LIPIDS AND CARDIOVASCULAR DISEASE

Diet, exercise and weight loss and dyslipidaemia

Peter M. Clifton

Alliance for Research in Exercise, Nutrition and Activity (ARENA), Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia

Summary

There is a large amount of controversy relating dietary fat intake and coronary artery disease. It has been strongly suggested that saturated fat is not harmful and that polyunsaturated fat is either not beneficial or even harmful. Given that dietary lipids and fibre can influence serum lipids which are strongly linked to the risk of coronary artery disease I have reviewed recent evidence linking diet and serum lipids to confirm a diet-heart disease link. Over 84 studies have been included in a recent meta-analysis and meta-regression which examined the effects of changes in fat type on lipid levels. An absolute 1% reduction in saturated fat or trans fat intake as a percentage of energy with replacement by n-6 polyunsaturated fat would lead to a reduction in low density lipoprotein (LDL) cholesterol of 0.05 mmol/L. In most Western countries the difference in intake between the highest quintile and the lowest quintile of saturated fat is about 7%, so moving from the highest to the lowest quintile should lower LDL cholesterol by 0.35 mmol/L or about 10%. This change should lower cardiovascular disease rates by at least 10%. Replacing this amount of saturated fat with carbohydrate of average quality would lower LDL cholesterol by 0.21 mmol/L and increase fasting triglyceride by 0.17 mmol/L. This combination of effects would have a neutral effect on cardiovascular disease rates. However, replacement of trans fat appears to reduce disease rates and total mortality. Substituting low glycaemic index carbohydrates for high glycaemic index carbohydrates will lower triglyceride by 15−25% and reduce cardiovascular risk. Large doses of fish oil will lower triglyceride with a mean lowering of 0.45 mmol/L for a 3.5 g/day amount. Large doses of soluble fibre (3.5−7.0 g/day) lower LDL cholesterol by 0.2−0.35 mmol/L with Konjac glucomannan being the most effective per gram. Plant sterols or stanols lower LDL cholesterol by about 10% for a 2 g/day dose, while exercise and weight loss lower cardiovascular risk predominantly by lowering fasting triglyceride. In conclusion, diet lowers LDL cholesterol and triglyceride and dietary changes should be ultimately linked to a reduced risk of heart disease.

INTRODUCTION

There is a large amount of controversy relating dietary fat intake and coronary artery disease and it has been strongly suggested that saturated fat is not harmful and that polyunsaturated fat is either not beneficial or even harmful. Given that dietary lipids and fibre can influence serum lipids which are strongly linked to the risk of coronary artery disease I have reviewed recent evidence linking diet and serum lipids to confirm a diet-heart disease link.

GENERAL CONSIDERATIONS

Lipid changes in response to diet occur quickly and in 2 weeks 80% of the maximal effect is seen with no further change beyond 4 weeks. If diet is maintained, then the effect on lipid levels is persistent long term. Regardless of the background diet or if the study is parallel or crossover, contrasting the effect of two diets on lipids at the end of 4 weeks is more than adequate to see a clear effect.[1,2] Washout periods are not required. Age, body mass index (BMI), or ethnicity appear not to interact with responses. Although non-high density lipoprotein (HDL) cholesterol and apoB, the major apolipoprotein in low density lipoprotein (LDL) and a marker of LDL particle number, are better markers of risk than LDL cholesterol, there are insufficient data to draw any useful conclusions about these markers from dietary or exercise interventions.

DIETARY FAT AND LIPIDS AND LIPOPROTEINS

Saturated, n-6 polyunsaturated and monounsaturated fat

In normal healthy subjects the effects of saturated, polyunsaturated fat and monounsaturated fat are well described in a meta-analysis of 60 clinical trials published in 2003 by Mensink *et al.*[1] and in an updated review of 84 clinical trials in 2016.[2] In this recent paper, 1% of energy from saturated fat elevated LDL cholesterol by 0.03 mmol/L when it replaced carbohydrate, while n-6 polyunsaturated fat lowered LDL cholesterol by 0.02 mmol/L when it replaced carbohydrate. HDL cholesterol was elevated by about 0.01 mmol/L by saturated and unsaturated fat in comparison with carbohydrate. Thus, an absolute 10% energy reduction in saturated fat (a very large dietary change) and replacement of this fat entirely with n-6 polyunsaturated fat would lower LDL cholesterol by 0.5 mmol/L or about 14−15%. If the 10% saturated fat were replaced entirely by carbohydrate then LDL cholesterol would fall by 0.3 mmol/L, HDL cholesterol would fall by 0.1 mmol/L

and triglyceride levels would rise by 0.24 mmol/L. A summary of dietary and exercise effects is shown in Table 1.

