

## Tables of evidence for low carb diets

### 1. Systematic reviews and meta-analysis of Low Carb diets for Type 2 Diabetes

Reference	Details	Key findings	Comments
<p>Castañeda-González LM, Gascon MB, Cruz AJ. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. <i>Nutricion Hospitalaria</i>. 2011;26(6):1270-6.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/22411372/">https://pubmed.ncbi.nlm.nih.gov/22411372/</a></p>	<p>Interventions lasting &gt; 12 weeks, comparing low carb with low fat, usual diet or low GI diets Adults age over 18 with T2D 8 RCTs</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- 5 studies showed greater weight reduction with LCD</li> <li>- The longest trial intervention studies did not show a difference in weight change.</li> <li>- Only two studies showed greater reduction of A1C with LCD, including the longest intervention trial with a low carbohydrate Mediterranean diet.</li> </ul> <p>Conclusions: This review shows that there are no consistent differences in weight and A1C changes over the long-term treatment with LCD and LFD, UCD or LGID."</p>	<p>Authors note that "the two studies with the longest follow-up (12 and 48 months) showed no statistical differences."</p> <p>However, while LC may not be superior to LF, it is not inferior either. Why then promote low fat diets, if patients prefer LC?</p>
<p>Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. <a href="https://pubmed.ncbi.nlm.nih.gov/23364002/">https://pubmed.ncbi.nlm.nih.gov/23364002/</a></p>	<p>Comparison of low-carbohydrate, vegetarian, vegan, low-glycemic index (GI), high-fiber, Mediterranean, and high-protein diets with control diets including low-fat, high-GI, American Diabetes Association, European Association for the Study of Diabetes, and low-protein diets. 20 RCTs, n = 3070</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- The low-carbohydrate, low-GI, Mediterranean, and high-protein diets all led to a greater improvement in glycemic control compared with their respective control diets, with the largest effect size seen in the Mediterranean diet.</li> <li>- Low-carbohydrate and Mediterranean diets led to greater weight loss</li> <li>- Increase in HDL seen in all diets except the high-protein diet.</li> </ul> <p>Conclusion: low-carbohydrate, low-GI, Mediterranean, and high-protein diets are effective in improving various markers of cardiovascular risk in people with diabetes and should be considered in the overall strategy of diabetes management.</p>	<p>Many diets can help people with T2D. A standard dietary guidelines diet is not one of them.</p>
<p>Fan Y, Di H, Chen G, Mao X, Liu C. Effects of low carbohydrate diets in individuals with type 2 diabetes: systematic review and meta-analysis.</p>	<p>Adults subjects &gt; age 18 with T2D 10 RCTs</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- Four studies showed greater weight reduction on low carbohydrate diets and in six there were no significant differences between groups. LCD was more effective in</li> </ul>	

<p>Int J Clin Exp Med. 2016 Jan 1;9(6):11166-74.</p> <p><a href="https://e-century.us/files/ijcem/9/6/ijcem0023504.pdf">https://e-century.us/files/ijcem/9/6/ijcem0023504.pdf</a></p>	<p>Outcomes assessed between 3 and 48 months</p>	<p>achieving weight loss that control diets were with a WMD in weight loss of -2.3 Kg.</p> <ul style="list-style-type: none"> <li>- There was a significant decrease in the percentage of HbA1c in subjects who consumed LCD compared with other diets and appeared to be beneficial in increasing HDL-C and decreasing TG with no significant reduction in TC or LDL-C.</li> </ul> <p>Conclusion: This review shows that there are consistent differences in weight and HbA1c changes with long-term treatment with LCD.</p>	
<p>Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Research and Care. 2017 Feb 1;5(1):e000354.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5337734/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5337734/</a></p>	<p>10 RCTs, n = 1376</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- In the first year of intervention, LCD led to lower HbA1c compared with HCD</li> <li>- The greater the carbohydrate restriction, the greater the glucose-lowering effect.</li> <li>- At 1 year or later, however, HbA1c was similar in the 2 diet groups. The effect of the 2 types of diet on BMI/body weight, LDL cholesterol, QoL, and attrition rate was similar throughout interventions.</li> </ul> <p>Conclusion: Low to moderate carbohydrate diets have greater effect on glycemic control in type 2 diabetes compared with high-carbohydrate diets in the first year of intervention.</p>	<p>While LCD may not be superior to LFD in the long term, it is not inferior either. Again, why promote low fat diets, if patients prefer LC?</p>
<p>Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: a systematic review and meta-analysis of randomized controlled trials. Diabetes research and clinical practice. 2017 Sep 1;131:124-31.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/28750216/">https://pubmed.ncbi.nlm.nih.gov/28750216/</a></p>	<p>9 RCTs, 734 subjects with T2D Follow up – 12 weeks to 2 years</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- LCD had a significant effect on HbA1c level.</li> <li>- For cardiovascular risk factors, the LCD intervention significantly reduced triglycerides concentration and increased HDL cholesterol concentration.</li> <li>- LCD was not associated with decreased level of total cholesterol and LDL cholesterol.</li> <li>- Subgroup analyses indicated that short term intervention of LCD was effective for weight loss.</li> </ul> <p>Conclusion: LCD intervention showed a beneficial effect on improving HbA1c level compared with the high or normal carbohydrate dietary, suggesting LCD might be effective for type 2 diabetes management. The result also suggested that LCD may be beneficial to cardiovascular risk factors.</p>	<p>Authors note that dietary carbohydrates are a major factor in blood glucose control and aggravate postprandial blood glucose responses.</p>

