of evidence (GRADE) low to moderate for all Subject of a published critique (Harcombe and Noakes 2016, South African Medical Journal, 106(12), 1179-82), which identified a number of flaws – most of which were deemed to penalise the low carbohydrate interventions

Fan et al 2016 Int J Clin Exp Med, 9(6), 11166-11174	Studies up to 30th May 2014 (no language restriction) RCTs in adults All participants with T2DM One group receiving a low carbohydrate diet, defined as max 130g/day, compared to any other diet	25 studies included in qualitative analysis, 10 studies included in meta-analyses (n = 1080)	All studies deemed to be of good quality – Jadad scores ranged from 3 to 5 (out of 5, 3 was the cut-point to be classed as good quality)	There was a significant decrease in HbA1c in subjects who consumed low carb diets compared with other diets (WMD: -0.33%, 95%CI -0.51 to -0.15; P<0.001, I^2=88.4%; 10 studies) LC diets were more effective for achieving weight loss than control diets (WMD: -2.4 Kg, 95%CI -3.7 to -1.1, P<0.001; 10 studies) Low-carbohydrate diets appeared to be beneficial in increasing HDL-C (WMD: 0.094 mmol/L, 95% CI 0.043 to 0.144, P<0.001) and decreasing TG (WMD: -0.28 mmol/L, 95% CI 0.393 to -0.167, P < 0.001) with no significant reduction in TC (WMD: 0.051 mmol/L; 95% CI -0.144, 0.246; P=0.61) or LDL-C (WMD: -0.027 mmol/L, 95% CI -0.108 to 0.053, P = 0.508). It was unclear how many studies each of these analyses was based on	High heterogeneity Includes Iqbal et al 2010 (Obesity, 18(9), 1733-8), where there was no difference in dietary intake between groups (and carbohydrate intake was actually higher in the control arm at multiple time points)
Snorgaard et al 2017 BMJ Open Diab Res & Care, 5(1), e000354	RCTs published in English or Scandinavian languages between January 2004 and October 2014 Population was subjects with T2DM (doesn't	10 studies included in meta-analyses (n = 1376)	Possible attrition bias but no other potential sources of bias identified. Concluded that the overall risk of bias was low to moderate	In LC diets mean HbA1c was 0.34% lower in studies shorter than 1 year (95%CI -0.63 to -0.06; 8 studies, n = 809). There was no real difference in studies that were longer than 1 year (7 studies, n = 839) Meta-regression demonstrated a reduction in HbA1c as carbohydrate intake decrease (r = -0.85, P < 0.01; 8 studies), though shorter- and longer-term data were combined. The two	Average reported carbohydrate intake was 30% at 1 year in the five studies that reported this (range = 27% to 45%, so were ALL above threshold) and was even higher at 24 months (mean 31%, 45% and 48% respectively in the three trial that reported this) Number of participants within each meta-analyses was small

	explicitly state adults) Comparing carbohydrate restriction (defined as <45% total energy) to control (with carbohydrate intake of 45-60%) Primary outcomes were HbA1c or BMI after 1 year or more, secondary outcomes same markers but less than 1 year - plus LDL-c, QoL and dropout rates			studies with the lowest daily carbohydrate intake showed the largest reductions in HbA1c Mean BMI in studies shorter than 1 year was 1.02 lower with LC (95%CI -2.58 to +0.54; 4 studies, n = 185) and was 0.43 lower in studies that were longer than 1 year (95%CI -1.38 to +0.53; 2 studies, n = 159) Reports on glucose lowering medication were available in seven studies. Medication reduction was significantly greater at 3 months and 6 months, and was "numerically lower" at 12 months There were no differences between groups for the number of reported adverse events, cardiovascular events, or mortality	High heterogeneity for HbA1c at less than a year (I^2 = 74%). No heterogeneity data presented for outcomes other than HbA1c Includes Iqbal et al 2010 (Obesity, 18(9), 1733-8), where there was no difference in dietary intake between groups (and carbohydrate intake was actually higher in the control arm at multiple time points) Included Saslow et al 2014 (PloS One, 9(4), e91027) even though not all participants had Type 2 diabetes In the discussion of Korsomo-Haugen et al 2018 (see below) it is asserted that the relationship observed in the regression analysis of this review was "totally dependent on the findings of two trials with a duration of 3 months that were not included in our analyses because they involved participants with prediabetes or an additional physical activity intervention."

