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Nutritional management of hyperapoB

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Abstract

Plasma apoB is a more accurate marker of the risk of CVD and type 2 diabetes (T2D) than LDL-cholesterol; however, nutritional reviews targeting apoB are scarce. Here we reviewed eighty-seven nutritional studies and present conclusions in order of strength of evidence. Plasma apoB was reduced in all studies that induced weight loss of 6–12 % using hypoenergetic diets (seven studies; 5440–7110 kJ/d; 1300–1700 kcal/d; 34–50 % carbohydrates; 27–39 % fat; 18–24 % protein). When macronutrients were compared in isoenergetic diets (eleven studies including eight randomised controlled trials (RCT); *n* 1189), the diets that reduced plasma apoB were composed of 26–51 % carbohydrates, 26–46 % fat, 11–32 % protein, 10–27 % MUFA, 5–14 % PUFA and 7–13 % SFA. Replacement of carbohydrate by MUFA, not SFA, decreased plasma apoB. Moreover, dietary enriching with *n*-3 fatty acids (FA) (from fish: 1·1–1·7 g/d or supplementation: 3·2–3·4 g/d EPA/DHA or 4 g/d EPA), psyllium (about 8–20 g/d), phytosterols (about 2–4 g/d) or nuts (30–75 g/d) also decreased plasma apoB, mostly in hyperlipidaemic subjects. While high intake of *trans*-FA (4·3–9·1 %) increased plasma apoB, it is unlikely that these amounts represent usual consumption. Inconsistent data existed on the effect of soya proteins (25–30 g/d), while the positive association of alcohol consumption with low plasma apoB was reported in cross-sectional studies only. Five isoenergetic studies using Mediterranean diets (including two RCT; 823 subjects) reported a decrease of plasma apoB, while weaker evidence existed for Dietary Approaches to Stop Hypertension (DASH), vegetarian, Nordic and Palaeolithic diets. We recommend using a Mediterranean dietary pattern, which also encompasses the dietary components reported to reduce plasma apoB, to target hyperapoB and reduce the risks of CVD and T2D.

Key words: **ApoB-lipoproteins: LDL: Cardiometabolic risks: Behaviour modification programmes**

Introduction

Atherogenic lipoproteins are chylomicrons, VLDL, intermediate-density lipoproteins, LDL and lipoprotein (a) (Lp(a)). Each of these particles contains one molecule of apoB, which encircles the particle providing an external supportive skeleton within which the particle exists[1]. Since each particle contains one molecule of apoB, whether as apoB48 carried on intestinal chylomicron particles or apoB100 carried on hepatic lipoproteins, plasma apoB represents the number of all atherogenic apoB-lipoproteins. Of these, LDL make up by far the largest percentage (about 90 % on average), and therefore plasma apoB is driven by LDL apoB[2–4]. Plasma total cholesterol, non-HDL-cholesterol (non-HDL-C) and LDL-cholesterol (LDL-C) are all highly correlated with apoB and the risk of vascular disease increases exponentially as the concentrations of all four increase in plasma. However, the lipid content and therefore the size of all the apoB particles can vary substantially[5].

In particular, LDL particles can contain an average mass of cholesterol or be cholesterol-enriched or cholesterol-depleted. When LDL particles are either cholesterol-enriched or cholesterol-depleted, LDL-C is an inaccurate measure of LDL number, particularly if plasma TAG is more than 1·5 mmol/l[1]. Hyperapobetalipoproteinaemia (or hyperapoB) was defined by Sniderman *et al.*[6] in 1980 as a proatherogenic lipoprotein phenotype characterised by elevated numbers of apoB-lipoproteins but normal or near-normal plasma LDL-C. In this phenotype, the discordance between the LDL-C and apoB is due to cholesterol-depleted LDL particles. Of note, in contrast to plasma TAG used for the calculation of LDL-C in the Friedewald equation, plasma apoB can be measured in non-fasting samples[1]. A plasma apoB of ≥1·2 g/l, which is about the 75th percentile of plasma apoB concentrations in a Canadian population[7], identifies subjects with hyperapoB[8].

Plasma apoB and CVD

Plasma apoB is a more accurate marker of cardiovascular risk than LDL-C or non-HDL-C[9]. A recent meta-analysis, comparing the number of clinical events prevented by different treatment

Abbreviations: CHO, carbohydrate; DASH, Dietary Approaches to Stop Hypertension; FA, fatty acid; hyperapoB, hyperapobetalipoproteinaemia; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; Lp(a), lipoprotein (a); MCFA, medium-chain fatty acid; Med diet, Mediterranean diet; non-HDL-C, non-HDL-cholesterol; RESMENA, Reduction of the Metabolic Syndrome in Navarra-Spain; RCT, randomised controlled trial; T2D, type 2 diabetes; TRL, TAG-rich lipoprotein; VLDL-C, VLDL-cholesterol.

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strategies, revealed that over a 10-year period, a non-HDL-C strategy would prevent 300 000 more events than an LDL-C strategy, whereas an apoB strategy would prevent 500 000 more events than a non-HDL-C strategy[9]. The measurement of plasma apoB was recommended in 2009 by the American Association for Clinical Chemistry Lipoproteins and Vascular Diseases Division Working Group on Best Practices as a more reliable indicator of risk than LDL-C[10]. It was also introduced to the Canadian dyslipidaemia guidelines in the same year as an alternative primary target of therapy[11] and continues to be recommended in the latest update of the guideline in 2014[1,12]. Particularly for subjects with intermediate CVD risk and/or insulin resistance, an apoB ≥1·2 g/l identifies patients at increased CVD risk who may benefit from pharmacotherapy despite a plasma LDL-C of <3·5 mmol/l[1]. Similarly in 2011, the European Atherosclerosis Society and European Society of Cardiology stated that non-HDL-C or apoB may better estimate the concentration of atherogenic particles than LDL-C, especially in high risk patients with diabetes or the metabolic syndrome[13]. The recent 2013 guidelines of the American College of Cardiology and the American Heart Association, however, do not encompass the use of plasma apoB for the screening and treatment target for CVD[14]. Since then a series of reports using discordance analysis have all shown that apoB is superior to either LDL-C or non-HDL-C to estimate cardiovascular risk[15,16].