<p>Mencía JV, Castillo RF, Cabrera MB, Gómez-Urquiza JL, García LA, de la Fuente GA. Diets low in carbohydrates for type 2 diabetics. Systematic review. <i>Nutricion hospitalaria</i>. 2017 Feb 1;34(1):224-34.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/28244795/">https://pubmed.ncbi.nlm.nih.gov/28244795/</a></p>	<p>15 RCTs</p>	<p>Conclusion: low carb diets can be effective in some aspects such as the reduction of HbA1c, body weight or triglycerides.</p>	<p>Spanish authors, abstract lacking in detail.</p>
<p>Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. <i>Diabetes Research and Clinical Practice</i>. 2018 May 1;139:239-52.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/29522789/">https://pubmed.ncbi.nlm.nih.gov/29522789/</a></p>	<p>25 RCTs , n = 2412 participants Caomparison of diets &lt; 45% DE as carbs with diets &gt; 45% DE as carbs</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- Carbohydrate-restricted diets, in particular those that restrict carbohydrate to &lt;26% of total energy, produced greater reductions in HbA1c at 3 months and 6 months, with no significant difference at 12 or 24 months.</li> <li>- There was no difference between moderately restricted (26-45% of total energy) and high carbohydrate diets at any time point.</li> </ul> <p>Conclusion: Although there are issues with the quality of the evidence, this review suggests that carbohydrate-restricted diets could be offered to people living with diabetes as part of an individualised management plan.</p>	<p>This is an Australian paper. One of the authors is S Colagiuri, who has been critical of LC advocates, for example, in his submission to the Parliamentary Inquiry into Diabetes. Once again, LC is not inferior, so LF should not be favoured over LC. Informed consent is crucial.</p>
<p>Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. <i>European journal of clinical nutrition</i>. 2018 Mar;72(3):311-25.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/29269890/">https://pubmed.ncbi.nlm.nih.gov/29269890/</a></p>	<p>Adults &gt; age 18 with T2D 18 RCTs, n = 2204</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- Low-carbohydrate intervention arm (LCIA) may promote favourable outcomes in terms of HbA1c, triglycerides and HDL cholesterol. The LCIA demonstrated reduced requirements for diabetes medication, which may have reduced the observed benefit of dietary carbohydrate restriction on HbA1c.</li> <li>- The meta-analyses showed statistical significance in favour of the LCIA for HbA1c, HDL cholesterol, triglycerides and Systolic BP</li> </ul> <p>Conclusion: Reducing dietary carbohydrate may produce clinical improvements in the management of type 2 diabetes.</p>	<p>It is a common but underappreciated fact that people with T2D who use LC dietary approaches need less medication, even while they achieve outcomes which are often better than people on standard care including high carb diets.</p>

		The authors note that their meta-analyses for weight, total cholesterol, LDL cholesterol and diastolic blood pressure did not demonstrate a statistically significant difference between interventions. Dietary adherence was an issue in most studies. They observe that a very low-carbohydrate diet (< 50 g/day) seems unrealistic in this population, however a low carbohydrate diet (< 130g/day) appears to be achievable. Improved clinical outcomes were observed in some studies as a result of achieving a low- or moderate-carbohydrate diet.	
van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate-compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. The American journal of clinical nutrition. 2018 Aug 1;108(2):300-31.  <a href="https://pubmed.ncbi.nlm.nih.gov/30007275/">https://pubmed.ncbi.nlm.nih.gov/30007275/</a>	Adults with T2D Comparison of effects of low carbohydrate (< 40% of DE) with low fat (< 30% of DE) RCTs > 4 weeks 33 RCTs, n = 2161	Findings: <ul style="list-style-type: none"> <li>- Lower carb resulted in greater decline in HbA1c, although the difference was reduced at 1 yr and disappeared at 2 yrs</li> <li>- Moderate certainty for small improvements of unclear clinical importance in plasma glucose, triglycerides and HDL favouring low carbohydrate food at half of the prespecified time points</li> <li>- Little to no difference in LDL or any of the secondary outcomes (body weight, waist circumference, blood pressure, quality of life.)</li> </ul> Conclusion: dietary carbohydrate restriction to maximum of 40% yields slightly better metabolic control in people with T2D	This is not a truly LC study as LC is defined as < 40% of DE. Compare with eg Jayedi et al (2022) which showed a dose dependent relationship between carbohydrate reduction and HbA1c.
Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. European journal of epidemiology. 2018 Feb;33:157-70. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871653/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5871653/</a>	Adults with T2D <ul style="list-style-type: none"> <li>- 56 RCTs, n = 4937</li> </ul> Comparing 9 dietary approaches (low-fat, Vegetarian, Mediterranean, high-protein, moderate-carbohydrate, low-carbohydrate, control, low GI/GL, Palaeolithic)	Findings <ul style="list-style-type: none"> <li>- For reducing HbA1c, the low-carbohydrate diet was ranked as the best dietary approach (SUCRA: 84%), followed by the Mediterranean diet (80%) and Palaeolithic diet (76%) compared to a control diet.</li> <li>- all dietary approaches significantly reduce HbA1c (- 0.82 to - 0.47% reduction) and fasting glucose (- 1.61 to - 1.00 mmol/l reduction) compared to a control diet.</li> </ul> Conclusion: Mediterranean diet is the most effective and efficacious dietary approach to improve glycaemic control in type 2 diabetes patients.	Which "Mediterranean"? The Harvard invention? True Med diet is not low fat, and does not restrict meat or seafood. Almost any diet is better than standard dietary guidelines approach.

