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Commentary

Low-carbohydrate diets for reducing cardiovascular risk and supporting weight loss in adults without specific diseases: a synthesis of systematic reviews

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Key words

Cardiology, Cardiovascular outcomes, Dietary intervention, Low-carbohydrate diet, Weight loss

Introduction

Cardiovascular disease remains the primary cause of death worldwide, with an estimated 17 million deaths occurring annually (GBD 2015 Risk Factors Collaborators, 2016; Roth et al, 2020). Cardiovascular disease refers to all types of conditions affecting the blood circulatory system, including but not limited to heart disease, ischaemic stroke, myocardial infarction, cardiac arrhythmias, cardiomyopathies, deep vein thrombosis, heart failure, cardiac valvopathies and pulmonary embolism (Thiriet, 2018). There are numerous drivers of cardiovascular disease, including behavioural (eg eating behaviours), cardiometabolic (eg hereditary risk), environmental (eg air pollution) and social risk factors (eg socioeconomic status) (Roth et al, 2020; National Institute for Health and Care Excellence, 2023). Although some risk factors of cardiovascular disease are nonmodifiable, risk can be reduced by altering behavioural factors such as smoking, unhealthy eating, alcohol consumption, physical inactivity and obesity (Ruan et al, 2018; World Health Organization, 2021). Evidence suggests that obesity and elevated body mass index are some of the greatest contributors to cardiovascular disease globally (Powell-Wiley et al, 2021). With an increasing prevalence of obesity and the concomitant rise in cardiovascular disease, there is a growing need to identify effective strategies that can simultaneously address both concerns. In recent years, one strategy focused on reducing dietary carbohydrate intake has gained popularity because of its potential to address the challenges of both obesity and cardiovascular disease.

A low-carbohydrate diet is primarily focused on reducing the consumption of carbohydrates, where they account for a lower proportion of calorific intake compared to conventional diets (eg the western diet) (Kelly et al, 2020). Some examples of low-carbohydrate diets include the Atkins diet, the paleo diet and the ketogenic diet (Merrill et al, 2020). Although some basic principles exist, there is no consistent or widely accepted definition within literature relating to a low-carbohydrate diet (Naude et al, <u>2022</u>). However, there is a general consensus that the threshold for low carbohydrate intake is usually accepted as less than 130 g/day, or less than 40% of total energy (Kelly et al, 2020). Conventional diets, such as those recommended by The Scientific Advisory Committee on Nutrition and the Dietary Guidelines for Americans, suggest that carbohydrates should make up 45-65 % of total daily calorie intake (approximately 250–300g per day), so low-carbohydrate diets typically adopt a restriction equal to or greater than half of the normal recommendation (ie carbohydrates equate to 20–30% of total energy) (Evert et al, 2019; Kelly et al, 2020; Mooradian, 2020). In clinical practise, low-carbohydrate diets are recommended through a range of approaches, but typically involve a restriction of grains, cereals, legumes, sweet beverages and starchy vegetables (Cucuzzella et al, 2019). These foods are often replaced with foods higher in fat and protein (eg meats, eggs, fish, nuts and seeds) (Naude et al, 2022).

There are three key mechanisms associated with how low-carbohydrate diets may improve cardiovascular risk factors and promote weight loss (Oh et al, 2023; Sun et al, 2023). The first premise is that by limiting carbohydrate intake, the body pivots to using fat as its primary energy source (Oh et al, 2023). Evidence suggests that restricting carbohydrate intake stimulates a process of glycogen depletion, prompting mobilisation of fat in the body (stored in the adipose tissue) (Oh et al, 2023. The pivot towards fat use has the potential to enhance weight loss, reduce body fat percentage and increasing fat-free mass by cutting down fat mass (Paddon-Jones et al, 2008). With sustained adherence and the potential changes to body composition (ie reduced body fat), it is likely that patients see an improvement in cardiovascular risk factors (Merrill et al, 2020). The second mechanism is that when patients restrict carbohydrate-rich foods, there may be a reduction in energy intake due to a decrease in appetite (Clemente-Suárez et al, 2022; Sun et al, 2023). The rise in fat intake and subsequent production of ketones increases satiety with a reduction of rebound hypoglycaemia (reducing hunger), resulting in a greater likelihood of patients achieving a caloric deficit, reducing body mass index and improving cardiovascular health (Hall et al, 2015; Crosby et al, 2021). The final underlying mechanism relates to the hypothesis that low-carbohydrate diets can lower insulin (a hormone that generates an anabolic fat-storing state in the body), which has the potential to improve cardiometabolic function and support weight loss (Ebbeling et al, 2018). This hypothesis suggests that lower insulin production may encourage the oxidisation of calories within lean muscle tissue, rather than the deposition of calories in fat cells (Ludwig and Friedman, 2014; Ludwig and Ebbeling, 2018). It has been proposed that sustained reduction in insulin throughout the body may lead to improvements in body composition (ie reducing body fat percentage), decreasing cardiovascular risk factors (Schwarz et al, 2018).

The recent popularity of low-carbohydrate diets has given rise to several systematic reviews. These systematic reviews have provided insights into the effectiveness and safety profile of low-carbohydrate diets, making them a valuable resource for health professionals, researchers and policymakers (Chawla et al, 2020; Dong et al, 2020; Naude et al, 2022). However, the substantial array of systematic reviews, as well as the variations in their findings, make it challenging for health professionals, researchers and policymakers to make definitive recommendations for clinical practice (Naude et al, 2022). This highlights an immediate need for a concise synthesis of systematic reviews to form a more comprehensive and nuanced understanding of the role of low-carbohydrate diets in reducing cardiovascular risk factors and supporting weight loss in adults. Therefore, the aim of this article is to provide a comprehensive commentary of up-to-date systematic reviews (within the last 3 years) on the effectiveness of low-carbohydrate diets in reducing cardiovascular risk and supporting weight loss in adults without specific diseases. The synthesis is intended to inform healthcare-related decisions, facilitate evidence-based recommendations and contribute to the management and prevention of cardiovascular disease.