Plasma apoB and type 2 diabetes

Emerging clinical and epidemiological evidence also links hyperapoB to the development of type 2 diabetes (T2D), in addition to CVD, in humans. Both diseases are viewed as chronic inflammatory disease, and apoB-lipoproteins, primarily LDL, are known to induce multiple derangements in inflammatory cascades that lead to atherosclerosis[17,18]. However, evidence from our laboratory[19], as well as others[20–22], has shown that plasma apoB, not total cholesterol or LDL-C, correlates strongly with plasma inflammatory markers in human subjects. Moreover, in non-diabetic obese subjects, plasma apoB but not LDL-C correlates positively with dysfunctional white adipose tissue *ex vivo* and delayed plasma clearance of dietary fat, hyperinsulinaemia, insulin resistance and activation of the IL-1β system *in vivo*[19,23–25], all of which are known risk factors for T2D. Epidemiological studies support that hyperapoB predicts the development of T2D before the onset of the disease by 3–10 years in Turkish[26], Canadian[27], Finnish[28] and South Korean[29] populations, independent of traditional risk factors such as central adiposity[26,27], inflammation[26], fasting glucose and glycated Hb[27,29].

Despite the central role of hyperapoB in the prediction and promotion of CVD and T2D and the inaccurate prediction of plasma apoB by lipids particularly in subjects with hyperlipidaemia, nutritional reviews and guidelines[11] for the treatment of dyslipidaemias have not addressed the regulation of apoB-particle number in plasma and focused mainly on their lipid content. Moreover, recent reviews on this topic mainly focused on the effect of dietary fatty acids (FA) and weight loss on plasma apoB-lipoproteins[30–32]. Accordingly, we reviewed recent published literature (within the last 10 years) on the effects of multiple dietary interventions and components on plasma apoB and other parameters (VLDL-cholesterol (VLDL-C), LDL-C, non-HDL-C, TAG, apoA1 and apoB:apoA1). All human studies in an adult population (>18 years old) that were written in English and corresponded to the search criteria 'diet and apoB' on PubMed on 25 May 2015 were included. Genetic variations affecting plasma lipoprotein-related parameters are reported to affect the response efficiency to dietary interventions or components[33–36]. However, as the present review aims to guide nutritional interventions targeting hyperapoB in clinical practice where data on the genetic background may not be readily available, studies examining specific gene–diet interactions were not included in this analysis. Given that the definitions of very-low- to high-carbohydrate (CHO) diets differ between studies, we used the definitions suggested by Feinman *et al.*[37], mostly driven from the American Diabetic Association Guidelines, and unified the definitions for CHO intake throughout the eighty-seven studies examined. Very-low, low-, moderate- and high-CHO diets were those providing less than 10 %, 10–25 %, 26–45 % and >45 % of energy from CHO, respectively[37]. Special emphasis was placed on data generated from randomised controlled trials (RCT) to determine the strength of evidence; however, prospective interventional and association studies were also included for completeness.

A comprehensive comparison of the eighty-seven studies included in the present review is provided in Table 1. When enough data were reported, the 95 % CI for the changes in plasma apoB and other lipoprotein parameters were calculated for the individual studies (Table 1). A table summarising the overall direction of changes in lipoprotein parameters based on the number of RCT supporting the findings is also provided (Table 2). Of note, the studies examined here that are summarised in Table 2 use data from the eighty-seven studies that examined plasma apoB in addition to other lipoprotein parameters to allow comparison between the parameters. Thus, the present review may not be comprehensive for the effect of the dietary components and patterns on plasma cholesterol, TAG and apoA1.

Effect of hypoenergetic diet-induced weight loss on plasma apoB

Obesity promotes cardiometabolic disease, and weight loss as modest as 5–10 % has been reported to ameliorate the risks of T2D and CVD[38–40]. Hypoenergetic diet (about 5440–7110 kJ; 1300–1700 kcal)-induced weight loss of about 6–12 % was reported to decrease plasma apoB, whether on a low-fat/high-CHO diet (≤30 % fat; >45 % CHO)[37,41,42], a higher-fat/moderate-CHO diet (>30 % fat; 26–45 % CHO)[37,43,44] or when combined with resistance training (4 % weight loss)[45]. Similar effects were reported for a very-low-energy diet (2510–3350 kJ (600–800 kcal); 6 % weight loss)[46]. Reduction in plasma apoB is proposed to be due to the reduction in VLDL production rate and conversion to LDL and to the increase in LDL catabolic rate[43], and appears to mirror that of TAG particularly in subjects with dyslipidaemia or the metabolic syndrome. Addition of ezetimibe (a cholesterol-lowering agent) to a hypoenergetic diet did not have an additional benefit on plasma TAG and

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VLDL-apoB100 concentrations and secretion rates[41]. Moreover, increasing the frequency of meals in RESMENA dietary pattern (seven *v.* five meals/d) did not induce a further decrease in plasma apoB[44]. (Note that The RESMENA-S study (Reduction of the Metabolic Syndrome in Navarra-Spain) is an RCT comparing two hypoenergetic diets with an energy deficit of 30 % of requirements; the RESMENA dietary pattern has a macronutrient distribution of 40/30/30 (CHO/fat/protein) and high meal frequency (seven meals/d), while the control diet is based on the American Heart Association guideline and has a macronutrient distribution of 55/30/15 and a lower meal frequency (three to five meals/d)[41].)

Of note, the effect of changes in fat depots on plasma apoB may be sex-dependent. In a 1-year study using a hypoenergetic diet combined with aerobic training in 107 obese men with dyslipidaemia, reduction in plasma apoB was dependent on the reduction in visceral adipose tissue[47]. In a study by our group in fifty-six postmenopausal obese women, a 6-month hypoenergetic diet induced a reduction in plasma apoB that was independent of changes in adiposity or visceral adipose tissue but dependent on baseline apoB[42], which in turn was negatively associated with the diet quality[48,49].