<p>Turton J, Brinkworth GD, Field R, Parker H, Rooney K. An evidence-based approach to developing low-carbohydrate diets for type 2 diabetes management: A systematic review of interventions and methods. <i>Diabetes, Obesity and Metabolism</i>. 2019 Nov;21(11):2513-25.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/31347236/">https://pubmed.ncbi.nlm.nih.gov/31347236/</a></p>	<p>This review performed a content analysis of safe and effective low carb diet protocols.</p> <p>40 studies of which:</p> <ul style="list-style-type: none"> <li>- 13 very low carb (&lt; 50 g carbs as DE)</li> <li>- 14 low carb &lt; 130g</li> <li>- Rest adapted carb intake according to participant progress</li> </ul> <p>18 studies prescribed ad libitum intake of energy. 22 studies were unrestricted or high protein</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- No LC diet protocol was found to be unsafe.</li> <li>- A range of approaches for developing low carb diet interventions for T2D were identified.</li> </ul> <p>3 primary components of low carb interventions are</p> <ul style="list-style-type: none"> <li>- Prescribed amount of carbohydrate</li> <li>- The types of foods included</li> <li>- The mode of delivery</li> </ul> <p>Conclusion: Multiple approaches for developing and delivering a low-CHO diet intervention for T2D management are safe and effective. A comprehensive set of core dietary components to consider in the formulation of low-CHO diet protocols were identified for use in clinical practice and to inform evidence-based guidelines for T2D management.</p>	<p>Intesting paper which focuses on how to develop a low carb dietary approach. The authors observe:</p> <p>No single amount of carbohydrate is effective for T2D.</p> <p>The various benefits of nutritional ketosis for T2D. Factors affecting diet adherence include socio-economic status and education level.</p> <p>Adherence of low carb diets may be greater with less restricted carb intake eg 15-20% of DE.</p> <p>Most LC interventions prescribe ad libitum energy with unrestricted amounts of protein and fat, and still achieve a substantial weight loss in people with T2D.</p> <p>Most LC interventions focus on minimally processed whole foods, including fats from whole foods.</p> <p>Intensive intervention delivery used in LC diet studies is consistent with existing literature for sustaining effective lifestyle change.</p>
<p>Korsmo-Haugen HK, Brurberg KG, Mann J, Aas AM. Carbohydrate</p>	<p>Adults with T2D, follow up &gt; 3 months</p>	<p>Findings</p>	<p>The weak conclusion is because this study is not really</p>

<p>quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2019 Jan;21(1):15-27.  <a href="https://pubmed.ncbi.nlm.nih.gov/30098129/">https://pubmed.ncbi.nlm.nih.gov/30098129/</a></p>	<p>23 studies, n = 2178          Comparing diets with &lt; 40% of DE with diets &gt; 40% of daily energy as carbohydrates</p>	<ul style="list-style-type: none"> <li>- Reductions were slightly greater with LCDs than with HCDs for HbA<sub>1c</sub> (-1.0 mmol/mol; CI, -1.9, -0.1 [-0.09%; CI, -0.17, -0.01]) and for triglycerides (-0.13 mmol/L; CI, -0.24, -0.02).</li> <li>- Changes in weight, HDL- and LDL-cholesterol, total cholesterol and blood pressure did not differ significantly between groups.</li> </ul> <p>Conclusion: The proportion of daily energy provided by carbohydrate intake is not an important determinant of response to dietary management, especially when considering longer term trials. A range of dietary patterns, including those traditional in Mediterranean countries, seems suitable for translating nutritional recommendations for individuals with diabetes into practical advice.</p>	<p>comparing low carb diets with high carb diets. The comparison is &lt; 40% vs &gt; 40% hence the minimal differences. Again, 'lower carb' is slightly better and definitely not inferior to other dietary patterns.          This study fails to provide evidence of the superiority of higher carb diets.</p>
<p>McArdle PD, Greenfield SM, Rilstone SK, Narendran P, Haque MS, Gill PS. Carbohydrate restriction for glycaemic control in type 2 diabetes: a systematic review and meta-analysis. Diabetic Medicine. 2019 Mar;36(3):335-48.  <a href="https://pubmed.ncbi.nlm.nih.gov/30426553/">https://pubmed.ncbi.nlm.nih.gov/30426553/</a></p>	<p>Adults with T2D, follow up &gt; 3 months – up to 4 years          25 RCTS, = 2132</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- The pooled effect estimate from meta-analysis was a weighted mean difference of -0.09%, suggesting no effect on HbA<sub>1c</sub> of restricting the quantity of carbohydrate.</li> <li>- A subgroup analysis of diets containing 50-130 g carbohydrate resulted in a pooled effect estimate of -0.49%, suggesting a clinically and statistically significant effect on HbA<sub>1c</sub> in favour of low-carbohydrate diets in studies of ≤6 months' duration.</li> </ul> <p>Conclusion: no overall pooled effect on HbA<sub>1c</sub> in favour of restricting carbohydrate; however, restriction of carbohydrate to 50-130 g per day had beneficial effects on HbA<sub>1c</sub> in trials up to 6 months.</p> <p><b>From the paper:</b> "Clinicians should inform patients with Type 2 DM there are a number of effective dietary approaches for improving glycaemic control, which may include restricting carbohydrate to 50-130g per day."</p>	<p>I do not have full access to the paper and thus cannot access the table which shows the degree of carbohydrate restriction in each study. I note that the subgroup analysis of lower carb (50 to 130g) showed beneficial effects.           Author McArdle has received honoraria from EliLilly and NovoNordisk</p>

