

## Letter to the Editor

# The cardiovascular risk reduction benefits of a low-carbohydrate diet outweigh the potential increase in LDL-cholesterol

The recent meta-analysis performed by Mansoor *et al.*<sup>(1)</sup> comparing the effect of low-carbohydrate (LC) and low-fat (LF) diets on weight loss and CVD risk factors is a welcome addition to the field. A number of meta-analyses comparing LC diets with other dietary protocols used to manage cardiometabolic disease risk have been published recently<sup>(2–4)</sup>. However, one particular problem with meta-analyses such as these involves the definition of 'low carbohydrate' in terms of percentage of energy or total daily intake in grams. In addition, differences between diets are likely to only be seen when the difference in carbohydrate or fat intakes between groups is large enough<sup>(4,5)</sup>. By applying a stricter definition of what constitutes a LC diet, Mansoor *et al.*<sup>(1)</sup> have been able to more robustly determine some of the effects of what many people would consider a true LC diet over a relatively long period of time ( $\geq 6$  months). These effects include greater weight loss and reduction in TAG levels, alongside an increase in both LDL- and HDL-cholesterol compared with the LF groups. Looking at the overall effect of LC diets, we disagree with the authors' conclusions that the benefits of LC diets on CVD risk factors are outweighed by a potential increase in 'highly atherogenic' LDL-cholesterol. The reasons for this are 2-fold:

1. Using LDL-cholesterol as a predictor of CVD risk has several limitations. The generation of atherogenic subfractions of LDL also appear to be reduced by interventions that improve insulin resistance (IR), such as adoption of the LC diet.
2. The benefits seen in terms of greater weight loss, greater increase in HDL-cholesterol and greater reduction in TAG on the LC diet are indicative of a greater effect on the metabolic dysregulation that appears to underlie the atherogenic dyslipidaemia typical of IR and the metabolic syndrome (MS).

The main reason why Mansoor *et al.*<sup>(1)</sup> appear to be concerned about the use of LC diets in the setting of CVD risk is the small, but significant, increase in LDL-cholesterol found in their meta-analysis. Interestingly, the assertion made by the authors that LDL-cholesterol is associated with increased CVD risk is based on two review papers from the stable of Krauss<sup>(6,7)</sup>. Nowhere in either paper is LDL-cholesterol mentioned as a strong predictor of CVD. Instead, much more appropriately, other characteristics of atherogenic dyslipidaemia are highlighted in these papers, especially in the context of IR and MS. This dyslipidaemia includes elevation of TAG-rich lipoproteins and atherogenic subfractions of LDL-cholesterol (such as a preponderance of small, dense LDL particles or sdLDL), and is

partly reflected by raised TAG and reduced HDL-cholesterol. In fact, Krauss & Siri<sup>(7)</sup> (reference 19 in the paper by Mansoor *et al.*<sup>(1)</sup>) show that levels of TAG and the TAG:HDL-cholesterol ratio are better indicators of an atherogenic LDL phenotype (also known as pattern B) than LDL-cholesterol, and suggest that high-carbohydrate, LF diets are in fact a risk factor for atherogenic LDL. A more recent review from the Krauss group also warned against the replacement of SFA with carbohydrates, as is the standard approach in LF diets. Carbohydrates, particularly refined and processed carbohydrates, may exert more deleterious effects on CVD than SFA<sup>(8)</sup>. This is at least in part because LDL pattern B appears to increase with percentage of energy from carbohydrates<sup>(8)</sup>. On the basis of the limited (but widely available) lipid metrics analysed by Mansoor *et al.*<sup>(1)</sup>, the increased HDL-cholesterol and decreased TAG seen in the LC groups, alongside a fairly negligible relative contribution of risk from LDL-cholesterol, would therefore suggest that LC diets are likely to improve CVD risk compared with LF diets.

Multiple lines of evidence suggest that LDL-cholesterol is a relatively poor marker of CVD risk. This includes one very large study of patients hospitalised with CVD, almost 50% of whom had LDL-cholesterol levels within the 'optimal' range ( $<100$  mg/dl or  $2.6$  mmol/l)<sup>(6)</sup>. Recent data also have found that VLDL-cholesterol or remnant cholesterol is a stronger promoter of atherosclerosis than LDL-cholesterol<sup>(9)</sup>. Owing to their larger size, remnants carry five to twenty times more cholesterol per particle than LDL-cholesterol. Traditional total LDL-cholesterol is calculated rather than directly measured and non-HDL-cholesterol (total cholesterol – HDL-cholesterol), which includes TAG carried on VLDL, is also considered a more robust marker for CVD risk<sup>(10,11)</sup>. However, rather than focusing on individual lipid parameters, a much more important approach would be to intervene in a way that affects the underlying aetiology of CVD, which, particularly in patients with obesity or MS, is increasingly thought to be caused by IR and hyperglycaemia<sup>(12)</sup>. IR increases CVD risk independent of more classical CVD risk markers such as dyslipidaemia, and is the major driving force behind development of those risk factors<sup>(12,13)</sup>. As discussed above, adopting the LC diet is more likely to induce a shift away from LDL pattern B as well as improve other indicators of IR such as low HDL-cholesterol, high TAG and weight gain. Importantly, at least one small trial of LC in obese participants with type 2 diabetes (T2DM) showed improvements in risk profile, and no evidence of negative effects or CVD, for up to 44 months<sup>(14)</sup>.