Thus, in all four RCT and three prospective interventional studies examining 335 healthy or dyslipidaemic overweight and obese subjects in total, hypoenergetic diet-inducing weight loss (about 6–12 % alone or 4 % with resistance training) over 4–52 weeks induced a reduction in plasma apoB and TAG (six studies for TAG), with less consistent changes in non-HDL-C, LDL-C and HDL-C, and no data for VLDL-C[41–47]. When examined, there was no effect on plasma apoA1 (four studies) and a decrease in plasma apoB:apoA1 (two studies) (Table 2). More studies are needed to evaluate whether sex differences exist in the regulation of plasma apoB by changes in body fat distribution, and to confirm whether plasma apoB:apoA1 is decreased with weight loss in overweight and obese subjects.

Effects of macronutrients on plasma apoB

Carbohydrates

Current Canadian and American guidelines for the prevention of chronic diseases recommend a balanced diet with 45–65 % CHO, 20–35 % fat and 10–35 % protein[50–52]. However, high CHO/low-fat-diets are associated with higher plasma total, VLDL- and chylomicrons-TAG in the fasting and postprandial states[14,53] and with higher apoB and Lp(a)[54–56]. For example, switching 140 healthy men from 4 weeks on a moderate CHO (45 %)/high-fat (40 %) diet to 4 weeks on a high CHO (65 %)/low-fat-diet (20 %) with equivalent 50:50 ratio of simple to complex CHO, increased plasma apoB, TAG, Lp(a) as well as apoC-III (an inhibitor of lipoprotein lipase, whose activity is vital to hydrolyse and clear plasma TAG)[56] (Table 1). The effects of these diets on plasma apoB and TAG are believed to be primarily due to higher CHO flux to the liver increasing *de novo* lipogenesis and production of apoB-lipoproteins[57]. Moreover, elevated TAG promotes cholesteryl ester transfer protein activity (CETP)[58], which favours the exchange of cholesterol on HDL and LDL particles with TAG on TAG-rich lipoproteins (TRL, namely VLDL and chylomicrons) and may explain lower plasma LDL-C and HDL-C with these diets[54–56].

Compared with high-CHO diets (49–65 %), moderate-CHO (26–45 %)/high-fat diets (38–46 %) were reported to improve plasma apoB, TAG and HDL-C but produced less consistent effects on plasma LDL-C[56,59–62] (Table 1). Notably, compared diets within each study[56,59–62] contained equivalent amounts of fibre (about 25–30 g/d) or equivalent simple:complex CHO ratio (50:50), excluding the confounding effects of these nutrients (as discussed in the Simple sugars and Dietary fibres sections below). The benefit of the reduction in CHO content, especially in regards to plasma apoB, appears to be dependent on the type of nutrient used to replace CHO. When the types of FA were compared concomitantly in a large RCT on 178 healthy overweight and obese men and compared with a high-CHO diet (54 % CHO), a moderate-CHO diet (26 % CHO) reduced plasma apoB (95 % CI –0·05, –0·16 g/l adjusted for weight) only in combination with a higher MUFA content (27 % MUFA, 9 % SFA, which also induced weight loss) not a higher SFA content (20 % MUFA, 15 % SFA)[59]. In line in a smaller cross-over RCT on forty healthy men, the reduction in CHO intake alone (50 % to 31 %) without a change in the percentage of fat, MUFA and SFA content (38, 15 and 15 %, respectively) did not affect plasma apoB[62]. Plasma apoB was only reduced when MUFA content was increased to 21 % and that of SFA was decreased to 8 % in the same moderate-CHO diet (31 %)[62]. Even within a high-CHO diet, a decrease in CHO content (55 to 50 %), accompanied by an increase in MUFA content (11 to 17 %) and equivalent amount of fibre, was reported to decrease plasma apoB, VLDL-C, TAG and increase HDL-C in hypercholesterolaemic men[63]. Larger studies are needed to determine which nutritional component has the largest effect on plasma apoB: the reduction in CHO, the increase in MUFA, or the decrease in SFA intake.

Further restriction in CHO intake to less than 10 % in very-low-CHO diets does not appear to influence plasma apoB, particularly when with high SFA intake usually associated with these diets (about 20 %) despite additional benefits on plasma TAG and HDL-C[64,65] (Table 1). This may explain why compared with the very-low-CHO Atkins diet (58 % fat; 30 % SFA), weight maintenance for 4 weeks on the very-high-CHO Ornish diet (9 % fat; 3 % SFA) decreased plasma apoB (95 % CI –0·03, –0·19 g/l)[66]. Notably, lowering SFA intake is also reported to increase flow-mediated vasodilatation (i.e. a measure of endothelial function)[67], which may add to the benefits of low-SFA diets.

Thus, in all four RCT and two prospective interventional studies examined including 452 subjects in total, plasma apoB was consistently reduced in healthy or hyperlipidaemic subjects with isoenergetic diets composed of 26–50 % CHO, 36–46 % fat, 14–32 % protein, 11–27 % MUFA, 5–14 % PUFA and 7–13 % SFA consumed over 3–4 weeks only[56,59–63]. Plasma TAG and HDL-C were also improved, while inconsistent or insufficient data were observed for non-HDL-C, LDL-C, VLDL-C and apoA1. None of the studies evaluated plasma apoB:apoA1 (Table 2). The macronutrient composition of these six studies[56,59–63] was used to generate the summary of the isoenergetic diets observed to reduce plasma apoB (reported in the Abstract and Conclusion).