Given that LDL cholesterol is a very strong predictor of coronary risk both from genetic studies examining high or low lifetime levels of LDL cholesterol[3,4] and interventions with statins and other drugs,[5] it would be expected that reducing LDL cholesterol by reducing saturated fat should be associated with a reduction in cardiovascular disease (CVD) risk. However, the data are not at all clear in healthy people, especially when saturated fat is replaced by carbohydrate. It would appear that CVD risk is unchanged, possibly due to the elevation of triglyceride.[6–8] However, replacement of saturated fat with unsaturated fat or high quality, fibre-rich carbohydrate is associated with a reduction in CVD risk.[9–11] Genetic differences in HDL cholesterol levels are not associated with CVD risk,[12–15] nor are drug-induced changes,[16–18] so any diet changes in HDL cholesterol are unlikely to be related to CVD risk either. In 102 cohorts[19] it was found that a 16% increase in triglyceride of about 0.25 mmol/L was associated with an increase in CHD of 18%. Thus, an absolute 10% drop in saturated fat intake should decrease CVD events by 7% for the reduction in LDL cholesterol[20] and increase CVD events by 9–18% for the elevation in triglyceride.[19] Similarly, calculating risk based on glycaemic load, an absolute 10% increase in carbohydrate (50 g in a 2000 kcal diet, which is about a 40–50 U glycaemic load increase) could increase CVD risk by 14–18%.[21] Another consideration is that an increase in carbohydrate leads to a smaller LDL particle size and more LDL particles for the same level of LDL cholesterol via the increase in triglyceride, plus an increase in lipoprotein (a) [Lp(a)].[22]

Thus, it is clear why replacing saturated fat with high glycaemic index, low fibre containing carbohydrate, such as sugar or refined starch, is of little benefit in reducing CVD risk. However, the Nurses' Health Study has shown that replacing saturated fat with fibre-rich, high quality carbohydrate does reduce CVD risk.[9]

Overall, replacing saturated fat with unsaturated fat without a change in carbohydrate intake has added benefit in terms of a lower LDL cholesterol with no change in triglyceride or Lp(a).

Trans fatty acids

Replacing trans fat with unsaturated fat will lower LDL cholesterol even more than replacing saturated fat with unsaturated fat,[1,23] but the effects on event rates in cohort studies would suggest that trans fats have effects beyond just LDL cholesterol.[8,9,24,25] The HDL cholesterol lowering seen with industrial trans fats is a very unusual response to fat, and even if not on the causal pathway of increased risk, may indicate the unusual metabolic responses to this fat. ApoA-I, the major apolipoprotein of HDL, also falls. Trans fats also increase Lp(a).[25]

Dietary cholesterol

Dietary cholesterol statistically significantly increased both serum total cholesterol in 17 trials (net change 0.3 mmol/L) and LDL cholesterol in 14 trials (net change 0.2 mmol/L), for an average cholesterol increase of 300 mg/day. Dietary cholesterol did not significantly change serum triglycerides or very low density lipoprotein (VLDL) concentrations.[26,27]

Epidemiology of cholesterol intake and CVD

Despite the limited effect of dietary cholesterol on fasting lipids, egg consumption of one per day doubles the risk of coronary heart disease in women and all cause mortality in men with type 2 diabetes, compared with an intake of one egg per week.[28,29] The incidence of type 2 diabetes is also increased with higher egg intake.[30,31]

Although there is now considerable controversy about the role of dietary saturated fat and cholesterol in promoting CVD in healthy people, the data in people with type 2 diabetes are relatively clear in the US Nurses' Health Study.[32] Between 1980 and 1998, 619 new cases of CVD (non-fatal myocardial infarction, fatal coronary heart disease, and stroke) occurred in 5672 women with type 2 diabetes. The relative risk (RR) of CVD for an increase of 200 mg cholesterol/1000 kcal was 1.37 (p=0.003). Each 5% of energy intake from saturated fat, as compared with equivalent energy from carbohydrates, was associated with a 29% greater risk of CVD (risk ratio 1.29, p=0.04). The Keys score [1.26 × (2 × % saturated fat − % polyunsaturated fat) + 1.5 × square root dietary cholesterol in mg] was the most powerful predictor after multivariate adjustment (p=0.001). The ratio of polyunsaturated to saturated fat was inversely associated with the risk of fatal CVD (p=0.007). Replacement of 5% of energy from saturated fat with an equivalent energy from monounsaturated fat was associated with a 37% lower risk of CVD.