Methods of the commentary

Search

A search of systematic reviews published within the last 3 years (from January 2020 to October 2023) was conducted. PubMed was used to search for relevant systematic reviews. The search terms included 'low-carbohydrate diet' in combination with: 'cardiovascular health,' 'weight loss,' 'obesity,' 'nutrition,' 'cardiovascular disease,' and 'systematic review.'

Inclusion criteria

The author only included studies with adults (≥18 years old) in which the review examined the effectiveness of low-carbohydrate diets (defined as <40% of overall energy consumption from

carbohydrates) and focused on a population without any specific diseases (eg type 2 diabetes). Only peer-reviewed systematic reviews published in scientific journals after January 1st 2020 were considered for inclusion. The author only included systematic reviews written in English, excluding those written in other languages. Systematic reviews including participants with and without specific diseases were included if data relating to those without specific diseases could be extracted separately.

Data extraction

The author extracted the data from the systematic reviews identified during study selection. The following data items were extracted: author, date, population, intervention, comparator, outcome(s), relative effect (with 95% confidence intervals) and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment for each outcome (if available).

Critical appraisal

Critical appraisal of each of the systematic reviews was conducted using the Assessment of Multiple Systematic Reviews 2 tool (Shea et al, <u>2017</u>). This critical appraisal tool provides a standardised approach to assessing the methodological quality of systematic reviews of healthcare interventions, and considers elements such as the appropriateness of study selection, data extraction and synthesis of results (Shea et al, <u>2017</u>; Chapman et al, <u>2022</u>).

Data synthesis

A narrative synthesis was conducted to report the findings of the commentary. The advantages of a narrative synthesis is it can increase the chances of findings being used in clinical practice and policy (an intension of this commentary) (Popay et al, 2006). This is because it adopts a textual approach to synthesising systematic reviews, enabling a clearer interpretation of the data from a range of included studies (eg randomised control trials) (Popay et al, 2006). It has also been deemed the most appropriate method of synthesis when there is a small number of included reviews and there is possibility of substantial heterogeneity (Shaw and Couzos, 2021).

Results of the systematic reviews

Following the study selection process, the author included a total of three systematic reviews which assessed the effects of low-carbohydrate diets for reducing weight and cardiovascular risk factors in adults with no specific diseases (Chawla et al, 2020; Dong et al, 2020; Naude et al, 2022).

Characteristics of included systemic reviews

The systematic review by Chawla et al (2020) included randomised controlled trials with adults comparing low-carbohydrate diets (≤40% of total energy intake) to low-fat diets (<30% total fat content) with no specific diseases. Studies were included in the review if weight loss was described as a primary outcome. Studies were excluded if they were conducted in populations with comorbidities such as diabetes, cancer, chronic obstructive pulmonary disease or other cardiovascular diseases, and if they were not randomised controlled trials. During study selection a total of 2753 articles were screened for eligibility. A total of 38 randomised controlled trials with 6499 participants were included in the systematic review (Chawla et al, 2020).

The systematic review by Dong et al ($\underline{2020}$), included randomised controlled trials with adults ($\underline{\geq}18$ years) who had no specific diseases comparing low-carbohydrate diet ($\underline{<}40\%$ of total

energy intake) to other surgical or drug intervention (to improve cardiovascular risk factors). Studies were excluded from the review if they were non-randomised controlled trials, were not available in English, had participants withdraw (incomplete data set) or if participants underwent other surgical interventions or drug intervention as part of the research. Following the screening of 1292 articles, a total of 12 randomised controlled trials with 1640 participants were included in the review (Dong et al, 2020).

The systematic review by Naude et al (2022) included randomised controlled trials with adults (≥18 years) who had a body-mass index greater than 25 kg/m² with and without specific diseases. Data for adults without specific diseases were presented separately, which allowed for inclusion of the review in this commentary. Included studies in the review compared low-carbohydrate diets (<40% of total energy intake) to balanced carbohydrate diets (45–65% of total energy), had a weight-reducing phase of 2 weeks or longer, and had to be implemented for the primary purpose of weight reduction. The review excluded studies with pregnant and lactating women, as well as studies in people with specific medical conditions such as bipolar disorder, polycystic ovary syndrome and chronic renal disease. The review also excluded quasi-randomised trials and crossover trials, whereby the first phase was less than 12 weeks. During the study selection process, a total of 2882 articles were screened for eligibility. A total of 61 randomised controlled trials were included, with 6925 participants (Naude et al, 2022).

Outcomes

Change in weight

In all three systematic reviews, there was a statistically significant greater reduction in weight in participants who consumed a low-carbohydrate diet compared to those in the various control groups (drug or surgical intervention, balanced carbohydrate diet or low-fat diet) (GRADE: moderate certainty evidence) (Chawla et al, 2020; Dong et al, 2020; Naude et al, 2022).

One review showed a statistically significant greater reduction in weight in participants who consumed a low-carbohydrate diet compared to those who received a balanced carbohydrate diet at \geq 12 months follow up (Naude et al, 2022). However, there was no evidence of difference in weight loss at \geq 12 months follow up in two of the systemic reviews (Chawla et al, 2020; Dong et al, 2020). There was also no evidence of difference in weight loss between low-carbohydrate diet and low-fat diets reported in the review by Chawla et al (2020), at \leq 6 months follow up (Appendix 1).

Change in body mass index

One systematic review reported on change in body mass index associated with low-carbohydrate diets when compared to those receiving balanced carbohydrate diets (Naude et al, 2022. The review by Naude et al (2022), found a statistically significant reduction in body mass index associated with the consumption of a low-carbohydrate diets when compared to those receiving balanced carbohydrate diets at \geq 12 months. The reviews by Chawla et al, 2020 and Dong et al, 2020 did not report on the outcome of body mass index.

Change in triglycerides

In all three systematic reviews, there was a statistically significant greater decrease in triglycerides in participants who consumed a low-carbohydrate diet compared to those in]drug or surgical intervention, balanced carbohydrate diet or low-fat diet ('Overall' and at <12 months follow up in

Chawla et al and Dong et al, and ≥ 12 months in Naude et al) (Chawla et al, 2020; Dong et al, 2020; Naude et al, 2022).

There was no evidence of difference in a reduction in triglycerides post-12-month follow up in the review by Chawla et al (2020). There was also no evidence of difference in triglycerides between low-carbohydrate and other surgical or drug intervention reported in the review by Dong et al (2020), at 6–11 months and 24 months follow up (Appendix 1).