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Table 1. Summary of nutritional interventions affecting plasma apoB and other lipoprotein-related parameters*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Effects of hypoenergetic diet-induced weight loss									
Faraj *et al.* (2010)[42] (Canada)	Pros	*n* 56 W; postmenopausal; aged about 58 years; BMI ≥ 27 kg/m^2; no CVD, no T2D, no lipid-lowering drugs	Balanced hypoenergetic/low-fat diet (planned: 30 % fat, 55 % CHO, 15 % protein, 500 kcal/d deficit, measured (*n* 24): about 1714 kcal, 31 % fat, 50 % CHO, 18 % protein, 10 % SFA, 11 % MUFA, 600 kcal/d deficit). 6 % weight loss. Dietary counselling	↓[a] independent of ↓ weight, fat mass or VAT	– (LDL-C)	–	–	– (apoA1)	26
Ng *et al.* (2007)[43] (Australia)	RCT, parallel	*n* 35 M; middle-aged; BMI about 34 kg/m^2; with MS, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: (A) weight maintenance diet (measured: about 2326 kcal, 39 % fat, 38 % CHO, 20 % protein, about 4 % weight gain) *v.* (B) hypoenergetic diet (measured: about 1667 kcal, 35 % fat, 39 % CHO, 20 % protein, about 12 % weight loss). Dietary counselling	B *v.* A ↓[b] apoB100	B *v.* A ↓[b] LDL-C	B *v.* A ↓[b]	–	B *v.* A ↓[b] apoB: apoA1 – (apoA1)	16
De la Iglesia *et al.* (2014)[44] (Spain)	RCT, parallel	*n* 84 analysed (41 W, 52 M enrolled); aged about 49 years; BMI > 30 kg/m^2; with MS, no chronic diseases	Compared two diets: (A) control hypoenergetic diet (measured: five meals/d, 1352 kcal, 39 % CHO, 18 % protein, 39 % fat, about 7 % weight loss) *v.* (B) RESMENA hypoenergetic diet (measured: seven meals/d, 1337 kcal, 34 % CHO, 23 % protein, 38 % fat, about 7 % weight loss, higher natural antioxidants, lower glycaemic load, trend for higher *n*-3 FA). Menus provided for RESMENA. Food exchange plan for control diet	Both A and B ↓[a]	A ↓[a] LDL-C	Both A and B ↓[a]	A ↓[a]	N/E	8
Vasudevan *et al.* (2013)[46] (USA)	Pros	*n* 12 analysed (14 W, 10 M enrolled); aged about 46 years; BMI > 30 kg/m^2; with MS, no CVD	Liquid very-low-calorie low-CHO high-protein diet (planned: 600–800 kcal/d, measured: about 6 % weight loss). Dietary counselling	↓[a]	↓[a] LDL-C, ↓[a] non-HDL-C	↓[a]	–	↓[a] apoA1	4–6
Valente *et al.* (2011)[45] (USA)	RCT, parallel	*n* 27 (16 W, 11 M); 41 % men; aged 60–75 years; BMI 25–40 kg/m^2	Compared two diets: (A) DASH hypoenergetic diet (measured: 1530 kcal, about 2 % weight loss) *v.* (B) DASH hypoenergetic diet + RT (40 min × 3 d/week) (measured: 1641 kcal, about 4 % weight loss). DASH diet ↓ fat-free mass, but not weight. DASH diet + RT ↓ fat mass and weight. Dietary counselling	B *v.* A ↓[b]	– (LDL-C)	B *v.* A ↓[b]	–	– (apoA1)	10
Chan *et al.* (2010)[41] (Australia)	RCT, parallel	*n* 25 (10 W, 15 M); aged about 57 years; BMI about 33 kg/m^2; centrally obese, insulin-resistant, mildly dyslipid, no T2D/CVD/lipid-lowering drugs	Compared two diets: (A) hypoenergetic/low-fat diet + placebo (measured: about 1388 kcal/d, 27 % fat, 49 % CHO, about 6 % weight loss) (*n* 10) *v.* (B) hypoenergetic/low-fat diet + ezetimibe (measured: about 1473 kcal/d, 30 % fat, 46 % CHO, about 7 % weight loss). Both diets (*v.* baseline): lower in fat and higher in CHO	Both A and B ↓[a] VLDL-apoB100 levels and secretion. (NS when corrected for weight loss)	–	Both A and B ↓[a] (NS when corrected for weight loss)	–	– (apoA1)	16
Pelletier-Beaumont *et al.* (2012)[47] (Canada)	Pros	*n* 107 M abdominally obese (BMI about 31 kg/m^2) *v.* *n* 60 M lean normolipid (BMI < 23 kg/m^2); aged 20–65 years; no T2D, no lipid-lowering drugs	Hypoenergetic diet (planned: 500 kcal/d deficit) with moderate aerobic activity (160 min/week) intervention (measured: about 7 % weight loss). Dietary counselling	↓[a] predicted by changes in VAT	↓[a] Non-HDL-C, ↑[a] LDL-C	↓[a]	↑[a]	↑[a] apoA1 ↓[a] apoB:apoA1	52
Effects of moderate- (26–45 %) *v.* high- (>45 %) CHO diets									
Shin *et al.* (2007)[56] (USA)	Pros	*n* 140 M; aged >20 years; BMI about 25 kg/m^2; healthy, no chronic disease, no lipid-lowering drugs	Compared two diets: (A) moderate-CHO/high-fat diet (planned: 45 % CHO, 40 % fat, 13 % SFA, 11 % MUFA, 14 % PUFA, 15 % protein) followed by (B) high-CHO/low-fat diet (planned: 65 % CHO, 20 % fat, 5 % SFA, 10 % MUFA, 5 % PUFA, 15 % protein). Ratio of simple:complex CHO about 50:50 in both diets. Monitoring for stable weight. Menus provided	B *v.* A ↑[b]	B *v.* A ↓[b] (LDL-C)	B *v.* A ↑[b]	B *v.* A ↓[b]	B *v.* A ↓[b] (apoA1)	4
Faghihnia *et al.* (2010)[61] (USA)	RCT, cross-over	*n* 63 (2 W, 61 M); aged >20 years; BMI about 27 kg/m^2; healthy, no T2D, no chronic disease, no lipid-lowering drugs	Compared two diets: (A) high-CHO/low-fat diet (planned: 65 % CHO, 20 % fat, 5 % SFA, 10 % MUFA, 5 % PUFA, 2 % *trans*, 15 % protein) *v.* (B) moderate-CHO/high-fat diet (planned: 45 % CHO, 40 % fat, 13 % SFA, 11 % MUFA, 14 % PUFA, and 3 % *trans*-FA, 15 % protein). Ratio of simple: complex CHO about 50:50 in both diets. Monitoring for stable weight. Dietary counselling	B *v.* A ↓[b]	B *v.* A ↑[b] LDL-C	B *v.* A ↓[b]	B *v.* A ↑[b]	B *v.* A ↑[b] apoA1	4