Table 1   Effects of diet, weight loss and exercise on lipid levels

Intervention	Dose	LDL-C	TG	Comments
Saturated fat replaced by CHO	10% of energy	−0.3 mmol/L	+0.17−0.25 mmol/L	
Trans fats replaced by CHO	10% of energy	−0.3 mmol/L	+0.17−0.25 mmol/L	Effect on CVD risk greater than lipid changes
n-6 polyunsaturated fat replaced by CHO	10% of energy	+0.2 mmol/L	+0.17−0.25 mmol/L	
n-3 polyunsaturated fat	3.5 g/day	+0.11 mmol/l	−0.45 mmol/L	No other diet changes
Plant sterols/stanols	3 g	−12% (0.3 mmol/L)	No change	
Dietary cholesterol	300 mg/day	+0.2 mmol/L	No effect	
Oat β-glucan	3.5 g/day	−0.19 mmol/L	No effect	
Barley β-glucan	6.9 g/day	−0.25 mmol/L	No effect	
Konjac glucomannan	3 g/day	−0.35 mmol/L	−23%	Meta-analysis did not examine TG
Exercise	Very variable dose	−3% (0.1 mmol/L)	−5% (0.08 mmol/L)	
Weight loss	5%	−0.2 mmol/L	−0.13 mmol/L	
Meal timing		−13.5% nibbling vs gorging	No change	No weight loss

CHO, carbohydrate; CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; TG, triglyceride.

Despite the association with CVD, interventions have shown no effect of dietary cholesterol on lipids in people with type 2 diabetes.[33]

Fish oil

Replacing saturated fat with n-3 polyunsaturated fat will lower LDL cholesterol as expected, but the effect will be weaker than that seen with n-6 polyunsaturated fat, probably because n-3 fats lower triglyceride by enhancing the conversion of VLDL to LDL.[34] A Cochrane meta-analysis in 2008[35] examined 23 randomised controlled trials: 1075 of the participants had type 2 diabetes with a mean treatment duration of 8.9 weeks. The mean dose of omega-3 polyunsaturated fatty acids (PUFA) used in the trials was 3.5 g/day added to their usual diet. Among those taking omega-3 PUFA triglyceride levels were significantly lowered by 0.45 mmol/L ($p<0.00001$) and VLDL cholesterol lowered by 0.07 mmol/L ($p=0.04$). LDL cholesterol levels were raised by 0.11 mmol/L ($p=0.05$). No significant change in levels of total or HDL cholesterol, HbA1c, fasting glucose, fasting insulin or in body weight was observed. The decrease in VLDL cholesterol levels was significant only in trials of longer duration and in hypertriglyceridaemic patients.

PLANT STEROLS

Plant sterols are the plant equivalent of cholesterol and are found in cell walls and membranes. They differ from cholesterol by small changes to the side chain. They can be found naturally in oil seeds and cooking oils and are a normal part of the diet, up to 400–800 mg/day. Stanols are structurally the same as sterols except for the removal of a double bond in the cholesterol nucleus. Foods such as milk, margarine, orange juice, cheese and chocolate are currently supplemented with sterols or stanols and deliver 2–2.5 g/day when consumed as directed.

Ras *et al.*[36] examined 124 studies with 201 strata testing plant sterols and stanols. Plant sterols and stanols were administered in 129 and 59 strata, respectively; the remaining used a mix of both. The average phytosterol dose was 2.1 (range 0.2–9.0) g/day. Phytosterol intakes of 0.6–3.3 g/day were found to gradually reduce LDL cholesterol concentrations by, on average, 6–12%. When plant sterols and stanols were analysed separately, clear and comparable dose-response relationships were observed. The LDL cholesterol lowering effect of both plant sterols and stanols continues to increase up to intakes of approximately 3 g/day to an average effect of 12%.

CARBOHYDRATES

Sugar

In a meta-analysis Te Morenga *et al.*[37] found that higher compared with lower sugar intakes significantly raised triglyceride concentrations [mean difference (MD) 0.11 mmol/L, $p<0.0001$], total cholesterol (MD 0.16 mmol/L, $p<0.0001$), and LDL cholesterol (MD 0.12 mmol/L, $p=0.0001$). Potential explanatory factors, including a weight change, in most instances explained <15% of the heterogeneity between studies ($I^2 = 36$–75%). Despite this, it would appear the explanation for a rise in LDL cholesterol was an accompanying increase in saturated fat along with the increase in sugar, as HDL cholesterol also increased.