<p>Choi YJ, Jeon SM, Shin S. Impact of a ketogenic diet on metabolic parameters in patients with obesity or overweight and with or without type 2 diabetes: a meta-analysis of randomized controlled trials. <i>Nutrients</i>. 2020 Jul 6;12(7):2005.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/32640608/">https://pubmed.ncbi.nlm.nih.gov/32640608/</a></p>	<p>Overweight or obese adults with or without T2D 14 RCTs comparing ketogenic diets (&lt; 20% of DE as carbohydrate) with various kinds low fat diets N = 734, including 444 people with T2D Duration variable from very short (examining short term metabolic parameters) up to 2 years</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- KD improved glycaemic control in people with T2D</li> <li>- KD led to better weight loss and improved lipid profiles (lower triglycerides and improved HDL-c) in all regardless of diabetes status</li> </ul> <p>Conclusion: ketogenic diets were more effective in improving metabolic parameters associated with glycemic, weight, and lipid controls in patients with overweight or obesity, especially those with preexisting diabetes, as compared to low-fat diets.</p>	<p>A paper that actually examines ketogenic diets ie very low carb.</p>
<p>Yuan X, Wang J, Yang S, Gao M, Cao L, Li X, Hong D, Tian S, Sun C. Effect of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with T2DM: a systematic review and meta-analysis. <i>Nutrition &amp; diabetes</i>. 2020 Nov 30;10(1):38.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7705738/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7705738/</a></p>	<p>Adults with T2D 13 studies, n = 567 Comparison Follow up of before intervention measurements of biomarkers with post-intervention measurements in same patients. Duration of follow up varied from 1 week to 1 year</p>	<p>Findings</p> <ul style="list-style-type: none"> <li>- Significant reductions in fasting glucose and HbA1c</li> <li>- Improvements in lipid profile including decreased triglycerides, Total Cholesterol, LDL-C and increased HDL-C.</li> </ul> <p>Conclusion: KD not only has a therapeutic effect on glycemic and lipid control among patients with T2DM but also significantly contributes to their weight loss.</p>	<p>Authors note that the reduction in HbA1c is of the same order of magnitude as reductions from diabetes meds. While not looking specifically at RCTs, this study reflects real world design ie what happens to biomarkers in patients with T2D before and after the ketogenic intervention.</p>
<p>Alarim, R.A., Alasmre, F.A., Alotaibi, H.A., Alshehri, M.A. and Hussain, S.A., 2020. Effects of the ketogenic diet on glycemic control in diabetic patients: meta-analysis of clinical trials. <i>Cureus</i>, 12(10).</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7641470/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7641470/</a></p>	<p>Heterogenous studies, adults with T2D 6 clinical trials, 2 were single arm 4 studies included in meta-analysis</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- KD superior to controls in terms of weight loss, improved glyemic control and improved lipid profile</li> </ul> <p>Conclusion: the results are significant enough to recommend KD as an adjunctive treatment for type two diabetes.</p>	<p>Authors comment that the effect of a high fat diet on serum lipids was profound and counter-intuitive. Increasing dietary fat does not increase serum lipids.</p>

<p>Goldenberg JZ, Day A, Brinkworth GD, Sato J, Yamada S, Jönsson T, Beardsley J, Johnson JA, Thabane L, Johnston BC. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. <i>bmj</i>. 2021 Jan 13;372.  <a href="https://www.bmj.com/content/372/bmj.m4743">https://www.bmj.com/content/372/bmj.m4743</a></p>	<p>Adults with T2D  23 RCTs comparing LC with mostly low fat control diets, duration at least 12 weeks</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- LC resulted in increased weight loss, reduced medication use, improved insulin sensitivity, and decreased triglycerides at 6 months</li> <li>- Improvements diminished at 12 months</li> </ul>	<p>While the benefits of LC may diminish by 12 months, once again there is no reason to prefer LF over LC based on this analysis.</p>
<p>Nicholas AP, Soto-Mota A, Lambert H, Collins AL. Restricting carbohydrates and calories in the treatment of type 2 diabetes: a systematic review of the effectiveness of 'low-carbohydrate' interventions with differing energy levels. <i>Journal of Nutritional Science</i>. 2021;10:e76.  <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8453456/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8453456/</a></p>	<p>Adults with T2D  LC defined as &lt; 130 g/day  15 studies of which 9 studied LCD with moderate or unrestricted energy intake. 6 studies used a low energy low carb diet (LED) (&lt; 1200 kCal/day)</p>	<p>Findings</p> <ul style="list-style-type: none"> <li>- Trials that restricted energy intake were not superior to those that allowed <i>ad libitum</i> low-carbohydrate feeding at 12 and 24 months.</li> <li>- An association was observed across studies between average weight loss and reduction in HbA1c at 6, 12 and 24 months, indicating that sustained weight loss is key to T2D remission.</li> </ul> <p>The authors note that despite differences, carbohydrate restriction is common in both dietary approaches: LCDs restrict carbohydrates as an explicit goal, whereas LEDs restrict carbohydrates as a consequence of achieving low-energy intake.</p> <p>Also: "There is currently much interest in the use of carbohydrate restriction to treat T2D. Over the past 5 years, ten meta-analyses, based on nearly fifty randomised controlled trials (RCTs), have aimed to address the question of whether diets low in carbohydrates produce greater improvements in weight and glycaemic control compared with higher carbohydrate control diets. <b>The majority of these meta-analyses have found a beneficial effect from carbohydrate restriction, and none have favoured higher carbohydrate comparators</b>, although several studies have found no difference between diets" (My emphasis)</p>	<p>Once again, begs the question of why peak bodies default to low fat high carbohydrate dietary guidelines.</p> <p>Another note from authors: "Previous systematic reviews have often included studies with higher thresholds of carbohydrate intake which limits understanding of the effects of 'true' low-carbohydrates diets."</p>