Korsmo-Haugen et al 2018 Diab Obes Metab, 21(1), 15-27	Studies published in English, Danish, Norwegian and Swedish between 1983 and January 2016 RCTs of more than 3 months duration in adults with T2DM Trials must have compared a low carbohydrate diet (defined as ≤40% total energy from carbs) to a diet with more than 40% energy from carbs	19 studies included in meta-analyses (according to PRISMA diagram, but can only identify 18 included based on forest plots. Other papers included in review that aren't explicitly excluded from meta-analyses are Samaha et al 2003 and Garge et al 1994, but no direct evidence they were included in any analysis)	Summary information presented for the 23 RCTs included in the systematic review rather than just the 19 in the meta-analysis. 10 of these had a high risk of bias, three had a low risk, and the remaining 10 were unclear No indication of publication bias.	LC diets were associated with greater overall reductions in HbA1c (−1.0 mmol/mol, 95% CI, −1.9 to −0.1; 16 studies), though the difference was small and the result was largely driven by the results of short-term studies and by trials associated with a high risk of bias Overall, a LC diet was not associated with greater weight loss than a LF diet (-0.35kg, 95%CI -0.91 to 0.21; 17 studies), but subgroup analysis suggested more positive results in short-term studies (≤6 months) than in studies with longer follow up Meta-analyses showed no significant difference between groups in effect on HDL-cholesterol (0.04 mmol/L, 95%CI −0.01 to 0.10; I^2 = 72%; 16 studies), LDL-cholesterol (−0.01 mmol/L; 95%CI −0.13 to 0.11; I^2 = 64%; 15 studies) and TC (0.04 mmol/L, 95%CI −0.12 to 0.20; I^2 = 71%; 14 studies), but showed a slightly greater reduction in TG with a LC diet (−0.13, 95% CI −0.24 to −0.02 mmol/L; I^2 = 57%; 16 studies) There was no significant difference in the effect of a LC diet on SBP or DBP when compared to control (SBP: −0.93 mmHg, 95%CI −2.24 to 0.37; I^2 = 0%; 16	High heterogeneity The cut-point to define low carbohydrate was high (but sensitivity analyses considered the effects of different amounts, mitigating for this)

				studies. DBP: −0.21 mm Hg, 95%CI −1.20 to 0.79; I^2 = 0%; 16 studies) The limited information given in the included studies suggests that there was a greater reduction in the use of diabetes medication (mainly insulin) in the LC groups, which may have masked a more positive impact on glycaemic control. However, only four studies found a significant difference in change in diabetes medication between the diets, and some of the studies repeated their analyses, adjusting for difference in medication, and found that it did not alter their conclusions The only serious adverse advent reported in any of the included studies was not in the LC group, with 12 of the 13 studies that included relevant information reporting that there were no serious adverse events or mild adverse events such as mild hypoglycaemia	
Huntriss et al 2018 Eur J Clin Nutr, 72(3), 311-325	Studies published in English up to June 2016 RCTs with adults with T2DM The intervention group had to be a	7 studies included in meta-analysis for HbA1c, 6 studies included in meta-analysis for weight	Not presented in paper solely for the studies included in the meta-analyses, but 15 of the 18 studies included were considered high risk on at least one of the criteria	HbA1c improved significantly more in those following LC diets (effect estimate = −0.28%, 95%CI −0.53 to −0.02, P = 0.03; I^2 = 54%; 7 studies) There was no difference in body weight change between diets (estimated effect = 0.28 kg, 95%CI −1.37 to 1.92, P = 0.74; I^2 = 75%; 6 studies)	Did not stipulate what they classed as low carb, so included studies which would not meet recognised definitions.