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Labonte *et al.* (2013)[60] (Canada)	RCT, parallel	*n* 16 (4 W, 12 M), postmenopausal, aged about 53 years, median BMI about 27 kg/m^2; hyperlipid, median no CVD, no T2D, no lipid-lowering drugs	Compared two diets: (A) low-MUFA/high-CHO portfolio diet (planned: 2368 kcal, 49 % CHO, 29 % fat, 5 % SFA, 13 % MUFA, 11 % PUFA, 22 % protein) *v.* (B) high-MUFA/moderate-CHO portfolio diet (planned: 2716 kcal, 34 % CHO, 45 % fat, 7 % SFA, 26 % MUFA, 12 % PUFA, 21 % protein). Both diets planned to contain equivalent amount of fibre (10·3 g viscous fibres/1000 kcal). Stable weight targeted. All food provided	B ↓[a] LDL-apoB pool size by increasing LDL clearance rate	Both A and B ↓[a] LDL-C	B ↓[a]	B ↑[a]	B ↑[b] apoA1	4
Mercanligil *et al.* (2007)[63] (Turkey)	Pros	*n* 15 M; aged 33–59 years; BMI <30 kg/m^2; hyperchol, no T2D, no lipid-lowering drugs	Compared two diets: (A) high-CHO/low-MUFA (measured: 2033 kcal, 55 % CHO, 31 % fat, 11 % MUFA, 9 % SFA, 9 % PUFA, 14 % protein) followed by (B) hazelnut-enriched high-CHO/high-MUFA diet (40 g/d hazelnuts, measured: 2284 kcal, 50 % CHO, 36 % fat, 17 % MUFA, 8 % SFA, 8 % PUFA, 14 % protein). Both diets planned to contain equivalent amount of fibre (25–30 g/d). Stable weight. Hazelnuts provided	B ↓[a]	B ↓[a] VLDL-C – (LDL-C)	B ↓[a]	B *v.* A ↑[a,b]	– (apoA1)	4
Krauss *et al.* (2006)[59] (USA)	RCT, parallel	*n* 178 M; aged about 50 years; BMI 26–35 kg/m^2; healthy, no CVD, no chronic disease, no lipid-lowering drugs	Compared four diets: (A) high-CHO/low-SFA (planned: 54 % CHO, 30 % fat, 7 % SFA, 13 % MUFA, 8 % PUFA, 16 % protein) *v.* (B) moderate-CHO/low-SFA (planned: 39 % CHO, 31 % fat, 8 % SFA, 13 % MUFA, 8 % PUFA, 29 % protein) *v.* (C) moderate-CHO/low-SFA (planned: 26 % CHO, 46 % fat, 9 % SFA, 27 % MUFA, 5 % PUFA, 29 % protein) *v.* (D) moderate-CHO/high-SFA diet (planned: 26 % CHO, 45 % fat, 15 % SFA, 20 % MUFA, 6 % PUFA, 29 % protein). Diets planned to contain equivalent amount of fibre (25 g/2000 kcal plus 2·5 g/500 kcal above 2000 kcal); CHO simple:complex ratio about 50:50. Weight loss after moderate-CHO/low-SFA diet. Menus and prepared entrées provided	C *v.* A –0·109 (–0·164, –0·054) (adjusted for weight changes)	– (LDL-C)	C *v.* A –0·14 (–0·21, –0·07) log mg/dl (adjusted for weight changes)	–	– (apoA1)	3
Mangravite *et al.* (2011)[62] (USA)	RCT, cross-over	*n* 40 M healthy; aged ≥ 18 years; BMI 20–35 kg/m^2; no CVD, no chronic disease, no lipid-lowering drugs	Compared three diets: (A) baseline diet (planned: 50 % CHO, 38 % fat, 15 % SFA, 15 % MUFA, 6 % PUFA, 13 % protein) *v.* (B) moderate-CHO/high-SFA/low-MUFA diet (planned: 31 % CHO, 38 % fat, 15 % SFA, 15 % MUFA, 5 % PUFA, 31 % protein) *v.* (C) moderate-CHO/low-SFA/high-MUFA diet (planned: 31 % CHO, 38 % fat, 8 % SFA, 21 % MUFA, 6 % PUFA, 32 % protein). Diets planned to contain equivalent amount of fibre (25 g/2000 kcal plus 2·5 g/500 kcal above this level) and CHO simple: complex CHO ratio about 50:50. Stable weight. Menus and two meals per d provided	C *v.* B ↓[b]	C *v.* B ↓[b] non-HDL-C and LDL-C	Both C and B *v.* A ↓[b]	C *v.* A ↓[b]	– (apoA1)	3
Effects of very low-CHO (<10 %)/high-fat diet									
Brinkworth *et al.* (2009)[64] (Australia)	RCT, parallel	*n* 69 (44 W, 25 M); aged 18–65 years; BMI about 33 kg/m^2; with abdominal obesity, ≥1 additional MS risk factor, 20 % taking lipid-lowering drugs, no CVD, no T2D	Compared two diets: (A) low-fat/high-CHO (measured: about 1624 kcal, 46 % CHO, 26 % fat, 6 % SFA, 6 % PUFA, 12 % MUFA, 22 % protein) *v.* (B) very-low-CHO/high-fat (measured: about 1644 kcal, 9 % CHO, 55 % fat, 20 % SFA, 7 % PUFA, 23 % MUFA, 32 % protein), both hypoenergetic (about 1600 kcal/d). Similar weight loss. Dietary counselling. Key foods provided	–	B 0·6 (0·2, 1·0) LDL-C – (non-HDL-C)	B –0·36 (–0·67, –0·05)	B 0·23 (0·06, 0·40)	N/E	52
Tay *et al.* (2008)[65] (Australia)	RCT, parallel	*n* 88 (57 W, 31 M); aged 18–65 years; BMI about 34 kg/m^2; with abdominal obesity, ≥1 additional MS risk factor, 20 % on lipid-lowering therapy, no CVD, no T2D	Compared two diets: (A) high-CHO/low-fat hypoenergetic diet (measured: about 1529 kcal; planned: 46 % CHO, 30 % fat, <8 % SFA, 24 % protein) *v.* (B) very-low-CHO/high-fat hypoenergetic diet (measured: about 1604 kcal; planned: 4 % CHO, 61 % fat, 20 % SFA, 35 % protein). Equivalent weight loss on both diets. Dietary counselling. Key foods provided	–	–	B –0·29 (–0·53, –0·05)	B 0·17 (0·07, 0·27)	N/E	24