Change in high-density lipoprotein cholesterol

In all three systematic reviews, there was a statistically significant increase in high-density lipoprotein cholesterol in participants who consumed a low-carbohydrate diet compared to those in the drug or surgical intervention, balanced carbohydrate diet or low-fat diet groups ('Overall' and at ≤12 months in Chawla et al, and >6 months in Dong et al and Naude et al) (Chawla et al, 2020; Dong et al, 2020; Naude et al, 2022).

There was no evidence of difference in high-density lipoprotein cholesterol in the review by Chawla et al (2020) at 24-month follow up (Appendix 1).

Change in low-density lipoprotein cholesterol

In two systematic reviews, there was an 'overall' statistically significant reduction in low-density lipoprotein cholesterol in participants who consumed a low-carbohydrate diet compared to those in the various control groups (drug or surgical intervention or low-fat diet) (Chawla et al, $\underline{2020}$; Dong et al, $\underline{2020}$).

One review found no evidence of difference in low-density lipoprotein cholesterol in participants who consumed a low-carbohydrate diet compared to those who consumed a balanced carbohydrate diet at ≥12 months (GRADE: moderate certainty evidence) (Naude et al, 2022). In addition, the review by Chawla et al (2020), showed no evidence of difference in low-density lipoprotein cholesterol in participants who consumed a low-carbohydrate diet compared to those who consumed a low-fat diet at 24-month follow up. Similarly, the review by Dong et al (2020), showed no evidence of difference in low-density lipoprotein cholesterol in participants who consumed a low-carbohydrate diet compared to those who received surgical or drug interventions at >6-months follow up (although the review did find a statistical significant difference 'overall' and at <6 months follow up) (Appendix 1).

Change in total cholesterol

In two systematic reviews by Chawla et al ($\underline{2020}$) and Dong et al ($\underline{2020}$), there was an 'overall' statistically significant reduction in total cholesterol in participants who consumed a low-carbohydrate diet compared to those in the various control groups (drug or surgical intervention or low-fat diet). In contrast, the review by Naude et al ($\underline{2022}$) found no evidence of difference in total cholesterol in participants who consumed a low-carbohydrate diet compared to those who consumed a balanced carbohydrate diet at ≥ 12 months.

Both Chawla et al (2020) and Dong et al (2020) found no evidence of difference in total cholesterol in participants who consumed a low-carbohydrate diet compared to a low-fat diet at >12-month follow up (although both reviews found a statistical significant difference 'overall' and at <6 months follow up) (Appendix 1).

Changes in systolic and diastolic blood pressure

Of the three included systematic reviews, only two reviews (Dong et al, 2020; Naude et al, 2022) reported on the outcome of blood pressure (systolic blood pressure and diastolic blood pressure). The review by Dong et al (2020) found that there was an 'overall' statistically significant reduction in systolic blood pressure and diastolic blood pressure in participants who consumed a low-carbohydrate diet compared to those received drug or surgical intervention. However, Dong et al (2020) found no evidence of difference in systolic blood pressure or diastolic blood pressure in participants who consumed a low-carbohydrate diet compared to a low-fat diet at >12-month follow up. Similarly, the review by Naude et al (2022), found no evidence of difference in systolic blood pressure or diastolic blood pressure in participants who consumed a low-carbohydrate diet compared to those who consumed a balanced carbohydrate diet at \geq 12 months (GRADE: moderate certainty evidence) (Appendix 1).

Adverse events

One systematic review reported on adverse events associated with low-carbohydrate diets when compared to those receiving a balanced carbohydrate diet (Naude et al, <u>2022</u>). The review by Naude et al (<u>2022</u>) found no evidence of difference in adverse events (eg constipation, diarrhoea, nausea, headaches, heartburn, fatigue, anxiety, depressive symptoms or stomach upsets) in participants who consumed a low-carbohydrate diet compared to those who consumed a balanced carbohydrate diet at ≥12 months (GRADE: very low certainty evidence). However, there was a statistically significant increase in incidence of halitosis at 6 months within the low-carbohydrate diets when compared to those receiving a balanced carbohydrate diets (Naude et al, <u>2022</u>) (Appendix 1).

Commentary

The synthesis of evidence presented by this commentary of three systematic reviews shows that low-carbohydrate diets may have beneficial effects on weight loss, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and total cholesterol in the short term (<12 months), when compared to a balanced carbohydrate diet, a low-fat diet, drug or surgical intervention. While statistically significant differences were observed in the short term (at 6-month follow up), the long-term impact on these outcomes remains less clear.

Critical appraisal of the systematic reviews

The three systematic reviews were appraised using the Assessment of Multiple Systematic Reviews 2 critical appraisal tool (*Table 2*) (Shea et al, <u>2017</u>). From this assessment, all three systematic reviews were judged to provide a comprehensive summary of current evidence. However, two studies only satisfied 14 of the 16 criteria, because they did not report sources of funding (Chawla et al, <u>2020</u>; Dong et al, <u>2020</u>), discuss potential heterogeneity (Chawla et al, <u>2020</u>), or state whether the review methods were established before the conduct of the review (ie provide details of a protocol) (Dong et al, <u>2020</u>).

Table 2. Critical appraisal using the Assessment of Multiple Systematic Reviews 2 tool for						
each of the included systematic reviews						
Assessment of Multiple Systematic Reviews	Chawla et al,	Dong et al,	Naude et al,			
2 items	<u>2020</u>	<u>2020</u>	<u>2022</u>			

1.	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2.	Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	No	Yes
3.	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4.	Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes
5.	Did the review authors perform the study selection in duplicate?	Yes	Yes	Yes
6.	Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7.	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes
8.	Did the review authors describe the included studies in adequate details?	Yes	Yes	Yes
9.	Did the review authors use a satisfactory technique for assessing the risk of bias in the individual studies that were included in the review?	Yes	Yes	Yes
10.	Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes
11.	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes
12.	If meta-analysis was performed did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes
13.	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Yes	Yes
14.	Did the review authors provide a satisfactory explanation for and discussion of, any	No	Yes	Yes

heterogeneity observed in the results of the review?			
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes
Total	14/16	14/16	16/16

^{*}RoB = Risk of Bias, PICO = Population, Intervention, Comparison, Outcome(s).