<p>Li S, Ding L, Xiao X. Comparing the efficacy and safety of low-carbohydrate diets with low-fat diets for type 2 diabetes mellitus patients: a systematic review and meta-analysis of randomized clinical trials. International Journal of Endocrinology. 2021 Dec 6;2021.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8668312/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8668312/</a></p>	<p>12 RCTs, duration &gt; 3 months, comparing low carb with low fat diets LC = &lt; 130 g/day N = 761</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- For primary outcomes (HbA1c and weight loss) LCDs were significantly better than LFD, especially in the subgroup using very LCD</li> <li>- Secondary outcomes: LC interventions significantly reduced triglycerides and increased HDL-c, with these benefits lasting between 1.5 and 2 years</li> <li>- Beneficial effects of body weight loss diminished over time</li> <li>- No difference in serum creatinine</li> </ul> <p>Conclusion: LCDS are superior to LFDs in improving HbA1c and body weight with a rewarding effect on some CV risk factors.</p>	<p>The authors note that the tendency for body weight to return to baseline value after 6 to 8 months in both diet arms reflects the difficulties of adherence to any dietary changes over relatively longer follow up periods. They observe no evidence that LCD has any adverse effects on CVD</p>
<p>Parry-Strong A, Wright-McNaughton M, Weatherall M, Hall RM, Coppell KJ, Barthow C, Krebs JD. Very low carbohydrate (ketogenic) diets in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism. 2022 Dec;24(12):2431-42.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9826205/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9826205/</a></p>	<p>RCTs with duration &gt; 6 months Comparing very low carb and ketogenic diets (VLC/KD) of &lt; 50g/day (&lt; 10% of DE) as carbs with controls ie carbs &gt; than VLCKD cut offs. Adults with diabetes and prediabetes</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- Heterogenous reporting of HbA1c outcomes made pooling difficult, however, the authors found that greater carbohydrate restriction generally led to improved glycaemic control</li> <li>- VLC/KD did not appear to worsen lipid profiles</li> <li>- Very limited data in prediabetes</li> </ul> <p>Conclusion: Evidence of improvement in HbA1c and lipids (with various caveats)</p>	<p>Comparison diets were highly variable, including low fat and calorie restricted diets, +/- orlistat, varying degrees of carbohydrate restriction. One of the authors, Jeremy Krebs, is on record as saying “there is nothing special about ketosis and that where weight loss is concerned, and that where weight loss in concerned, the primary issue is total energy intake.” This suggests that Dr Krebs has some biases of his own.</p>
<p>Jayedi A, Zeraattalab-Motlagh S, Jabbarzadeh B, Hosseini Y, Jibril AT, Shahinfar H, Mirrafiei A, Hosseini F, Bidar SS. Dose-dependent effect of carbohydrate restriction for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized controlled</p>	<p>RCTs of diets &gt; 45% of DE as carbs 50 trials, n = 4291 Adults with T2D</p>	<p>Findings:</p> <p>Each 10% reduction in carbohydrate reduced HbA1c, fasting plasma glucose, and body weight Also reductions in total cholesterol, LDL-c, triglycerides, and systolic BP. Levels of HbA1c, FPG, body weight, TG and SBP decreased linearly with the decrease in carbohydrate intake from 65% to 10%</p>	<p>Authors note that favorable effects of carbohydrate-restricted diets in improving cardiometabolic outcomes in patients with type 2 diabetes can be attributable to their effects on reducing hunger, pancreatic and hepatic fat</p>

<p>trials. The American Journal of Clinical Nutrition. 2022 Jul;116(1):40-56  <a href="https://pubmed.ncbi.nlm.nih.gov/35537861/">https://pubmed.ncbi.nlm.nih.gov/35537861/</a></p>		<p>Conclusion: Carbohydrate restriction can exert a significant and important reduction on levels of cardiometabolic risk factors in patients with type 2 diabetes. Levels of most cardiometabolic outcomes decreased linearly with the decrease in carbohydrate intake.</p>	<p>content, insulin resistance, pancreatic beta-cell work, and glucotoxicity, as well as to a reduction in ad libitum energy intake.  Also that attenuation of benefits after 6 months may be attributable to decreased adherence to LCD, a feature far from unique to LCD.</p>
<p>Apekey TA, Maynard MJ, Kittana M, Kunutsor SK. Comparison of the Effectiveness of Low Carbohydrate Versus Low Fat Diets, in Type 2 Diabetes: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2022 Oct 19;14(20):4391.  <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9609579/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9609579/</a></p>	<p>22 RCTs (open or blinded) of LC vs LF of &gt; 12 weeks duration  N = 1391 mostly obese adults with T2D or prediabetes  LC defined as &lt; 130 g/day or &lt; 26% of DE  LF defined as &gt; 130 g carbs daily</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- LC diet significantly reduced body weight, BMI, fasting insulin and triglycerides and increased total cholesterol and HDL-C levels at the short-to-intermediate term, with a decrease in the requirement for antiglycaemic medications at intermediate-to-long term.</li> </ul> <p>Conclusion: Except for reducing HbA1c levels and adiposity parameters at short-to-intermediate terms, a LC diet appears to be equally effective as a LF diet in terms of control of cardiometabolic markers and the risk of adverse events in obese patients with T2D</p>	<p>Once again, LC generally superior in some areas and as effective and safe. Thus there is no rationale for recommending LF over LC.</p>

## 2. Other meta-analyses comparing low carb with low fat diets

Reference	Details	Key findings	
<p>Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity</p>	<p>Trials lasting &gt; 6 months  Adults with BMI &gt; 28  13 articles met inclusion criteria  N = 1222</p>	<p>Findings</p> <ul style="list-style-type: none"> <li>- Significant differences between the groups for weight, high-density lipoprotein cholesterol, triacylglycerols and systolic blood pressure, favouring the low-carbohydrate diet.</li> <li>- A higher attrition rate in the low-fat compared with the low-carbohydrate groups suggesting a patient preference for a low-</li> </ul>	