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Miller *et al.* (2009)[66] (USA)	RCT, cross-over	*n* 18 (9 W, 9 M); aged ≥20 years; BMI <30 kg/m^2; healthy, no metabolic or systemic disease, no lipid-lowering drug	Compared three diets: (A) Ornish (high-CHO/low-fat; measured: about 1641 kcal, 9 % fat, 3 % SFA) *v.* (B) South Beach (low-CHO/low-glycaemic index, measured: about 1608 kcal, 31 % fat, 14 % SFA) *v.* (C) Atkins (very-low-CHO/high-fat/high-SFA/high-cholesterol, measured: about 1724 kcal, 58 % fat, 30 % SFA) aiming to maintain weight. Stable weight. Dietary counselling	A *v.* C –0·112 (–0·190, –0·034)	A *v.* C –0·639 (–0·965, –0·313) LDL-C B *v.* C –0·515 (–0·840, –0·189) LDL-C	A *v.* C 0·26 (0·03, 0·49) log mg/dl	A *v.* C –0·26 (–0·45, –0·06) A *v.* B –0·25 (–0·45, –0·06)	A *v.* C –0·208 (–0·323, –0·093) apoA1 A *v.* B –0·196 (–0·311, –0·081) apoA1	4
Effects of fructose									
Swarbrick *et al.* (2008)[69] (USA)	Pros	*n* 7 W; postmenopausal; aged 50–72 years; BMI 27–33 kg/m^2	Compared two diets: (A) 4-week low-fructose diet (planned: <3 % fructose, 55 % CHO, 30 % fat, 15 % protein) followed by (B) 10-week high-fructose diet (planned: 25 % fructose, 55 % CHO, 30 % fat, 15 % protein). Weight loss on fructose diet. All food provided including sweetened beverages	B *v.* A ↑[b]	– (LDL-C)	B *v.* A ↑[b] postprandial TAG	–	N/E	10
Stanhope *et al.* (2011)[71] (USA)	Parallel	*n* 48 (21 W, 27 M); aged 18–40 years; BMI 18–35 kg/m^2; no T2D; no lipid-lowering drugs	Compared three diets: (A) high-glucose diet (planned: 25 % glucose, 55 % CHO, 30 % fat, 15 % protein) *v.* (B) high-fructose diet (planned: 25 % fructose, 55 % CHO, 30 % fat, 15 % protein) *v.* (C) high-HFCS diet (planned: 25 % HFCS, 55 % CHO, 30 % fat, 15 % protein). Stable weight. Sweetened beverages provided. Habitual diet	B *v.* A ↑[a,b] C *v.* A ↑[a,b]	C *v.* A ↑[a,b] LDL-C and non-HDL-C B ↑[a] LDL-C and non-HDL-C	B and C ↑[a] postprandial RLP-TAG	–	C *v.* A ↑[a,b] apoB: apoA1 B *v.* A ↑[a,b] apoB: apoA1	1·7
Effects of fibre									
Shrestha *et al.* (2006)[76] (USA)	RCT, cross-over	*n* 33 (22 W, 11 M); aged 35–65 years; BMI 25–35 kg/m^2; hyperchol, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: (A) placebo cookies (0 g/d of soluble fibre and plant sterols) (measured: about 1977–2293 kcal, 41–49 % CHO, 35–41 % fat, 14–17 % protein) *v.* (B) treatment cookies (7·68 g/d psyllium soluble fibre and 2·6 g/d plant sterols) (measured: about 2005–2156 kcal, 45–50 % CHO, 36–39 % fat, 15–17 % protein). Stable weight. Cookies provided. Habitual diet	B *v.* A ↓[b]	B *v.* A ↓[b] LDL-C	–	–	N/E	4·3
Moreyra *et al.* (2005)[77] (USA)	RCT, parallel	*n* 68 (20 W, 48 M); aged 31–77 years; BMI ≤32 kg/m^2; hyperlipid on simvastatin, 9 % T2D, 62 % had CHD or atherosclerotic disease	Compared three treatments: (A) simvastatin (20 mg) + placebo *v.* (B) simvastatin (10 mg) + placebo *v.* (C) simvastatin (10 mg) + Metamucil (11 g/d psyllium soluble fibre)	C *v.* A and B ↓[b]	C *v.* B ↓[b] LDL-C	–	C *v.* A and B ↓[b]	–	8
Sola *et al.* (2012)[78] (Spain)	RCT, parallel	*n* 113 (67 W, 46 M); aged 43–65 years; BMI ≤35 kg/m^2; pre- or stage 1 hypertensive, hyperchol, ≥1 additional CVD risk factor, no T2D, no chronic disease, no lipid-lowering drugs	Compared four diets: (A) control cocoa cream (measured: about 2109 kcal, about 41 % CHO, about 41 % fat, about 10 % SFA, about 19 % MUFA, about 8 % PUFA, about 15 % protein) *v.* (B) cocoa + hazelnut (30 g/d) cream (measured: about 2064 kcal, about 40 % CHO, about 42 % fat, about 10 % SFA, about 22 % MUFA, about 6 % PUFA, about 15 % protein) *v.* (C) cocoa + hazelnuts + phytosterols (2 g/d) (measured: about 2151 kcal, about 45 % CHO, about 39 % fat, about 10 % SFA, about 19 % MUFA, about 5 % PUFA, about 15 % protein) *v.* (D) cocoa + hazelnuts + phytosterols + soluble fibre (20 g/d) (measured: about 2029 kcal, about 44 % CHO, about 41 % fat, about 10 % SFA, about 22 % MUFA, about 6 % PUFA, about 16 % protein). B higher in MUFA, B, C and D lower in PUFA (*v.* A). Stable weight	C *v.* A ↓[a,b] apoB100 D *v.* A ↓[a,b] apoB100	C *v.* A ↓[a,b] LDL-C D *v.* A ↓[a,b] LDL-C	–	–	C *v.* A ↓[a,b] apoB: apoA1 D *v.* A ↓[a,b] apoB: apoA1 – (apoA1)	4
Comerford *et al.* (2011)[79] (USA)	RCT, cross-over	*n* 28 (20 W, 8 M); aged 18–65 years; BMI 25–30 kg/m^2; healthy, no T2D, chronic disease, or lipid-lowering drugs	Compared two treatments: (A) control (cellulose) (measured: 2051 kcal) *v.* (B) active (α-cyclodextrin) (measured: 1875 kcal). Weight loss with active phase (0·4 kg)	–	B *v.* A ↓[b] LDL-C	–	–	N/E	4·3