Implications for clinical practice and policy

This synthesis of three recent systematic reviews concludes that low-carbohydrate diets may offer short-term benefits for weight loss, triglyceride reduction, and management of cholesterol (eg high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and total cholesterol) (Chawla et al, $\underline{2020}$; Dong et al, $\underline{2020}$; Naude et al, $\underline{2022}$). However, the evidence shows that these benefits are likely to diminish at 12 months (Chawla et al, $\underline{2020}$; Dong et al, $\underline{2020}$; Naude et al, $\underline{2022}$). The short-term effectiveness of low-carbohydrate diets in achieving weight reduction and reducing cardiovascular risks highlights its potential as a transitory intervention, although additional evidence-based interventions are likely needed to sustain these benefits in the longer term (≥ 12 months) (Chawla et al, ≥ 1202). These findings hold important implications for cardiac nurses and cardiologists in managing cardiovascular risk among patients, particularly those with overweight or obesity.

The findings show that low-carbohydrate diets may reduce triglyceride levels, which may inform cardiologists when recommending dietary intervention for patients with conditions such as hypertriglyceridaemia (Das et al, 2020). However, the evidence suggests that patients may only benefit from a low-carbohydrate dietary intervention within the short term (<12 months), and thus any recommendations made by clinicians should reflect this (Dong et al, 2020; Naude et al, 2022). The findings also suggest that low-carbohydrate diets may increase high-density lipoprotein cholesterol in the short-term, making low-carbohydrate diets a potential intervention to manage cholesterol levels within the first 6 months (Dong et al, <u>2020</u>). Although the long-term effectiveness of a low-carbohydrate diet in improving cholesterol levels remains unclear, cardiac nurses may use the findings to inform patients of the short-term benefits of a dietary intervention for the early management of cholesterol. However, both cardiologists and cardiac nurses should routinely monitor patients to assess sustainability and side effects of a low-carbohydrate dietary intervention, given the dearth of existing data on adverse events (Naude et al, 2022). Clinicians should actively educate patients about potential side effects of low-carbohydrate dietary interventions, specifically the increased risk of halitosis (as found in one review in this commentary) as this may help to reduce frequent visits to primary healthcare (Naude et al, 2022). With the limited strength of evidence and small effect sizes, clinicals should be cautious to recommend low-carbohydrate diets as the sole approach to reducing cardiovascular risk, but rather they may be implemented to complement existing interventions (ie pharmaceutical intervention, where needed).

In addition to the adverse events reported by the systematic reviews in this commentary, the literature has highlighted other challenges for clinicians to consider before the implementation of a low-carbohydrate diet (Cucuzzella et al, 2019; Churuangsuk et al, 2020; Caroline and Emma, 2021). Several studies have shown that a low-carbohydrate diet often leads to the avoidance of whole grains, starchy vegetables and some fruits, which has the potential to substantially reduce patient's vitamin and mineral intake (dependant on individual food choices) (Palma-Duran et al, 2017; Cucuzzella et al, 2019; Churuangsuk et al, 2020). Cardiologists and cardiac nurses should carefully monitor patients to identify vitamin or mineral deficiencies, and where required, recommend supplementation with a multivitamin (Cucuzzella et al, 2019). Cardiologists and cardiac nurses should give particular consideration to deficiencies associated with thiamine, folic acid, vitamin c, iron and magnesium, as previous evidence has shown that a low-carbohydrate diet may substantially lower the intake of these vitamins and minerals (in the short term) (Gardner et al, 2010; McKenna et al, 2013). In addition to vitamins and mineral deficiencies, clinicians should take care to monitor patients for dehydration, hypovolemia and fatigue, as low-carbohydrate diets have also been found to decrease the reabsorption of sodium and other electrolytes (Cucuzzella et al, 2019). To manage this, patients with a low-carbohydrate diet should be advised to consume around 4–6 grams of salt per day, and supplement where required (Mente et al, 2016).

Most current clinical guidelines do not advocate for low-carbohydrate diets for the purpose of weight reduction and sustained weight reduction (National Institute for Health and Care Excellence, 2014; NHS, 2023). Both the National Institute for Health and Care Excellence (2014) and the NHS (2023) recommend balanced dietary intake that includes fruit, vegetables and meals based on potatoes, bread, rice, pasta and other starchy foods, which are all high in carbohydrates). This dietary advice primarily focuses on reducing calorie intake rather than restricting specific macronutrients (eg carbohydrates), for the purpose of achieving weight reduction and reducing cardiovascular risk (NHS, 2023). However, some organisations such as the Scientific Advisory Committee on Nutrition and The British Dietetic Association actively recommend low-carbohydrate diets (ie consuming between 50–130g carbohydrates daily) for people living with type 2 diabetes (not recommended for general population) for the effective management of weight, improved glycaemic control and cardiovascular risk (British Dietetic Association, 2018; Scientific Advisory Committee on Nutrition, 2021). These recommendations acknowledge that a low-carbohydrate diet may not be effective longer-term, so should only be implemented in the short-term (up to 6 months) (Scientific Advisory Committee on Nutrition, 2021). This aligns with the findings of the included systematic reviews, which showed no evidence of low-carbohydrate diets being effective at reducing weight or improving cardiovascular risk compared to other dietary approaches (eg low-fat diet or balanced carbohydrate diet) in the longer term (>12 months) (Chawla et al, 2020; Dong et al, 2020).

Implications for research

To better understand the safety profile of low-carbohydrate diets for reducing cardiovascular risk and supporting weight loss, further studies are needed that include a larger sample of participants who are representative of the general population. Future studies should explicitly include a range of adverse patient outcomes (such as halitosis, headache, constipation, fatigue). Given the current dearth of data on adverse events, it is important that the safety profile of low-carbohydrate diets is swiftly established, particularly given the recent identification of vitamin and mineral deficiencies associated with the intervention (Gardner et al, <u>2010</u>).