Glycaemic index

In a meta-analysis of 28 trials comparing high to low glycaemic index diets Goff *et al.*[38] found that LDL cholesterol was lowered by 0.16 mmol/L with no effect on HDL or triglycerides.

Fibre

Oat β-glucan

Ho *et al.*[39] examined 58 trials with 3974 participants and found a median dose of 3.5 g/day of oat β-glucan significantly lowered LDL cholesterol (−0.19 mmol/L, $p<0.00001$), non-HDL cholesterol (−0.20 mmol/L, $p<0.00001$), and apoB (−0.03 g/L, $p<0.0001$ compared with control interventions. There was evidence for considerable unexplained heterogeneity in the analysis of LDL cholesterol ($I^2 = 79\%$) and non-HDL cholesterol ($I^2 = 99\%$).

Konjac glucomannan

Ho *et al.*[40] examined twelve studies ($n = 370$), eight in adults and four in children, and found Konjac glucomannan (average 3 g/day) significantly lowered LDL cholesterol (MD −0.35 mmol/L, $p<0.001$) and non-HDL cholesterol (MD −0.32 mmol/L, $p<0.001$. Data from six trials suggested no significant impact of Konjac glucomannan on apoB (−0.05 g/L, $p=0.2$), but there were limited data and considerable heterogeneity, so more trials are required.

Barley β-glucan

Fourteen trials ($n = 615$) were included in the final analysis.[41] A median dose of 6.5 and 6.9 g/day of barley β-glucan for a median duration of 4 weeks significantly reduced LDL cholesterol (MD −0.25 mmol/L) and non-HDL cholesterol (MD −0.31 mmol/L), respectively, with no significant changes to apoB levels, compared with control diets. There was evidence of considerable unexplained heterogeneity in the analysis of non-HDL cholesterol ($I^2 = 98\%$).

EXERCISE

Kelley examined six trials with 788 men and women and found that exercise lowered triglyceride only, while diet and a combination of diet and exercise lowered LDL more than exercise alone.[42] In trials examining exercise only, and in women only, it lowered LDL by 3% and triglyceride by 5%.[43] Exercise seems to be particularly valuable in reducing the rise in triglyceride seen when fat is reduced and replaced by carbohydrate both in the fasting and postprandial state.[44,45]

WEIGHT LOSS

Dattilo and Kris-Etherton[46] performed a meta-analysis of 70 weight loss studies examining the effect of weight loss on blood lipids and lipoproteins. Weight loss led to significant decreases $p<0.001$ in total cholesterol, LDL cholesterol, VLDL cholesterol and triglyceride with modest correlations between extent of weight loss and change accounting for 9–14% of the variance in the lipids. Composition of the weight loss diet was not analysed nor was the effect of continuing energy restriction versus energy balance for these lipid species. Lipids may not change if there has been a partial weight regain or a return to an adverse diet. In a review of 83

studies with measured cardiovascular factors, interventions causing weight loss overall lowered LDL cholesterol by 0.2 mmol/L and triglyceride by 0.13 mmol/L.[47] In a review of five trials that examined different macronutrient composition in weight loss, low carbohydrate diets led to a greater triglyceride reduction at 6 months (0.25 mmol/L difference between diets) but a reduced LDL cholesterol reduction (0.14 mmol/L difference between diets).[48]

In a cohort of 1388 obese children treated for 1 year with weight loss, triglycerides were reduced by 2.3 mg/dL (0.03 mmol/L) per 0.1 BMI standard deviation score (SDS) reduction.[49]

TIME DEPENDENT EFFECTS

Jenkins *et al.*[50] found that hourly nibbling versus three standard meals/day reduced LDL cholesterol by 13.5%. This probably occurred because more calories were taken in the first half of the day. Jakubowicz *et al.* fed a weight reducing diet contrasting a 700 kcal breakfast with a 700 kcal dinner and found triglyceride reduction was greater with the former by nearly 50%.[51] However, others have found no effects on lipids swapping lunch for dinner.[52]

CONCLUSIONS

Changes in dietary fat and fibre intake and weight loss lower LDL cholesterol, while weight loss and exercise and lower carbohydrate diets lower serum triglyceride. Both of these changes should reduce the risk of heart disease.