<p>and its comorbidities. Obesity reviews. 2009 Jan;10(1):36-50.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/18700873/">https://pubmed.ncbi.nlm.nih.gov/18700873/</a></p>		<p>carbohydrate/high-protein approach as opposed to the Public Health preference of a low-fat/high-carbohydrate diet.</p> <p>Conclusion: Evidence from this systematic review demonstrates that low-carbohydrate/high-protein diets are more effective at 6 months and are as effective, if not more, as low-fat diets in reducing weight and cardiovascular disease risk up to 1 year.”</p>	
<p>Santos FL, Esteves SS, da Costa Pereira A, Yancy Jr WS, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obesity reviews. 2012 Nov;13(11):1048-66.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/22905670/">https://pubmed.ncbi.nlm.nih.gov/22905670/</a></p>	<p>17 clinical investigations 1,141 obese patients</p>	<p>Findings:</p> <ul style="list-style-type: none"> <li>- the LCD to be associated with significant decreases in body weight, body mass index, abdominal circumference, systolic blood pressure, diastolic blood pressure, plasma triglycerides, fasting plasma glucose, glycated haemoglobin, plasma insulin and plasma C-reactive protein, as well as an increase in high-density lipoprotein cholesterol.</li> <li>- Low-density lipoprotein cholesterol and creatinine did not change significantly, whereas limited data exist concerning plasma uric acid.</li> </ul> <p>Conclusion: LCD was shown to have favourable effects on body weight and major cardiovascular risk factor</p>	<p>I am only able to access the abstract</p>
<p>Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. British Journal of Nutrition. 2013 Oct;110(7):1178-87.</p> <p><a href="https://www.ncbi.nlm.nih.gov/books/NBK138038/">https://www.ncbi.nlm.nih.gov/books/NBK138038/</a></p>	<p>Overweight or obese adults &gt; age 18 and BMI &gt; 27.5 Minimum follow up &gt; 12 months 13 RCTS, 1569 patients</p>	<p>Findings</p> <ul style="list-style-type: none"> <li>- Patients assigned to a very-low-carbohydrate ketogenic diet had statistically significant greater weight loss than those assigned to a low fat diet (13 RCTS; 1,415 patients.)</li> <li>- “Patients assigned to a very-low-carbohydrate ketogenic diet had significantly decreased and diastolic blood pressure and significantly increased HDL cholesterol and LDL cholesterol compared with patients on a low fat diet. There was no significant heterogeneity for any of these outcomes.</li> <li>- No significant difference between treatment groups in changes in systolic blood pressure (11 trials), fasting blood glucose (eight trials), insulin (six trials), HbA<sub>1c</sub> (four trials) and C-reactive protein (four trials).</li> </ul> <p>Conclusion: Individuals assigned to a very-low-carbohydrate ketogenic diet achieved greater long-term reductions in body weight, triacylglycerol and diastolic blood pressure and greater increases in LDL</p>	

		cholesterol and HDL cholesterol levels than those assigned to a low fat diet.	
Sackner-Bernstein J, Kanter D, Kaul S. Dietary intervention for overweight and obese adults: comparison of low-carbohydrate and low-fat diets. A meta-analysis. PloS one. 2015 Oct 20;10(10):e0139817.  <a href="https://pubmed.ncbi.nlm.nih.gov/26485706/">https://pubmed.ncbi.nlm.nih.gov/26485706/</a>	RCTs from 8 weeks to 2 years duration 17 trials, n = 1797	Findings: <ul style="list-style-type: none"> <li>- This trial-level meta-analysis of randomized controlled trials comparing LoCHO diets with LoFAT diets in strictly adherent populations demonstrates that each diet was associated with significant weight loss and reduction in predicted risk of ASCVD events. However, LoCHO diet was associated with modest but significantly greater improvements in weight loss and predicted ASCVD risk in studies from 8 weeks to 24 months in duration.</li> </ul> Conclusion: future evaluations of dietary guidelines should consider low carbohydrate diets as effective and safe intervention for weight management in the overweight and obese	In short, low carb should be confirmed as an option for people with obesity and diabetes.
Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of Low-Fat vs. Other Diet Interventions on Long-Term Weight Change in Adults: A Systematic Review and Meta-Analysis. The lancet. Diabetes & endocrinology. 2015 Dec;3(12):968.  <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4667723/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4667723/</a>	53 RCTs in adults comparing lower and higher fat interventions for weight loss Trials lasting > 1 year N = 68,128	Findings: <ul style="list-style-type: none"> <li>- Low fat only superior when compared with “usual diet.”</li> <li>- Weight loss trials achieving a greater difference in fat intake at follow up significantly favoured higher fat dietary interventions.</li> <li>- The effect of low fat diets on body weight depend on the intensity of the intervention in the comparison group.</li> </ul> Conclusion: <ul style="list-style-type: none"> <li>- Evidence from RCTs does not support low fat diets over other dietary interventions.</li> <li>- Nutrition guidelines should cease recommending low fat diets for weight loss given the clear lack of long-term efficacy over other similar intensity dietary interventions.</li> </ul>	Given that this review was published in 2015, it begs the question as to why dietary guidelines in Australia and around the world continue to promote ‘lean meat’ and ‘dairy, mostly low- fat.’
Mansoor N, Vinknes KJ, Veierød MB, Retterstøl K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. British Journal of Nutrition. 2016 Feb;115(3):466-79.	Intervention duration > 6 months Previously healthy subjects (with CV risk factors) 11 RCTs, 1369 participants	Findings: <ul style="list-style-type: none"> <li>- Participants on LC diets (Atkins-like, carb intake &lt; 20% of DE) experienced greater reduction in body weight and triglycerides, and increased HDL.</li> <li>- The authors note a modest increase in LDL and comment on “opposite change in 2 important CV risk factors” – greater weight loss and increased LDL-C.</li> </ul>	There are multiple reviews that show that LDL-c is a poor maker of CVD risk. LCD have been shown repeatedly to improve the most reliable markers of CV risk. See for example Diamond et al(1),