Further research is also needed to explore patient adherence to low-carbohydrate diets and areas for improvement. Previous research has highlighted that cultural, religious and economic barriers often pose substantial challenges to patient adherence of low-carbohydrate diets, but these concerns have yet to be comprehensively explored (Arias-Gastelum et al, 2020; Osman et al, 2020; Kumar et al, 2022). Overcoming barriers to adherence is critical if low-carbohydrate dietary

interventions are to be successful in improving short-term outcomes associated with weight loss and cardiovascular risk factors.

Conclusions

The findings of this commentary provide some modest implications for clinical practice by considering low-carbohydrate diets as a potential short-term intervention for patients seeking weight loss and reduced cardiovascular risk factors. Clinicians must carefully consider the sustainability of these interventions with regard to their longer-term effects and the dearth of evidence relating to adverse patient outcomes. If implemented, cardiologists and cardiac nurses should ensure ongoing monitoring and frequently follow up with patients to assess the effectiveness on health outcomes (particularly longer term, >12 months), while addressing any adverse events that may arise. Further research should focus on developing a core outcome set for future randomised controlled trials, with a particular focus on adverse patient outcomes to establish the safety profile of low-carbohydrate diets for reducing cardiovascular risk factors and supporting weight loss.

Reflective questions

- What factors should be considered when recommending a low-carbohydrate diet for reducing cardiovascular risk and supporting weight loss?
- What are the key limitations of existing evidence relating to the short- and long-term effectiveness of low-carbohydrate diets for reducing cardiovascular risk factors and supporting weight loss?
- What considerations may be made regarding dietary supplementation for patients consuming a low-carbohydrate diet to avoid adverse patient outcomes?

Key points

- 1. Low-carbohydrate diets may have favourable effects on weight loss, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and total cholesterol in the short term (<12 months) when compared to other interventions (ie balanced carbohydrate diet, a low-fat diet or drug intervention).
- 2. The long-term effectiveness (>12 months) of low-carbohydrate diets on outcomes of weight loss, changes in triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and total cholesterol levels remains unclear.
- 3. Further research is needed to establish the safety profile of low-carbohydrate diets for reducing cardiovascular risk and supporting weight loss.
- 4. Health professionals should carefully consider the sustainability of low-carbohydrate dietary interventions with regard to their longer-term effects and the dearth of evidence relating to adverse patient outcomes.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Appendix 1

Table 1.	Characteristic	s and findings o	f the included systematic	reviews			
Study	Population and setting	Intervention and comparator	Outcome	Relative effect (95% CI)	Heterogeneity (12)	Number of studies	GRADE (certainty of evidence)
Chawla	Adults ≥18	Low-	Change in weight (kg):	MD 1.00 (95% CI	88.8%	59	Not
et al,	years of age	carbohydrate	overall	-1.53 to -0.46)	00.070	studies	reported
2020	with no	vs low-fat	Overan	1.55 to 0.40)	0.4.70/	Studies	reported
2020	specific	diets	1.2 .1	MD 0 02 (050/ CI	84.5%	1.7	NT 4
	diseases	413. 15	1–3 months	MD 0.93 (95% CI -1.88 to 0.02)		17	Not
				-1.88 to 0.02)	96.1%		reported
	Setting:		3–6 months			27	
	universities,			MD 1.47 (95% CI	57.4%		Not
	medical		6–12 months	-3.85 to 0.92)		Not	reported
	centres, and				0%	reported	
	research		>12 months	MD 1.30 (95% CI	070	_	Not
	centres		> 12 months	-2.20 to -0.57)		13	reported
						13	
				MD 0.83 (95% CI			Not
				-0.95 to 2.60)			reported
			Change in HDL-C:	MD 0.07 (95% CI	Not reported	Not	Not
			Overall	0.08 to 0.09)	1	reported	reported
					67.2%	_	_
			1–3 months	MD 0.12 (95% CI	07.270	28	Not
			1 5 months	0.08 to 0.15)	56.40/	studies	reported
			3–6 months	0.00 10 0.10)	56.4%	5000105	reported
			5-0 monuis	MD 0.07 (95% CI		22	Not
				0.05 to 0.10)	68.4%	studies	reported
			6–12 months	0.03 to 0.10)		Studies	reported
				3 5 5 6 6 5 6 5 6 5 6 5 6 5 6 5 6 5 6 5	81.5%	4.0	
			>12 months	MD 0.05 (95% CI		18	Not
				0.03 to 0.08)		studies	reported
				MD 0.03 (95% CI		2 studies	Not
				-0.07 to 0.13)			reported
			Change in TC: Overall	MD 0.14 (95% CI	Not reported	Not	Not
				0.08 to 0.19)		reported	reported
			1–3 months		84.4%		
				MD 0.42 (95% CI		23	Not
			3–6 months	0.23 to 0.61)	57.5%	studies	reported
			6–12 months	MD 0.10 (95% CI	49.0%	17	Not
			0 12 months	0.03 to 0.21)	12.070	studies	reported
			>12 months		00/		
	<u> </u>	l	>12 months		0%	l	