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Effects of low-SFA/high-MUFA diet									
Mozaffarian & Clarke (2009)[81] (meta-analyses)	Meta-analysis	25 RCT	Isoenergetic replacement of SFA by MUFA (effect for each 1 % energy)	↓	↓ LDL-C	–	↓	– (apoA1)	
Jebb *et al.* (2010)[82] (UK)	RCT, parallel	*n* 548 (318 W, 230 M); aged 30–70 years; BMI about 28 kg/m^2; at risk of MS, no CVD, noT2D, no lipid-lowering drugs	Compared five diets: (A) control high-SFA/high-glycaemic index (measured: about 1999 kcal, about 42 % CHO, about 38 % fat, about 16 % SFA, about 12 % MUFA, about 6 % PUFA, about 82 g or 16 % protein) *v.* (B) high-MUFA/high-glycaemic index (measured: about 1923 kcal, about 45 % CHO, about 36 % fat, about 10 % SFA, about 16 % MUFA, about 7 % PUFA, about 79 g or 16 % protein) *v.* (C) high-MUFA/low-glycaemic index (measured: about 1978 kcal, about 45 % CHO, about 36 % fat, about 10 % SFA, about 16 % MUFA, about 7 % PUFA, about 84 g or 17 % protein) *v.* (D) low-fat/high-glycaemic index (measured: about 1853 kcal, about 51 % CHO, about 28 % fat, about 9 % SFA, about 10 % MUFA, about 5 % PUFA, about 81 g or 17 % protein) *v.* (E) low-fat/low-glycaemic index (measured: about 1739 kcal, about 52 % CHO, about 26 % fat, about 8 % SFA, about 10 % MUFA, about 5 % PUFA, about 78 g or 18 % protein). Weight loss on low-fat diets (0·8 kg). Dietary counselling. Key food sources provided	B + C and D + E *v.* A ↓[b]	B + C and D + E *v.* A ↓[a,b] LDL-C	–	B + C and D + E *v.* A ↓[a,b]	B + C and D + E *v.* A ↓[b] apoA1 B + C and D + E *v.* A ↓[b] apoB:apoA1	24
Berglund *et al.* (2007)[83] (USA)	RCT, cross-over	*n* 85 completed (33 W, 52 M); aged 21–65 years, BMI about 28 kg/m^2, high-risk (HDL-C ≤30th percentile, TAG ≥70th percentile, insulin ≥70th percentile), no CVD, no T2D, no lipid-lowering drugs	Compared three diets: (A) high-SFA American diet (measured: 49 % CHO, 36 % fat, 16 % SFA, 14 % MUFA, 6 % PUFA, 15 % protein) *v.* (B) high-MUFA diet (measured: 49 % CHO, 36 % fat, 9 % SFA, 21 % MUFA, 6 % PUFA, 16 % protein) *v.* (C) high-CHO diet (measured: 55 % CHO, 29 % fat, 8 % SFA, 16 % MUFA, 6 % PUFA, 16 % protein). Stable weight. All food provided except one meal/week	B *v.* A ↓[b]	B *v.* A ↓[b] LDL-C	–	B *v.* A ↓[b]	B *v.* A ↓[b] apoA1	7
Mangravite *et al.* (2011)[62] (USA)	RCT, cross-over	*n* 40 M healthy; aged ≥18 years; BMI 20–35 kg/m^2; no CVD, no chronic disease, no lipid-lowering drugs	Compared three diets: (A) baseline diet (planned: 50 % CHO, 38 % fat, 15 % SFA, 15 % MUFA, 6 % PUFA, 13 % protein) *v.* (B) moderate-CHO/high-SFA/low-MUFA diet (planned: 31 % CHO, 38 % fat, 15 % SFA, 15 % MUFA, 5 % PUFA, 31 % protein) *v.* (C) moderate-CHO/low-SFA/high-MUFA diet (planned: 31 % CHO, 38 % fat, 8 % SFA, 21 % MUFA, 6 % PUFA, 32 % protein). Stable weight. Menus and two meals per d provided	C *v.* B ↓[b]	C *v.* B ↓[b] non-HDL-C and LDL-C	Both C and B *v.* A ↓[b]	C *v.* A ↓[b]	– (apoA1)	3
Allman-Farinelli *et al.* (2005)[84] (Australia)	RCT, cross-over	*n* 15 (10 W, 5 M); aged 35–69 years; BMI 23–29 kg/m^2; no chronic disease, no drugs	Compared two diets: (A) high-SFA (measured: 48 % CHO, 33 % fat, 21 % SFA, 10 % MUFA, 3 % PUFA, 17 % protein) *v.* (B) high-MUFA (measured: 48 % CHO, 33 % fat, 9 % SFA, 20 % MUFA, 4 % PUFA, 17 % protein). Stable weight. Dietary counselling. Spreads provided	B *v.* A trend for ↓[b] ($P > 0{\cdot}01$)	B *v.* A ↓[b] LDL-C	B *v.* A ↓[b]	–	– (apoA1)	5–10
Van Dijk *et al.* (2012)[85] and Bos *et al.* (2010)[86] (Netherlands)	Controlled, parallel	*n* 49 (27 W, 22 M); aged 45–60 years; BMI ≥25 kg/m^2; with abdominal obesity, healthy, no T2D, no lipid-lowering drugs	Compared three diets: (A) Western-type high-SFA diet (measured: about 2556 kcal, 47 % CHO, 37 % fat, 19 % SFA, 11 % MUFA, 5 % PUFA, 14 % protein) *v.* (B) Western-type high-MUFA diet (measured: about 2484 kcal, 46 % CHO, 40 % fat, 11 % SFA, 20 % MUFA, 7 % PUFA, 11 % protein) *v.* (C) MED-type high-MUFA diet (measured: about 2460 kcal, 41 % CHO, 40 % fat, 11 % SFA, 21 % MUFA, 7 % PUFA, 15 % protein). Similar weight loss. Food provided (90 % of energy intake)	B *v.* A –0·10 (–0·17, –0·03) C *v.* A –0·15 (–0·21, –0·09)	B *v.* A –0·38 (–0·65, –0·11) LDL-C C ↓[a] LDL-C	Both B and C ↓[a]	–	N/E	8