	low carbohydrate diet "as stated by the author", and had to have a lower carbohydrate intake than the control group Studies that were shorter than 48 weeks were not included in the meta-analyses			SBP improved significantly more in those following LC diets (estimated effect = -2.74 mmHg, 95%CI -5.27 to -0.20, P = 0.03; I^2 = 43%; 7 studies). There was no difference in DBP change between diets (estimated effect = -0.99 mmHg, 95%CI -2.24 to 0.25, P = 0.12; I^2 = 15%; 7 studies) HDL-c improved significantly more in those following LC diets (estimated effect = 0.06 mmol/L, 95%CI 0.04 to 0.09, P < 0.00001; I^2 = 1%; 7 studies) TG improved significantly more in those following LC diets (estimated effect = -0.24 mmol/L, 95%CI -0.35 to -0.13, P < 0.00001; I^2 = 0%; 7 studies) There was no difference in TC change (estimated effect = -0.08 mmol/L, 95%CI -0.23 to 0.08, P = 0.35; I^2 = 60%; 7 studies) or LDL-c change between diets (estimated effect = -0.05 mmol/L, 95%CI -0.13 to 0.19, P = 0.54; I^2 = 0%; 5 studies) All 14 studies included that reported medication changes reported a greater reduction in the LC groups. Where assessed, this was statistically significant in 9/11 studies (82%)	

Sainsbury et al 2018 Diab Res and Clin Prac, 139, 239-252	Studies published in English between 1st Jan 1980 and 31st Aug 2016 RCTs comparing carbohydrate restricted diets (≤45% total energy) with high carbohydrate diets (>40% total energy) in adults with Type 1 or Type 2 diabetes	25 studies (28 papers) included in meta-analyses (n = 2412) [note: 14 were included as "moderate carb" diets]	Fifteen studies reported using random sequence generation, while the remaining studies did not provide sufficient information Use of allocation concealment was poorly reported across the majority of studies (n = 22). Due to inherent difficulties in blinding participants and personnel in dietary intervention studies, it was assumed, unless otherwise stated, that no blinding was conducted. Consequently, there was a high risk of bias across all studies for self-reported outcomes due to possible bias in patient's self-reported dietary intake and the analysis of food records Eight studies were classified as being at high or unclear risk for the other biases domain due to stated conflicts	There was a significantly greater reduction in HbA1c on the LC diet (< 26% of total energy) than the high carbohydrate diet at 3 months (WMD -0.47%, 95% CI -0.71 to -0.23) and 6 months (WMD -0.36%, 95% CI -0.62 to -0.09) There were no significant differences between diet groups for HbA1c change at 12 months (WMD -0.09%, 95% CI -0.21 to 0.03) or 24 months (WMD -0.11%, 95% CI -0.38 to 0.15) At 3 months there was greater weight loss on the LC diet (< 26% of total energy) compared to the high carbohydrate diet (WMD - 2.47kg, 95% CI -3.33 to -1.60) There was no difference between LC and high carbohydrate diets for weight loss at 6 or 12 months Where reported, the authors reported that "there was a greater reduction in medication use for participants on carbohydrate-restricted diets compared with high carbohydrate diets at every time point. Carbohydrate restriction either reduced the dosage of oral medications and/or insulin, or saw an elimination of medication for participants across all studies that	Definition of low carbohydrate was higher than recognised standards (though analyses did sub-divide, including a "low carb" group defined as <26% total energy) Due to high risk of performance and detection bias, and inconsistency in the estimates of effect across studies, the evidence of HbA1c change was graded low quality 14 of the included studies were isocaloric (between diets) by design