Address for correspondence: Prof Peter Clifton, Alliance for Research in Exercise, Nutrition and Activity (ARENA), Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, PO Box 2471, Adelaide, SA 5000, Australia. E-mail: Peter.clifton@unisa.edu.au

References

1. Mensink RP, Zock PL, Kester AD, *et al*. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003; 77: 1146−55.
2. Mensink RP. *Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis*. Geneva: World Health Organisation, 2016.
3. Kent ST, Rosenson RS, Avery CL, *et al*. PCSK9 loss-of-function variants, low-density lipoprotein cholesterol, and risk of coronary heart disease and stroke: data from 9 studies of blacks and whites. *Circ Cardiovasc Genet* 2017; 104: e001632.
4. Linsel-Nitschke P, Götz A, Erdmann J, *et al*. Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease – a Mendelian Randomisation study. *PLoS One* 2008; 3: e2986.
5. Silverman MG, Ference BA, Im K, *et al*. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016; 316: 1289−97.
6. Siri-Tarino PW, Sun Q, Hu FB, *et al*. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010; 91: 535−46.
7. Chowdhury R, Warnakula S, Kunutsor S, *et al*. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014; 160: 398−406.
8. de Souza RJ, Mente A, Maroleanu A, *et al*. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* 2015; 351: h3978.
9. Li Y, Hruby A, Bernstein AM, *et al*. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol* 2015; 66: 1538−48.
10. Wang DD, Li Y, Chiuve SE, *et al*. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med* 2016; 176: 1134−45.
11. Hooper L, Martin N, Abdelhamid A, *et al*. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev* 2015; 6: CD011737.
12. Frikke-Schmidt R. Genetic variation in the ABCA1 gene, HDL cholesterol, and risk of ischemic heart disease in the general population. *Atherosclerosis* 2010; 208: 305−16.
13. Haase CL, Tybjaerg-Hansen A, Qayyum AA, *et al*. LCAT, HDL cholesterol and ischemic cardiovascular disease: a mendelian randomization study of HDL cholesterol in 54,500 individuals. *J Clin Endocrinol Metab* 2012; 97: E248−56.
14. Frikke-Schmidt R, Nordestgaard BG, Stene MC, *et al*. Association of loss-of-function mutations in the abca1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. *JAMA* 2008; 299: 2524−32.
15. Voight BF, Peloso GM, Orho-Melander M, *et al*. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; 380: 572−80.
16. Kaur N, Pandey A, Negi H, *et al*. Effect of HDL-raising drugs on cardiovascular outcomes: a systematic review and meta-regression. *PLoS One* 2014; 9: e94585.
17. Schwartz GG, Olsson AG, Abt M, *et al*. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 367: 2089−99.
18. Boekholdt SM, Arsenault BJ, Hovingh GK, *et al*. Levels and changes of HDL cholesterol and apolipoprotein A-I in relation to risk of cardiovascular events among statin-treated patients: a meta-analysis. *Circulation* 2013; 128: 1504−12.
19. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, *et al*. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010; 375: 1634−9.
20. Cholesterol Treatment Trialists' CTT Collaborators, Mihaylova B, Emberson J, *et al*. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; 380: 581−90.
21. Ma XY, Liu JP, Song ZY. Glycemic load, glycemic index and risk of cardiovascular diseases: meta-analyses of prospective studies. *Atherosclerosis* 2012; 223: 491−6.
22. Faghihnia N, Tsimikas S, Miller ER, *et al*. Changes in lipoprotein (a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J Lipid Res* 2010; 51: 3324−30.
23. Brouwer I. *Effect of Trans-Fatty Acid Intake on Blood Lipids and Lipoproteins: A Systematic Review and Meta-Regression Analysis*. Geneva: World Health Organization, 2016.
24. Nestel P. Trans fatty acids: are its cardiovascular risks fully appreciated? *Clin Ther* 2014; 36: 315−21.
25. Mozaffarian D, Aro A, Willett WC. Health effects of trans-fatty acids: experimental and observational evidence. *Eur J Clin Nutr* 2009; 63 (Suppl 2): S5−21.
26. Berger S, Raman G, Vishwanathan R, *et al*. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr* 2015; 102: 276−94.
27. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. *Am J Clin Nutr* 2001; 73: 885−91.
28. Hu FB, Stampfer MJ, Rimm EB, *et al*. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA* 1999; 281: 1387−94.
29. Djousse L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. *Am J Clin Nutr* 2008; 87: 964−9.
30. Liese AD, Weis KE, Schulz M, *et al*. Food intake patterns associated with incident type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2009; 32: 263−8.
31. Djousse L, Gaziano JM, Buring JE, *et al*. Egg consumption and risk of type 2 diabetes in men and women. *Diabetes Care* 2009; 32: 295−300.
32. Tanasescu M, Cho E, Manson JE, *et al*. Dietary fat and cholesterol and the risk of cardiovascular disease among women with type 2 diabetes. *Am J Clin Nutr* 2004; 79: 999−1005.
33. Fuller NR, Caterson ID, Sainsbury A, *et al*. The effect of a high-egg diet on cardiovascular risk factors in people with type 2 diabetes: the

