

Response to Letter to the Editor

Low-carbohydrate diets increase LDL-cholesterol, and thereby indicate increased risk of CVD

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We would like to thank Wood *et al.*⁽¹⁾ for their comments on our recent meta-analysis ‘Effects of low-carbohydrate diets *v.* low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials’⁽²⁾. We appreciate their valuable contributions, but would like to clarify certain points of the arguments presented.

In the meta-analysis, we found that subjects consuming a low-carbohydrate diet (LC diet) had more favourable changes in HDL-cholesterol and TAG levels, but less favourable changes in LDL-cholesterol levels, compared with subjects consuming a low-fat diet (LF diet). On the basis of these findings and the previously established atherogenic properties of LDL-cholesterol, we cautioned against routinely recommending a LC diet to the general public to induce weight loss and reduce CVD risk factors.

Wood *et al.*⁽¹⁾ challenge these views by (1) suggesting that LDL-cholesterol is a limited predictor of CVD risk, and (2) that despite increases in LDL-cholesterol the overall effects of the LC diet (increased HDL-cholesterol and decreased TAG) indicate the better alternative for improving metabolic dysregulation.

First, based on current evidence, we do not agree that LDL-cholesterol is a limited predictor of CVD risk. Studies have demonstrated that LDL-cholesterol is the main culprit in instigating plaque formation and producing atherosclerosis, and that other risk factors such as smoking, high blood pressure, diabetes and other genetic factors, some of which are poorly understood, contribute to increased plaque formation^(3,4). Illustrative of this point is familial hypercholesterolaemia (FH), a disorder in which genetic mutations usually cause defective LDL receptors, and thereby greatly increase plasma concentrations of LDL-cholesterol; excessive circulating LDL-cholesterol contributes to increased deposits in the arterial walls, creating plaques, thus resulting in early-onset CVD⁽⁴⁾. Furthermore, also supporting the notion that LDL-cholesterol is a major factor associated with CVD are the effects observed in subjects on lipid-lowering therapy; major randomised-clinical trials (RCT) in which subjects at high risk of heart attacks were treated with statins, lowering LDL-cholesterol, showed significant reduction in the number of myocardial infarction events and even all-cause mortality^(5–8). A valuable observation is that despite subjects fulfilling several other risk factors for CVD (diabetes,

hypertension, smoking, etc.) the reduction in relative risk was in the end similar regardless of other risk factors^(4,5). Meta-analyses also support these findings^(9,10). Wood *et al.*⁽¹⁾ speculate whether the effects of statins reducing the number of events on hard end points may be caused by the so-called pleiotrophic effects. However, lovastatin, simvastatin, atorvastatin, fluvastatin, pravastatin, pitavastatin and rosuvastatin are different molecules with a range of different metabolic properties. Some are water soluble, some lipid soluble and some are metabolised to active components. Nonetheless, these molecules share one important property – they all inhibit the hydroxy-methyl CoA reductase – which is the rate-limiting enzyme in cholesterol synthesis. Many lines of evidence document that their anti-atherogenic properties rely on their ability to reduce LDL-cholesterol⁽⁴⁾. Lowering LDL-cholesterol by blocking intestinal cholesterol uptake with ezetimibe has also demonstrated significant reduction in hard end points, providing evidence that reduction of LDL-cholesterol is a key factor⁽¹¹⁾. In addition, LDL-cholesterol can be reduced by several SNP, and studies exploring genetic variations or Mendelian randomisation studies have shown that such SNP cause reduced risk for atherosclerosis^(4,12–15).

Wood *et al.*⁽¹⁾ focus on how dietary intervention such as the LC diet limits the production of the more atherogenic small-dense (sd) LDL-cholesterol, in favour of large/buoyant and supposedly far less atherogenic (ld) LDL-cholesterol. We agree that particle size and density are interesting in terms of CVD risk, but the evidence to support this argument is scarce with very few metabolic studies exploring the impact of LDL phenotype in response to dietary intervention⁽¹⁶⁾. With regard to our meta-analysis, only one study commented on LDL particle size⁽¹⁷⁾, and therefore we cannot draw any conclusions regarding this argument. However, to emphasise their point, Wood *et al.*⁽¹⁾ cite a known review article on clinical significance of LDL heterogeneity⁽¹⁸⁾, but leave out the part in which the authors of this review also emphasise that, although sd-LDL-cholesterol has been associated with increased risk of CVD, evidence also suggest that ld-LDL-cholesterol is associated with CVD (i.e. both ends of the size spectrum). This is further supported by findings in subjects with FH, where ld-LDL-cholesterol is known to be the dominant phenotype⁽¹⁹⁾. Importantly, although dietary interventions might influence

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particle size, other factors such as age, sex, medication and genetic predispositions are also contributing factors in determining the predominant LDL phenotype in an individual⁽¹⁸⁾. With this in mind, it is difficult to understand why Wood *et al.*⁽¹⁾ can support a LC diet, when the evidence on the beneficial effects of alterations in phenotype so far has been ambiguous and inconclusive. In contrast to the arguments presented by Wood *et al.*, the use of particle size in clinical practice to quantify risk of CVD has been considered, but has so far been disregarded because of its failure to prove superiority to the lipid risk factors we use today. Several demonstrations indicate that particle size comes second to predict risk, whereas both sd-LDL- and ld-LDL-cholesterol are atherogenic^(3,18,20,21) and contribute to increased levels of LDL-cholesterol, and thereby increase CVD risk. Owing to the lack of evidence supporting the benefit in establishing particle size, it is currently not standard practice to determine a person's LDL phenotype before recommending a specific diet in clinical practice, nor are there established guidelines or reference ranges for recommended levels of different LDL phenotypes. Thus, we question whether it is medically responsible to recommend a diet to the general public that has repeatedly shown to increase LDL-cholesterol levels, when the evidence suggests that increased and high LDL-cholesterol (regardless of particle size) predispose for CVD.

This brings us to the second point from Wood *et al.*⁽¹⁾, that increased levels of HDL-cholesterol, decrease in TAG and a 2 kg greater weight loss in LC dieters in our meta-analysis is convincing evidence that the LC diet improves metabolic dysregulation. Numerous studies have examined the association of increased HDL-cholesterol in plasma with CVD, both as a consequence of genetic mutations in Mendelian randomisation studies and as a consequence of pharmacotherapy, and the authors have similarly concluded that increasing the levels of HDL-cholesterol in plasma does not decrease the risk of CVD^(22–26). Furthermore, the importance of TAG has not been proven to be an independent risk factor. Both epidemiological studies⁽²⁷⁾, and now a recent Mendelian randomisation study as well⁽²⁸⁾, have indicated association of increased levels of TAG with CVD^(27–29). However, clinical trials examining the effects of lowering TAG and how this directly translates to reduction in CVD, when HDL-cholesterol is adjusted for, are lacking⁽³⁾. Thus, we need RCT testing the effects of TAG-lowering therapy, before we have any evidence that reduction in TAG reduces CVD risk. Studies are currently being conducted to examine the effect of TAG on CVD risk. Why Wood *et al.* are willing to accept the uncertainties of these findings and the lack of supporting data as evidence of their theory is not clear to us.

Overall, evidence so far supports that increased LDL-cholesterol is a causal factor for atherosclerosis and an independent risk factor for CVD. On the other hand, evidence that increasing HDL-cholesterol reduces CVD risk is lacking, and clinical RCT on the independent effects of lowering TAG on CVD risk is non-existing. Thus, based on current evidence, we do not find any good reasons to encourage clinicians to uncritically recommend a LC diet to overweight and obese patients to induce weight loss.

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