<a href="https://pubmed.ncbi.nlm.nih.gov/26768850/">https://pubmed.ncbi.nlm.nih.gov/26768850/</a>		<p>Conclusion: Our findings suggest that the beneficial changes of LC diets must be weighed against the possible detrimental effects of increased LDL-cholesterol.</p>	<p>O'Neill(2) and Diamond et al (3).</p>
<p>Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. Nutrition Reviews. 2019 Mar 1;77(3):161-80.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/30544168/">https://pubmed.ncbi.nlm.nih.gov/30544168/</a></p>	<p>Inclusion criteria: Large RCTs ( n &gt;100) of &gt; 6 months duration</p> <p>8 RCTs, n = 1633</p>	<p>The paper examined the effects of LC vs LF on dyslipidemia in overweight and obese adults</p> <ul style="list-style-type: none"> <li>- LC diets showed no significant difference in LDL-c after 6, 12 and 24 months. Overall pooled analysis favoured LF, but this was clinically insignificant</li> <li>- HDL and triglycerides outcomes favoured carbohydrate restriction. This was more marked with very-low carbohydrate content</li> </ul> <p>Conclusion: Dietary guidelines should consider carbohydrate restriction as an alternative dietary strategy for the prevention/management of dyslipidemia for populations with cardiometabolic risk.</p>	
<p>Chawla S, Tessarolo Silva F, Amaral Medeiros S, Mekary RA, Radenkovic D. The effect of low-fat and low-carbohydrate diets on weight loss and lipid levels: a systematic review and meta-analysis. Nutrients. 2020 Dec 9;12(12):3774.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7763365/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7763365/</a></p>	<p>38 RCTs in adults with no comorbidities, n = 6499 LC defined as &lt; 40% of DE as carbs LF defined as &lt; 30% of DE as fat Study duration 1 to 24 months</p>	<p>Findings: at 6 to 12 months</p> <ul style="list-style-type: none"> <li>- LC favoured for weight loss, HDL, triglycerides</li> <li>- LF favoured for LDL and total cholesterol</li> </ul> <p>Conclusion: Low-carbohydrate diets are effective at improving weight loss, HDL and TG lipid profiles. However, this must be balanced with potential consequences of raised LDL and total cholesterol in the long-term."</p> <p>TC and LDL are meaningful. Arguably, the size of the LDL particle is more meaningful, in older people, lower LDL is associated with increased mortality, metabolic syndrome is a more powerful predictor of CVD than LDL .</p> <p>eg Pichler et al Wang et al, Liu et al Cao et al</p>	<p>Total cholesterol and LDL-C are poor markers of CV risk. The size of the LDL particle is more meaningful,(4) while lower LDL is associated with increased all-cause mortality.(5) (6) Metabolic syndrome is a more powerful predictor of CVD than LDL-c.(7)</p>

3. Other significant review papers

Paper	Relevant findings
<p>Wheatley SD, Deakin TA, Arjomandkhah NC, Hollinrake PB, Reeves TE. Low carbohydrate dietary approaches for people with type 2 diabetes—A narrative review. <i>Frontiers in nutrition</i>. 2021:415.</p> <p><a href="https://www.frontiersin.org/articles/10.3389/fnut.2021.687658/full">https://www.frontiersin.org/articles/10.3389/fnut.2021.687658/full</a></p>	<ul style="list-style-type: none"> <li>• Low Carb diets (LCDs) are non-inferior to existing standard of care. The findings from multiple systematic reviews supports the use of LCDs as a suitable option for people with T2D.</li> <li>• Low fat diets are promoted without hesitancy or qualification, whereas LC diets are approached with caution. It is inappropriate to hold LCDs to a level of evidence higher than that which other dietary approaches meet.</li> <li>• LCDs reduce hunger, and reduce need for medication. The latter is a powerful motivator for individuals.</li> <li>• Many people are motivated to use LCDs despite lack of support from their health care providers.</li> <li>• Many studies do not report medication usage or changes</li> <li>• LCDs reduces hepatic fat storage and insulin resistance</li> <li>• With LCDs, changes in LDL may be physiological, not pathological</li> <li>• Patients should be supported to make dietary choices that fit their needs and preferences</li> <li>• LCDs should be one of the options offered and the possible benefits made clear</li> <li>• Clinical support for the LC option promotes dietary adherence</li> <li>• Concerns about the long term impact of LCDs are not supported by the available evidence</li> </ul>
<p>Griauzde DH, Lopez KS, Saslow LR, Richardson CR. A pragmatic approach to translating low-and very low-carbohydrate diets into clinical practice for patients with obesity and type 2 diabetes. <i>Frontiers in nutrition</i>. 2021;8.</p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/34350205/">https://pubmed.ncbi.nlm.nih.gov/34350205/</a></p>	<ul style="list-style-type: none"> <li>• The cornerstone of Evidence-based Medicine (EBM) are the best available evidence, clinical judgement and patient preferences</li> <li>• Guidelines recommendations should only guide, not dictate, treatment for particular individuals</li> <li>• Shared decision making entails consideration of patient preferences, needs and health goals</li> <li>• Therapeutic carbohydrate reduction is one of many evidence-based treatment approaches</li> <li>• Persistent recommendations by providers to reduce caloric intake represents treatment failure, not patient failure</li> <li>• Dietary carbohydrate is non essential for human health</li> <li>• Dietary carbohydrate restriction does not require calorie counting, and can alleviate excessive hunger and food cravings</li> </ul> <p>Practical steps for clinicians to translate LCD research findings into clinical practice are</p> <ol style="list-style-type: none"> <li>1. Offer dietary carbohydrate reduction as an evidence-based treatment option</li> <li>2. Reduce intake of common dietary culprits of weight gain and metabolic dysregulation</li> <li>3. Tailor the degree of carbohydrate reduction to patient preferences and needs</li> <li>4. Mitigate possible side effects and risks, with regular monitoring and appropriate de-prescription of medication</li> <li>5. Support weight maintenance with lifestyle counselling</li> </ol>