Min Min		1	Т	T	T = ==	T	1	Ι
Change in LDL-C: Overall Change in LDL-C: Overall Change in LDL-C: Overall MD 0.11 (95% CI S2,7%6 22 Studies Not reported S2,7%6 S3,1%6 Studies Studies					0.02 to 0.18)		studies	reported
Change in LDL-C: Overall Change in LDL-C: Overall Change in LDL-C: Overall MD 0.11 (95% CI S2,7%6 22 Studies Not reported S2,7%6 S3,1%6 Studies Studies								
Change in LDI-C: Overall 1-3 months MD 0.19 (95% CI 0.25 to 0.52) S2.7% 28 Not reported Not repor							1 study	
Dong Adults 18 Low-care and hospitals Adults 18 Carbohydrate and hospitals Adults 18 Carbohydrate centres, research centres and hospitals Adults 18 Carbohydrate centres, research centres and hospitals Adults 10 Change in TG: Overall Adults 12-23 months Adults 12-23 months Adults 10 Change in TG: Overall Adults 10 Change								
Dong et al. 2020 Adults ≥18 years of age at al. 2020 Setting: Universities, medical centres, research centres and hospitals						Not reported		
1-3 months				Overall	0.07 to 0.11)		reported	reported
Dong et al. 2020 Dong et al. 2020 Dong intervention Change in TG: Overall Dong Secting: Universities, medical centres, research centres and hospitals Dong its						82.7%	•	
Not reported Not				1–3 months				
Adults ≥ R care and hospitals Adul					0.25 to 0.52)	59.1%	studies	reported
Dong et al. 2020 Adults ≥18 years of age (2020 Universities, medical centres, research centres and hospitals Not position				3–6 months	1			
212 months MD 0.07 (95% CI 0% 18 studies Not reported Not reported Not reported 18 studies Not reported N						24.7%		
Setting: Universities, medical exerties and hospitals Setting: Universities, medical exerties and hospitals Setting: Universities, medical exerties and hospitals Setting: Universities and hospitals Setting: Unive				6–12 months	0.06 to 0.22)		studies	reported
Dong ct al, 2020 Adults ≥ 18 ct al, 2020 Setting: Universities, medical centres, research centres and hospitals Nortice and hospitals Nortic						0%	4.0	
Dong et al, 2020 Adults ≥18 years of age at al, 2020 Setting: Universities, medical centres, research centres and hospitals				>12 months				
Dong et al, 2020 Adults ≥18 years of age and lospitals					0.02 to 0.12)		studies	reported
Dong et al, 2020 Adults ≥18 years of age and lospitals								
Change in TG: Overall MD - 0.13 (95% C1 - 0.17 to - 0.09)							2 studies	
Dong et al, 2020 Adults ≥18 years of age 2020 Not reported				Change in TC, Orranall	-0.03 to 0.17)	Not non out od	Not	
Dong et al, 2020 Adults ≥18 (searces centres, research centres and hospitals Adults ≥18 (centres				Change in 10. Overall		Not reported		
Adults 218 Adults 218 2				1.2 4	(1 0.17 to 0.07)	NI 4 1	reported	reported
Adults ≥18 Carbohydrate vs other surgical centres, research centres and hospitals Setting: Universities, medical centres (Carbohydrate vertice) Carbohydrate vs other centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, research centres and hospitals Carbohydrate vs other surgical centres, resear				1–3 months	MD 0.26 (050/	Not reported	20	Not
Dong et al, 2020 Adults ≥ 18 years of age 2020 Universities, medical centres and hospitals Adults ≥ 18 Change in HDL-C; Overall Change in HDL-C; Overall MD -0.17mmol/1 (95% CI -0.13 to -0.01) MD -0.18mmol/1 (95% CI -0.32 to -0.01) MD -0.08mmol/1 (95% CI -0.03) MD -0								
Adults ≥18 Carbohydrate vish no specific diseases Carbohydrate centres, research centres and hospitals Carbohydrate Carbohydrate centres and hospitals Carbohydrate Carbohy				3–6 months	C1 0.54 to 0.16)	Not reported	studies	reported
Adults ≥18 Carbohydrate vish no specific diseases Carbohydrate centres, research centres and hospitals Carbohydrate Carbohydrate centres and hospitals Carbohydrate Carbohy					MD 0.15 (05%		22	Not
Adults ≥18 get al, 2020 Dong et al, 2020 Setting: Universities, medical centres, research centres and hospitals Setting: Universities, medical centres, research centres and hospitals Change in HDL-C: Overall (95% CI - 0.27 to 0.01) MD - 0.08 mmol/l (95% CI - 0.32 to - 0.01) MD - 0.08 mmol/l (95% CI - 0.32 to - 0.01) Setting: With no specific diseases Setting: Universities, medical centres, research centres and hospitals MD - 0.17 mmol/l (95% CI - 0.27 to 0.11) MD - 0.17 mmol/l (95% CI - 0.32 to - 0.01) MD - 0.08 mmol/l (95% CI - 0.32 to - 0.01) MD - 0.08 mmol/l (95% CI - 0.32 to - 0.01) MD - 0.08 mmol/l (95% CI - 0.13 to 0.09) Change in HDL-C: Overall MD - 0.08 mmol/l (95% CI - 0.13 to 0.09) MD - 0.08 mmol/l (95% CI - 0.13 to 0.09) MD - 0.08 mmol/l (95% CI - 0.13 to 0.09) MD - 0.08 mmol/l (95% CI - 0.27 to 0.01) Situdies Teported Not reported Teported Teported Not reported Teported Teporte				6–12 months		Not reported		
Dong et al, years of age with no specific diseases Setting: Universities, medical centres, research centres and hospitals Setting: Universities, medical centres, research centres, resear					C1 0.23 to 0.07)		studies	reported
Dong et al, 2020 Adults ≥18 carbohydrate with no specific diseases Setting: Universities, medical centres, research centres and hospitals Change in HDL-C: Overall MD -0.02mmol/I (95% CI -0.32 to -0.01) MD -0.17mmol/I (95% CI -0.32 to -0.01) Not reported Not r				>12 months	MD 0.10 (05%	Not reported	16	Not
Dong et al, 2020 Adults ≥18 Carbohydrate vs other surgical diseases Setting: Universities, medical centres, research centres and hospitals Change in HDL-C: Overall MD -0.15mmol/l (95% CI -0.23 to -0.07) Change in HDL-C: Overall MD -0.15mmol/l (95% CI -0.23 to -0.07) Change in HDL-C: Overall MD -0.02mmol/l (95% CI -0.32 to -0.15) Town of the studies of the								
Dong Adults ≥ 18 Carbohydrate vision Change in TG: Overall MD - 0.15mmol/1 (95% CI - 0.23 to - vision Carbohydrate vision Carbohydrate vision Carbohydrate vision vision Carbohydrate vision visio					0.10 10 0.01)		Studies	reported
Dong Adults ≥ 18 Carbohydrate vision Change in TG: Overall MD - 0.15mmol/1 (95% CI - 0.23 to - vision Carbohydrate vision Carbohydrate vision Carbohydrate vision vision Carbohydrate vision visio					MD 0 004 (95%		2 studies	Not
Dong et al, 2020 Adults ≥ 18 years of age with no specific diseases Low-companient of the studies or drug intervention Change in TG: Overall (95% CI -0.23 to - 0.07) 75% (11 studies studies studies studies reported studies reported (95% CI -0.32 to - 0.15) 7 studies studies reported (95% CI -0.23 to - 0.15) Not reported (95% CI -0.23 to - 0.15) Not reported (95% CI -0.23 to - 0.15) Not reported (95% CI -0.27 to 0.11) Not reported (95% CI -0.32 to - 0.11) Not reported (95% CI -0.13 to 0.09) Not reported (95% CI -0.32 to - 0.11) Not reported (95% CI -0.13 to 0.09) Not reported (95% CI -0.27 to 0.12) Not reported (95% CI -0.27 to 0.12) Not reported (95% CI -0.27 to 0.12) Not reported (95% CI -0.27 to 0.25) Not reported (95% CI -0.09 to 0.25) Not rep							2 studies	
et al, 2020 years of age with no specific diseases vision or drug intervention 12-23 months 12-23 months MD -0.23mmol/l (95% CI -0.32 to - 0.15) Not reported 6 studies Not reported 6 studies Not reported 6 studies Not reported 12-23 months MD -0.08mmol/l (95% CI -0.32 to - 0.11) Not reported Not repor	Dong	Adults ≥18	Low-	Change in TG: Overall		75%	11	
Setting: Universities, medical centres, research centres and hospitals Change in HDL-C: Overall		years of age			(95% CI -0.23 to -		studies	reported
Specific diseases Surgical diseases Setting: Universities, medical centres, research centres and hospitals Change in HDL-C: Overall Change in HDL-	<u>2020</u>			<6 Months	0.07)	22%		
Setting: Universities, medical centres, research centres and hospitals 12-23 months 12-23			surgical				7 studies	Not
Setting: Universities, medical centres, research centres and hospitals 12-23 months 12-23		diseases		6–11 months	MD -0.23mmol/l	88%		reported
12-23 months 12-2							6 studies	
MD -0.08mmol/1			intervention	12_23 months	0.15)	70%		Not
MD -0.08mmol/l (95% CI -0.27 to 0.11)				12 23 months		7070	6 studies	reported
research centres and hospitals MD -0.17mmol/I (95% CI -0.32 to -0.01) MD -0.02mmol/I (95% CI -0.13 to -0.09) Change in HDL-C: MD 0.1mmol/I (95% CI 0.08 to -0.12) Solve CI -0.12 to -0.12 to -0.01 MD -0.02mmol/I (95% CI 0.08 to -0.12) Solve CI 0.09 to -0.12 to -0.13 to -0.09 to -0.12 to -0.57) MD 0.08mmol/I (95% CI 0.27 to -0.57) MD 0.12mmol/I (95% CI 0.09 to -0.57)				24 months		0%		
Centres and hospitals MD -0.17mmol/1 (95% CI -0.32 to - 0.01) Not reported		/		24 monuis	,	070	3 studies	
MD -0.17mmol/l (95% CI -0.32 to - 0.01)					0.11)		2 Studies	reported
MD -0.02mmol/l (95% CI -0.13 to 0.09)					MD 0.17 17			
MD -0.02mmol/l (95% CI -0.13 to 0.09)								
MD -0.02mmol/l (95% CI -0.13 to 0.09)								reported
Change in HDL-C: MD 0.1mmol/I 41% 10 Not					, , , , , , , , , , , , , , , , , , ,			
Change in HDL-C: MD 0.1mmol/I 41% 10 Not					MD =0.02mmo1/1			
Change in HDL-C: MD 0.1mmol/l 41% 10 Not reported								
Change in HDL-C: MD 0.1mmol/l (95% CI 0.08 to 0.12) 52% 7 studies reported								
Overall (95% CI 0.08 to 0.12) 52% 7 studies reported 6 Months MD 0.08mmol/l (95% CI 0.27 to 0.57) 12–23 months MD 0.12mmol/l (95% CI 0.09 to 0.57) MD 0.12mmol/l (95% CI 0.09 to 0.57) MD 0.12mmol/l (95% CI 0.09 to 0.57) A studies reported reported of studies of studies reported of studies of studies reported of studies of s				Change in HDL-C:		41%	10	Not
<6 Months							studies	reported
Comparison of the content of the c					0.12)	52%		
6–11 months (95% CI 0.27 to 0.57) 7 studies Not reported Not (95% CI 0.09 to 0.57)				<6 Months			7 studies	
6–11 months (95% CI 0.27 to 0.57) 12–23 months (95% CI 0.27 to 0.57) MD 0.12mmol/l (95% CI 0.09 to 0%) 7 studies Not reported						39%		reported
12–23 months MD 0.12mmol/l (95% CI 0.09 to 0% 0% 0% 0% 0% 0%				6–11 months	,		7 studies	
12–23 months MD 0.12mmol/l (95% CI 0.09 to	1				0.57)	46%		
MD 0.12mmol/l (95% CI 0.09 to 0%				12–23 months			6 studies	reported
03/0 CT 0.07 to						0%		
0.15)				24 months		370	3 studies	
					0.13)			
15	Ì		ĺ					Ì