Diabetes and Egg DIABEGG study—a 3-mo randomized controlled trial. *Am J Clin Nutr* 2015; 101: 705−13.

34. Huff MW, Telford DE. Dietary fish oil increases conversion of very low density lipoprotein apoprotein B to low density lipoprotein. *Arteriosclerosis* 1989; 9: 58−66.

35. Hartweg J, Perera R, Montori V, *et al*. Omega-3 polyunsaturated fatty acids PUFA for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008; 1: CD003205.

36. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. *Br J Nutr* 2014; 112: 214−9.

37. Te Morenga LA, Howatson AJ, Jones RM, *et al*. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. *Am J Clin Nutr* 2014; 100: 65−79.

38. Goff LM, Cowland DE, Hooper L, *et al*. Low glycaemic index diets and blood lipids: a systematic review and meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis* 2013; 23: 1−10.

39. Ho HV, Sievenpiper JL, Zurbau A, *et al*. The effect of oat β-glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: a systematic review and meta-analysis of randomised-controlled trials. *Br J Nutr* 2016; 116: 1369−82.

40. Ho HVT, Jovanovski E, Zurbau A, *et al*. A systematic review and meta-analysis of randomized controlled trials of the effect of konjac glucomannan, a viscous soluble fiber, on LDL cholesterol and the new lipid targets non-HDL cholesterol and apolipoprotein B. *Am J Clin Nutr* 2017; 105: 1239−47.

41. Ho HV, Sievenpiper JL, Zurbau A, *et al*. A systematic review and meta-analysis of randomized controlled trials of the effect of barley β-glucan on LDL-C, non-HDL-C and apoB for cardiovascular disease risk reduction. *Eur J Clin Nutr* 2016; 70: 1239−45.

42. Kelley GA, Kelley KS, Roberts S, *et al*. Comparison of aerobic exercise, diet or both on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. *Clin Nutr* 2012; 31: 156−67.

43. Kelley GA, Kelley KS, Tran ZV. Aerobic exercise and lipids and lipoproteins in women: a meta-analysis of randomized controlled trials. *J Womens Health (Larchmt)* 2004; 13: 1148−64.

44. Koutsari C, Karpe F, Humphreys SM, *et al*. Exercise prevents the accumulation of triglyceride-rich lipoproteins and their remnants seen when changing to a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol* 2001; 21: 1520−5.

45. Koutsari C, Hardman AE. Exercise prevents the augmentation of postprandial lipaemia attributable to a low-fat high-carbohydrate diet. *Br J Nutr* 2001; 86: 197−205.

46. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992; 56: 320−8.

47. Nordmann AJ, Nordmann A, Briel M, *et al*. Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis. *Obes Rev* 2016; 17: 1001−11.

48. Nordmann AJ, Nordmann A, Briel M, *et al*. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; 166: 285−93.

49. Reinehr T, Lass N, Toschke C, *et al*. Which amount of BMI-SDS reduction is necessary to improve cardiovascular risk factors in overweight children? *J Clin Endocrinol Metab* 2016; 101: 3171−9.

50. Jenkins DJ, Wolever TM, Vuksan V, *et al*. Nibbling versus gorging: metabolic advantages of increased meal frequency. *N Engl J Med* 1989; 321: 929−34.

51. Jakubowicz D, Barnea M, Wainstein J, *et al*. High caloric intake at breakfast vs dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)* 2013; 21: 2504−12.

52. Madjd A, Taylor MA, Delavari A, *et al*. Beneficial effect of high energy intake at lunch rather than dinner on weight loss in healthy obese women in a weight-loss program: a randomized clinical trial. *Am J Clin Nutr* 2016; 104: 982−9. https://www.ncbi.nlm.nih.gov/pubmed/27581472.