<p>Kelly T, Unwin D, Finucane F. Low-Carbohydrate diets in the management of obesity and type 2 diabetes: a review from clinicians using the approach in practice. International journal of environmental research and public health. 2020 Apr;17(7):2557.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177487/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177487/</a></p>	<ul style="list-style-type: none"> <li>• International guidelines now recognize the validity and endorse LCDs as a therapeutic approach in appropriate patients; health care providers should be aware of the evidence supporting LCDs.</li> <li>• The criticisms applied to LCD interventions (expense, lack of sustainability, and risk of weight re-gain) apply to many dietary interventions, including very low energy diets.</li> <li>• A lack of methodological rigour is a generic challenge in RCTS of dietary interventions.</li> <li>• Rather than “a calorie is a calorie,” it must be recognized that the type of food ingested has an impact on appetite and subsequent eating behaviors.</li> <li>• High insulin levels, as seen in insulin resistance, are known to reduce satiety and influence eating behaviours while downregulating the availability of fatty acids from adipose stores as energy.</li> <li>• People typically report reduced hunger and increased satiety after changing to LCD, while calorie counting is not required</li> <li>• Clinicians need to be familiar with the principles of de-prescribing for people with diabetes who initiate LCDs, and continue to monitor cardiovascular risk factors</li> </ul>
<p>Webster CC, Murphy TE, Larmuth KM, Noakes TD, Smith JA. Diet, diabetes status, and personal experiences of individuals with type 2 diabetes who self-selected and followed a low carbohydrate high fat diet. Diabetes, metabolic syndrome and obesity: targets and therapy. 2019;12:2567.</p> <p><a href="https://www.dovepress.com/diet-diabetes-status-and-personal-experiences-of-individuals-with-type-peer-reviewed-fulltext-article-DMSO">https://www.dovepress.com/diet-diabetes-status-and-personal-experiences-of-individuals-with-type-peer-reviewed-fulltext-article-DMSO</a></p>	<p>This observational study of 28 people who had T2D remission with a LCD of at least 6 months found the following themes:</p> <ul style="list-style-type: none"> <li>• Most participants experienced reduced hunger and cravings, and felt more in control of their eating behaviour, leading to less snacking and less frequent meals. Participants did not feel deprived or that “willpower” was required to control their food consumption.</li> <li>• Participants felt more in control of their health, reporting improved health and reduced medication use. These outcomes were described as empowering and motivating.</li> <li>• The main negative aspect of LCD was socializing was more difficult due to lack of appropriate food options and negative attitudes towards low carbohydrate diets. This reflects problems with normal food environments rather than any limitations inherent in the LC approach.</li> <li>• Additionally, despite their success in improving their health, many participants reported lack of support from and hostile interactions with health care providers, potentially leading to suboptimal medical supervision.</li> </ul> <p>The above findings are consistent with my experience of patients who seek me out because they are interested in improving their metabolic health and they are fed up with being bullied by GPs who do not understand the value of the LC approach.</p>

## References

1. Diamond DM, O'Neill BJ, Volek JS. Low carbohydrate diet: are concerns with saturated fat, lipids, and cardiovascular disease risk justified? *Curr Opin Endocrinol Diabetes Obes.* 2020 Oct;27(5):291–300.
2. O'Neill BJ. Effect of low-carbohydrate diets on cardiometabolic risk, insulin resistance, and metabolic syndrome. *Curr Opin Endocrinol Diabetes Obes.* 2020 Oct;27(5):301–7.
3. Diamond DM, Bikman BT, Mason P. Statin therapy is not warranted for a person with high LDL-cholesterol on a low carbohydrate diet. *Curr Opin Endocrinol Diabetes Obes.* 2022;
4. Pichler G, Amigo N, Tellez-Plaza M, Pardo-Cea MA, Dominguez-Lucas A, Marrachelli VG, et al. LDL particle size and composition and incident cardiovascular disease in a South-European population: The Hortega-Liposcale Follow-up Study. *Int J Cardiol.* 2018 Aug 1;264:172–8.
5. Sung KC, Huh JH, Ryu S, Lee JY, Scorletti E, Byrne CD, et al. Low Levels of Low-Density Lipoprotein Cholesterol and Mortality Outcomes in Non-Statin Users. *J Clin Med.* 2019 Oct 1;8(10):E1571.
6. Kawamoto R, Kikuchi A, Akase T, Ninomiya D, Kumagi T. Low density lipoprotein cholesterol and all-cause mortality rate: findings from a study on Japanese community-dwelling persons. *Lipids Health Dis* [Internet]. 2021 Sep 12 [cited 2022 Jun 12];20(1):105. Available from: <https://doi.org/10.1186/s12944-021-01533-6>
7. Wang X. Main Defects in Studies of Lipid-Lowering Drugs: Metabolic Diseases Rather than Lipids is the Risk Factor of Atherosclerotic Diseases. 2022.