	T T	1	MD 0 121/1	1	I	NI-4
			MD 0.12mmol/l (95% CI 0.08 to			Not reported
			0.15)			reported
			0.13)			
			1/1 0 00 1/1			Not
			MD 0.08mmol/l			reported
			(95% CI 0.04 to			
		Cl	0.12) MD 0.13 mmol/l	30%	9 studies	Not
		Change in TC: Overall	(95%CI 0.08 to	30%	9 studies	reported
			0.19)			reported
		<6 Months	0.17)	15%	4 studies	
			MD 0.01 1/1			Not
		6–11 months	MD 0.21 mmol/l	62%	4 studies	reported
			(95%CI 0.07 to 0.34)			
		12–23 months	0.54)	0%	4 studies	Not
			MD 0 10 1/1			reported
		24 months	MD 0.18 mmol/l	Not reported	2 studies	
			(95%CI 0.09 to			Not
			0.27)			reported
			10000			
			MD 0.05 mmol/l			Not
			(95%CI -0.05 to			reported
			0.14)			
			MD 0.13mmol/l			
			(95%CI -0.06 to			
		Change in I DI C	0.31) MD 0.11 mmol/l	71%	10	Not
		Change in LDL-C: Overall		/1%	studies	
		Overall	(95%CI 0.02 to 0.19)		studies	reported
			0.17)	67%		
		<6 Months	MD 0.22 1/1		7 studies	Not
			MD 0.32mmol/l	79%		reported
		6–11 months	(95%CI 0.14 to 0.49)		7 studies	
			0.49)	0%		Not
		12–23 months	NFD 0.01 1/1		6 studies	reported
			MD 0.01mmol/l	0%		
		24 months	(95%CI -0.16 to 0.10)		3 studies	Not
			0.10)			reported
			NFD 0.01 1/1			
			MD 0.01 mmol/l			Not
			(95%CI -0.08 to 0.10)			reported
			0.10)			
			MD 0.09mmol/l			
			(95%CI -0.02 to 0.19)			
		Change in weight (kg):	MD -1.58kg (95%	49%	9 studies	Not
		Overall	CI -1.58 to -0.75)	1270) studies	reported
				69%	6 studies	-F
		<6 Months	MD -1.14kg	0970	o studies	Not
		>0 IVIOIIIIS	(95%CI -1.65 to -	400/		reported
		6 11 41	0.63)	49%	5 studies	Toponica
		6–11 months	,,,,			Not
			MD -1.73kg (95%	0%	5 studies	reported
		12–23 months	CI -2.7 to -0.76).			reported
			21 2.7 10 0.70).	0%	2 studies	NI-4
		24 months	MD -1.16kg (95%			Not
			CI -2.44 to 0.12)			reported
			2.77 10 0.12)			N
			MD 0 521 (050)			Not
			MD 0.53kg (95%			reported
		Change in CDD.	CI -1.33 to 2.39)	00/	0 ctud:	Not
		Change in SBP: Overall	MD -1.41mmHg (95%CI- 2.26 to -	0%	9 studies	
		Overall	(95%CI- 2.26 to - 0.56)			reported
1			0.50)	0%	7 studies	