The potential benefits of the LC diet for CVD risk become even more important in relation to two more highly atherogenic subfractions of LDL – glycated LDL (glycLDL) and oxidised LDL (oxLDL); oxLDL is more likely to accumulate within the arterial intima than LDL-cholesterol in general, and measurement of oxLDL far outperforms more standard lipid parameters (including LDL-cholesterol, HDL-cholesterol, TAG and their ratios) in terms of CVD prediction<sup>(15–17)</sup>. The sdLDL associated with LDL pattern B is more likely to be glycated to glycLDL<sup>(18,19)</sup>. In turn, glycLDL is more likely to be oxidised to oxLDL<sup>(20)</sup>. As IR both prolongs the circulation time of LDL-cholesterol and increases the proportion of sdLDL, the combination will lead to an increase in glycation of sdLDL and subsequent oxLDL production<sup>(21,22)</sup>. Compared with LF, LC diets provide greater improvements in the parameters associated with IR, and are also associated with improved glycaemic control<sup>(14)</sup>. In addition, IR, MS and T2DM are associated with inflammation and oxidative stress that lead to a dysfunctional HDL-cholesterol phenotype, which is an independent risk factor and predictor of CVD<sup>(23)</sup>. Compared with LF diets, LC diets address underlying IR, and can produce greater reductions in inflammatory burden<sup>(24,25)</sup>. Therefore, LC diets can reduce the production of the most atherogenic subtype of LDL (sdLDL), minimise subsequent glycation and oxidation of those LDL particles and prevent HDL-cholesterol dysfunction, slowing the initiation and progression of atherosclerosis in those at greatest risk of CVD.

This view is supported by a meta-analysis performed by Sackner-Bernstein *et al.*<sup>(3)</sup>, who compared LC *v.* LF diets among overweight and obese individuals. They used a shorter minimum intervention time (8 weeks) compared with the study by Mansoor *et al.*<sup>(1)</sup>, but nevertheless describe a likely benefit of the LC diet compared with the LF diet. This was determined by assessing the between-treatment changes in factors that affect the atherosclerotic CVD (ASCVD) risk score (age, total cholesterol, HDL-cholesterol and systolic blood pressure). The likelihood of greater benefit from the LC diet was more than 98% in all analysed subgroups (stratified by CVD risk and race). Although they admit that the ASCVD score is not perfect, it allowed them to move ‘beyond the crude estimates possible from focus on an individual parameter such as HDL-cholesterol or LDL-cholesterol’. This is important because the risks and diagnoses of cardiometabolic diseases (including obesity, T2DM and CVD) are multi-factorial, and any treatment approach must similarly have a multi-factorial effect. This is one reason why targeted changes in just LDL-cholesterol or HDL-cholesterol using pharmacological interventions have shown surprisingly small effects on the absolute risk of CVD outcomes<sup>(26,27)</sup>. Although statins lower LDL-cholesterol, their beneficial effects may be mediated through other mechanisms, such as attenuating inflammation and oxidative stress<sup>(28)</sup>. Targeted LDL-cholesterol lowering is also significantly less successful at reducing CVD events compared with targeting LDL particles<sup>(29)</sup>. In fact, randomised studies of dietary approaches that lower LDL-cholesterol have also not been shown to affect the risk of cardiovascular events<sup>(30,31)</sup>.

We agree with the authors that trials looking at hard end points (such as CVD mortality) would be ideal in order to truly

discern optimal macronutrient compositions for those at risk of CVD. However, as randomised controlled trials of the sufficient length and magnitude are unlikely to ever be performed, we must apply a broad range of evidence, including the current meta-analysis, to help ascertain the effect of dietary manipulations on CVD risk. Although the exact mechanisms of LC diets (improved insulin dynamics, spontaneous reduction in energy intake, increased protein intake, etc.) are still debated, and they are by no means a panacea, the most robust effect of any single long-term dietary intervention in terms of improvement in parameters of IR, dysglycaemia, atherogenic lipidaemia and CVD risk, is the restriction of carbohydrate intake<sup>(5,14,25)</sup>. Despite the authors’ conclusions to the contrary, we believe that the current meta-analysis supports this premise.

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The authors would like to apologise to steak and butter, and welcome them back to the dinner table.

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