			of interest from funding sources Overall, nine studies were classified as being low at risk, seven at high risk, and nine at unclear risk of bias Eggers test revealed publication bias was present at 3 months (p = 0.005) but not at 6 (p = 0.125) or 12 months (p = 0.052).	reported on medication outcomes." Methods of measuring medication use were variable across studies	
Meng et al 2017 Diab Res and Clin Prac, 131, 124-131	RCTs up to January 2017 in patients with T2DM (doesn't explicitly state adults) No publication timing or language restrictions Low carbohydrate groups defined as less than 130g or 26% energy per day, compared to normal or high carb	9 studies included in meta-analyses (n = 734)	5 of 9 trials were considered high quality (based on modified Jadad score). Primary issue with the other studies was the lack of blinding and concealment of allocation Visual inspection of funnel plots and Egger test suggests no evidence of publication bias for the LCD on FPG (P=0.28), HbA1c (P=0.98), TC (P=0.78), TG (P=0.75), HDL-c	HbA1c decreased significantly more in LC groups compared to control groups (WMD -0.44%, 95% CI -0.61 to -0.26, P < 0.01; I^2 = 20%; 9 studies) There was no difference in the change in fasting plasma glucose between groups (WMD -0.05 mmol/l, 95% CI -0.58 to 0.47, P = 0.84; I^2 = 0%; 5 studies) There was no difference in the change in body weight between groups (WMD -0.94 mmol/l, 95% CI -1.92 to 0.05, P = 0.06; I^2 = 36%; 8 studies) LC reduced TG significantly more than the control groups (WMD -0.33 mmol/l, 95% CI -0.45 to -0.21, P < 0.01; I^2 = 0%; 9 studies)	Includes Iqbal et al 2010 (Obesity, 18(9), 1733-8), where there was no difference in dietary intake between groups (and carbohydrate intake was actually higher in the control arm at multiple time points)

			(P=0.57), LDL-c (P=0.37), and weight loss (P=0.80)	LC improved HDL-c significantly more than the control groups (WMD 0.07 mmol/l, 95% CI 0.03 to 0.11, P < 0.01; I^2 = 41%; 8 studies) There was no difference in the change in TC (WMD 0.06 mmol/l, 95% CI -0.08 to 0.21, P=0.33; I^2 = 0%; 6 studies) or LDL-c between diets (WMD 0.04 mmol/l, 95% CI -0.08 to 0.16, P=0.33; I^2 = 0%; 7 studies)	
Van Zuuren et al 2018 Am J Clin Nutr, 108, 1-32	Studies published up to 21st March 2017 No explicit mention of whether there were any language restrictions RCTs and controlled clinical trials (CCTs) which compared a low carbohydrate diet (defined as ≤40% total energy from carbs) with low fat (defined as ≤30% total energy from fat) over a	17 studies included in meta-analyses (meta-analyses by study duration, n ranged from 42 to 539 for each analysis)	Summary information presented for all studies included in the systematic review, not just those included in meta-analyses. 19/33 RCTs were judged to be high risk and 14 had unclear risk; 1/33 CCTs had a moderate risk, 2 had a serious risk	HbA1c improved more in LC groups in short-term (studies up to 8 weeks in duration: mean difference -1.38%, 95%CI -2.64 to -0.11, P = 0.03; I^2 = 68%; 2 studies), medium term (8-16 weeks: -0.55%, 95%CI -0.93 to -0.17, P = 0.005; I^2 = 54%; 4 studies), and longer-term studies (≥26 weeks: -0.38%, 95%CI -0.58 to -0.14, P = 0.001; I^2 = 0%; 4 studies) When only studies that were 2 years In duration were included however there was no difference in HbA1c change between groups (mean difference 0.02%, 95%CI -0.37 to 0.41, P = 0.93; I^2 = 13%; 3 studies) Body weight reduced significantly more in the LC group in studies lasting between 8 and 16 weeks (mean difference −2.04 kg, 95% CI −3.23 to −0.85 kg), though there was no	Definition of low carbohydrate was higher than recognised standards No apparent attempt to group based on target, or actual, carbohydrate intake High heterogeneity in many of the analyses.