		1	I			1	
			<6 Months	MD -2.97mmHg (95% CI -4.62 to -	0%	6 studies	Not reported
			6–11 months	1.31)	19%	5 studies	NI-4
			12–23 months	MD -0.99mmHg (95% CI -2.43 to	0%	3 studies	Not reported
			24 months	0.45)			Not reported
				MD -1.06mmHg (95% CI -2.99 to			Not
				0.88)			reported
				MD -0.39mmHg (95% CI -2.31 to 1.52)			
			Change in DBP: Overall	MD -1.71mmHg (95% CI -2.36 to -	14%	8 studies	Not reported
			<6 Months	1.06)	26%	6 studies	Not
			6–11 months	MD -2.76mmHg (95% CI -4.07 to -	0%	5 studies	reported
			12–23 months	1.46)	0%	4 studies	Not reported
			24 months	MD -2.11mmHg (95% CI -3.28 to - 0.93)	46%	3 studies	Not reported
				MD -0.50mmHg			Not
				(95% CI -2.05 to 1.05)			reported
				MD -1.06mmHg (95% CI -2.33 to 0.20)			
Naude et al, 2022	Adults with BMI >25kgm ²	Low- carbohydrate vs balanced	Change in weight (kg): (at 3 to <12 months)	MD -1.07 kg (95% CI 1.55 to 0.59)	51%	37 studies	Moderate
<u> 2022</u>	with no specific diseases	carbohydrate diet	(at ≥12 months)	MD -0.93 kg (95% CI 1.81 to	40%	14 studies	Moderate
	Setting: outpatient		Change in BMI (kg/m²): (at ≥12	0.04) MD -0.61 kg/m ² (95% CI -0.99 to -	0%	5 studies	Not reported
	clinics and medical		months) Change in SBP	0.23) MD -1.37 mmHg	34%	11	Not
	centres		(mmHg) (at ≥12 months)	(95% CI -2.99 to 0.24)		studies	reported
			Change in DBP (mmHg) (at ≥12 months)	MD 0.09 mmHg (95% CI -1.29 to 1.12)	44%	11 studies	Moderate
			Change in TG (mmol/L) (at ≥12	MD -0.11mmol/L (95% CI -0.16 to -	0%	13 studies	Not reported
			months) Change in HDL-C (mmol/L) (at ≥12	0.06) MD 0.06 mmol/L (95% CI 0.02 to	48%	13 studies	Not reported
			months) Change in LDL-C (mmol/L) (at ≥12	0.10) MD 0.04 mmol/L (95% CI -0.05 to	33%	13 studies	Moderate
			months) Change in TC (mmol/L) (at ≥ 12 months)	0.12) MD 0.01 mmol/L (95% CI -0.1 to 0.12)	41%	11 studies	Not reported
			monuis)	0.12)			

	Adverse events:	RR 1.06 (95% CI	0%	4 studies	Very low
	Constipation (at 3- <12 months)	0.81 to 1.38)			
	monuis)	RR 0.98 (95% CI	Not reported	2 studies	Not
	Diarrhoea	0.33 to 2.93)	Not reported	1 study	reported
	Nausea	RR 0.14 (95% CI	Not reported	1 study	Not reported
		0.01 to 2.65)	•		
	Flatulent	RR 0.68 (95% CI	Not reported	1 study	Not reported
	Heartburn	0.39 to 1.17)	Not reported	1 study	Not
	Halitosis	RR 0.49 (95% CI 0.23 to 1.01)	Not reported	1 study	reported
	Fatigue	RR 1.99 (95% CI	55%	2 study	Not reported
	Headaches	1.32 to 2.99)	Not reported	1 study	Not
	Anxiety	RR 0.80 (95% CI			reported
	Alixiety	0.47 to 1.36)	Not reported	1 study	
	Depressive symptoms	RR 1.25 (95% CI 0.26 to 6.02)	Not reported	1 study	Not reported
	Stomach upsets	,			Not
		RR 1.00 (95% CI 0.07 to 15.26)			reported
		,			Not
		MD -0.30 (95% CI -1.36 to 0.76)			reported
		C1 -1.30 to 0.70)			Not
		RR 1.00 (95% CI 0.41 to 2.45)			reported

^{*} MD = mean difference, RR = risk ratio, mmol/l = millimoles per litre, mmHg = millimetre of mercury, KG = kilogram, TC = total cholesterol, TG = triglycerides, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, CI = confidence interval, GRADE = grading of recommendations assessment, development and evaluation.