	period of at least 4 weeks in adults with T2DM Only included data from crossover trials that had incorporated wash-out periods of ≥4 wk between interventions			difference at other time points. For WC and BMI there was little difference between diets at any time point TG was improved significantly more in the LC groups in studies between 16 and 26 weeks long (mean difference -0.22 mmol/l, 95%CI -0.37 to -0.08, P = 0.02; I^2 = 41%; 6 studies), and in long-term studies, whether this is classed as being >26 weeks (-0.25 mmol/l, 95%CI -0.47 to -0.00, P = 0.002; I^2 = 73%; 5 studies) or only includes studies with a duration of 2 years (-0.19 mmol/l, 95%CI -0.32 to -0.05, P = 0.007; I^2 = 0%; 2 studies). There was a trend towards greater improvements in TG in the LC groups at all time points HDL-c was improved significantly more in the LC groups in long-term studies, whether this is classed as being >26 weeks (mean difference = 0.11 mmol/l, 95%CI 0.05 to 0.18, P = 0.0007; I^2 = 66%; 4 studies) or only includes studies with a duration of 2 years (0.12 mmol/l, 95%CI 0.07 to 0.17, P < 0.00001; I^2 = 0%; 2 studies). There was a trend towards greater improvements in HDL-c in the LC groups at all time points There were no differences in changes in LDL-c between diets at any time point (12 studies)	

				There were no differences in changes in SBP between diets at any time point (7 studies), and for DBP the only difference was for studies lasting 6 months where there was a greater reduction for LC (mean difference−1.91 mm Hg, 95% CI −3.63, −0.18 mm Hg) "Notably, and significantly, in all of the studies that included patients taking medication and that adequately reported eventual adaptations (n=4), with the exception of one, glucose lowering drug doses were reduced in participants who consumed low-carbohydrate food, but not in those consuming low-fat food. Unfortunately, inconsistent methods of quantification and reporting precluded reliable statistical analysis of changes in drug doses"	
McArdle et al 2019 Diabetic Medicine, 36(3), 335-348	Studies published in any language between 1976 and April 2018 RCTs including adults with T2DM with a minimum intervention duration of 8 weeks and reported	25 studies in meta-analysis (n = 2132 for primary outcomes) [note: 12 were included as "moderate carb" diets]	The principal risk of bias stemmed either from the poor description of the randomization sequence and allocation concealment or from there being no description of the pre-study dietary intake of participants ('other bias'). This represented more than one-third of	Meta-analyses conducted for HbA1c for all studies found no overall effect of modifying carbohydrate (WMD –0.09%, 95%CI –0.27 to 0.08, P = 0.30; I^2 72%; 25 studies). Subgroup analysis of studies meeting the definition of very low carbohydrate (<50 g per day) also found no overall effect (WMD –0.13%, 95%CI –0.34 to 0.08, P = 0.28; I^2 19%; 8 studies, though actual mean carb intake was only below 50g in two of them). Analysis of the subgroup of LC diet	Actual carbohydrate intake reported would not qualify multiple studies to fit in the subgroup analyses they were included in; e.g. the very low carbohydrate analyses included Davis et al 2009 (Diabetes Care, 32, 1147-52), Tay et al 2015 (Am J Clin Nutr, 102, 780-90) and Sato et al 2017 (Clinical Nutrition, 36(4), 992-1000) when reported intake was >50g/day

	outcomes at a minimum of 12 weeks, and with the proportion or quantity of dietary carbs restricted in the intervention group Studies also had to report a measure of actual carbohydrate intake during or at the end of the intervention		studies included in the review	studies (50–130 g per day) showed a statistically and clinically significant result in favour of the intervention diet (WMD –0.49%, 95%CI –0.75 to –0.23, P < 0.001; I^2 0%; 5 studies). All studies in this subgroup were of ≤6 months in duration No overall effect on weight was observed (WMD –0.13 kg, 95%CI –0.33 to 0.08, P = 0.22; I^2 78%; 25 studies). In the low-carbohydrate subgroup there was a statistically significant pooled effect in favour of restricted carbohydrate (WMD –0.43 kg, 95%CI –0.74 to –0.12, P = 0.006; I^2 24%; 5 studies) Of the 25 studies, 11 did not fully report outcomes for blood pressure and, in those that did, changes were unremarkable and rarely reached statistical significance Complete blood lipid outcomes were reported in 17 of the 25 studies. Statistically significant differences between groups were seen in just seven of the studies and the most commonly observed difference was a greater increase in HDL cholesterol in the moderate-carbohydrate group	Includes Iqbal et al 2010 (Obesity, 18(9), 1733-8), where there was no difference in dietary intake between groups (and carbohydrate intake was actually higher in the control arm at multiple time points). This was one of only two papers classified as very low carbohydrate that didn't favour the intervention group Appears to have missed papers that meet inclusion criteria: e.g. Stern et al (2004) Ann Intern Med, 140(10), 778-85; Mayer et al (2014) Diabetes, Obesity & Metabolism, 16, 90-3; Guldbrand et al (2012) Diabetologia, 55(8), 2118-27 – which reports longer-term outcomes from the same study as Jonasson et al (2014) Annals of Medicine, 46(3), 182-7; and Tay et al (2018) Diabetes, Obesity & Metabolism,20(4), 858-71 – which reports longer-term outcomes from the same study as Tay et al (2014) Diabetes Care, 37, 2909-18 and Tay et al (2015) The American Journal of Clinical Nutrition, 102, 780-90

LC = low carbohydrate, LF = low fat, WMD = weighted mean difference, 95%CI = 95% confident intervals, BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, TG = triglycerides, LDL = low-density lipoprotein, HDL = high-density lipoprotein

Appendix 2. Summary of randomised controlled trials comparing low carbohydrate dietary approaches with any control diet in people with Type 2 diabetes (minimum 50 participants and three months duration, with carbohydrate intake below 130g/day or 26% total energy in intervention group)

Article Reference	Participants	Study Duration	Intervention Group Carbohydrate Target	Low Carbohydrate Group Actual Carbohydrate Intake	Control/ Comparison group	Completion rates	Key Outcomes
Stern et al 2004* Ann Intern Med, 140, 778–85	54 with Type 2 diabetes	12 months	<30g/day	120g/day (SD 93g) [230±150g/day in control group]	Participants on the conventional diet were instructed to reduce caloric intake by 500 calories per day, with less than 30% of calories derived from fat	Low carb: 18/27 (67%) Control: 16/27 (59%)	HbA1c reduced by 0.8±1.0 (from 7.4±1.6% to 6.6±1.4%) in low carb, and by 0.1±1.6% (from 7.3±1.1% to 7.2±1.9%) in control. Between group difference was -0.7% (-1.6 to 0.2), P = 0.102 Other results (e.g. weight and blood lipids) are not presented separately for people with Type 2 diabetes Changes in medication were not reported Adverse outcomes were not reported separately for people with Type 2 diabetes
Daly et al 2006 Diabet Med, 23, 15-20	102	3 months	≤70g/day	109.5g/day (SEM 6.4g) [168.6±10.8g/day in control group]	Standard healthy eating advice, focusing on reducing fat intake. This was combined with instructions to reduce portion size	Low carb: 40/51 (78%) Control: 39/51 (76%)	Body weight reduced more in the low carb group (-3.55±0.63kg v -0.92±0.40; 95%CI of change 1.16 to 4.09 more in low carb, P = 0.001) TC:HDL ratio improved more in the low carb group (-0.48±0.11 v -0.10±0.10, 95%CI of change 0.09 to 0.68, P = 0.011)

							TG, SBP and HbA1c all also improved more in the low carb group but P > 0.05 Insulin was reduced in approximately 85% of users in the low carb group, and only 22% in the control group. 16% of users in the control group increased insulin, compared to 5% in the low carb group. Use of oral hypoglycaemic agents remained unchanged in both groups No adverse events were reported
Westman et al 2008 Nutr Metab (Lond), 5, 36	97	6 months	<20g/day	13% total energy; 49g/day (SD 33g) [44% total energy; 149±46g/day in control group]	A low-glycemic index, reduced-calorie diet (500kcal less than calculated energy intake) Approximately 55% of daily caloric intake from carbohydrate	Low carb: 21/38 (55%) Control: 29/46 (63%)	HbA1c reduced more in the low carb group (-1.5% v -0.5%, P = 0.03) Body weight reduced more in the low carb group (-11.1kg v -6.9%, P = 0.008) Fasting glucose, fasting insulin and body mass index all also improved more in the low carb group but P > 0.05 4 individuals in the low carb group were able to omit insulin by the end of the study, compared to 1 in the control group (all 5 were taking less than 20 units at baseline). A further 4 participants in the low carb arm reduced their insulin needs, compared to 2 in the control arm. Of those taking oral hypoglycaemic medications 95.2% in the low carb arm were able to reduce their medication, compared to 62.1% in the control group

							No serious adverse events were reported. No differences between groups for other side-effects (headaches, constipation, diarrhoea, insomnia or back pain)
Goldstein et al 2011 e-SPEN, 6, e178-86	52	12 months	25g/day for 6 weeks, increasing to a maximum 40g/day	85g/day (SD 35g) [208g±61g in control group)]	Standard American Diabetes Association calorie-restricted diet (up to 1500kcal for men and 1200kcal for women)	Low carb: 14/26 (54%) Control: 16/26 (62%)	There were no differences between groups for weight, HbA1c, fasting blood glucose, blood pressure, or blood lipids At 3-months: 17/26 participants in the low carb group had reduced hypoglycaemic medications, compared to 11/26 in the control group No adverse events were reported, and explicitly states that there were no identified incidents of hypoglycaemia
Guldbrand et al 2012** Diabetologia, 55, 2118–2127	61	6 months**	20% total energy	25% total energy (SD 8%) at 3-6 months [49±6% in control group]	30% total energy from fat (less than 10% from saturated fat) 55-60 % from carbohydrate 10-15% from protein	Low carb: 26/30 (87%) Control: 28/31 (90%)	There were no significant changes between the groups for weight, BMI, wait, HbA1c, blood pressure or blood lipids. Even though there was not a statistically significant difference between the groups, the improvements in HbA1c and HDL were statistically significant in the low carb group but not in the control group Reductions in insulin dose were statistically significantly higher in the low carb group No adverse events were reported

Tay et al 2018*** Diabetes Obes Metab, 20, 858-871	115	24 months	<50g/day	83g/day (95%CI 73g to 94g) at 22-24 months [216g/day (206g to 227g) in control group]	53% total energy from carbohydrate, with a focus on low-glycemic index foods 17% protein <30% total energy from fat (15% monounsaturated, 9% polyunsaturated, <10% saturated)	Low carb: 33/58 (57%) Control: 28/57 (49%)	Improvements in weight, body fat, fasting blood glucose, HbA1c and blood pressure were similar between groups Triglycerides and HDL were improved in the low carb group but not in the control group, with the difference between statistically significant (though probably not clinically meaningful) Low carb group had greater reductions in diabetes medication requirements, with over twice the number of participants reducing requirements by 20% or more (22 versus 9) No adverse events were reported

* An earlier publication from the same trial, but with a shorter follow up, was also identified: Samaha et al 2003 (New England Journal of Medicine, 348, 2074-81)
** Although this paper includes results at 12 and 24 months the six month outcomes are reported here, as this is the latest time point at which carbohydrate intake was below the threshold to be classified as a LCD Jonasson et al 2014 (Annals of Medicine, 46, 182-187) also reported outcomes from this study
*** Two previous publications from the same trial were also identified: Tay et al 2014 (Diabetes Care, 37, 2909-2918) and Tay et al 2015 (Am J Clin Nutr, 102(4), 780-790)