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Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	Time (weeks)
Effects of low-SFA/high-PUFA diet									
Mozaffarian & Clarke (2009)[81] (meta-analyses)	Meta-analysis	25 RCT	Isoenergetic replacement of SFA by PUFA	↓	↓ LDL-C	–	↓	– (apoA1)	
Effects of low-MUFA/high-PUFA diet									
Mozaffarian & Clarke (2009)[81] (meta-analyses)	Meta-analysis	25 RCT	Isoenergetic replacement of MUFA by PUFA	–	↓ LDL-C	–	–	– (apoA1)	
Binkoski *et al.* (2005)[87] (USA)	RCT, cross-over	*n* 31 enrolled (19 W, 12 M); aged 25–64 years; BMI ≤30 kg/m^2; with moderate hyperchol, no chronic disease, no lipid-lowering drugs	Compared three diets: (A) average American *v.* (B) high-MUFA rich in olive oil (measured: 56 % CHO, 30 % fat, 8 % SFA, 17 % MUFA, 4 % PUFA, 15 % protein) *v.* (C) high-PUFA rich in sunflower-seed oil (measured: 55 % CHO, 30 % fat, 8 % SFA, 14 % MUFA, 8 % PUFA, 15 % protein). Monitoring for stable weight. All meals provided	–	C *v.* B ↓[b] LDL-C	–	–	C *v.* B ↓[b] apoA1	4
Effects of marine-derived *n*-3 PUFA (EPA and DHA)									
Bays *et al.* (2011)[98] (multi-site, international	RCT, parallel	*n* 218 analysed (54 W, 175 M enrolled); aged >18 years, BMI ≤45 kg/m^2, with hypertriacylglycerolaemia, 55 % at CVD risk, 28 % with T2D, 25 % on statins	Compared three treatments: (A) placebo *v.* (B) AMR101 at 2 g/d *v.* (C) 4 g/d (≥96 % EPA, no DHA, 0·2 % tocopherol)	C *v.* A ↓[b]	C and B *v.* A ↓[b] non-HDL-C and ↓[b] VLDL-C – (LDL-C)	C and B *v.* A ↓[b]	–	N/E	12
Zhang *et al.* (2012)[101] (China)	RCT, parallel	*n* 126 W; aged 35–70 years; BMI about 27 kg/m^2, hypertriacylglycerolaemia, no T2D, no CVD, no lipid-lowering drugs	Compared four diets: 80 g (A) common meats mix (pork/chicken/beef/lean fish, 0·1 g/d marine *n*-3 FA) (measured: about 1728 kcal, about 54 % CHO, about 31 % fat, about 8 % SFA, about 12 % MUFA, about 9 % PUFA, about 18 % protein) *v.* oily fish (1·1–1·7 g/d marine *n*-3 FA); (B) salmon (measured: about 1651 kcal, about 52 % CHO, about 32 % fat, about 7 % SFA, about 11 % MUFA, about 10 % PUFA, about 17 % protein); (C) herring (measured: about 1678 kcal, about 52 % CHO, about 32 % fat, about 7 % SFA, about 12 % MUFA, about 9 % PUFA, about 17 % protein); and (D) pompano (measured: about 1673 kcal, about 54 % CHO, about 32 % fat, about 8 % SFA, about 11 % MUFA, about 9 % PUFA, about 17 % protein). All four diets: higher in protein (*v.* baseline). Three fish diets: higher in *n*-3 PUFA. Meat diet: higher in SFA. Menus provided	B ↓[a] C ↓[a] D ↓[a]	– (LDL-C)	B *v.* A ↓[a,b] C *v.* A ↓[a,b] D ↓[a]	–	– (apoA1 or apoB:apoA1)	8
Wong *et al.* (2013)[103] (Australia)	RCT, parallel	*n* 22 M; aged about 55 years; BMI 27–46 kg/m^2; abdominal obesity, hyperlipidaemia, no CVD/T2D, no lipid-lowering drugs	Compared two treatments: (A) placebo (measured: about 2297 kcal, 38 % CHO, 36 % fat, 20 % protein) *v.* (B) 4 g/d Lovaza (3·2 g/d marine *n*-3 FA, 46 % EPA, 38 % DHA) (measured: about 2244 kcal, 42 % CHO, 32 % fat, 22 % protein). Stable weight	B *v.* A ↓[b] VLDL-apoB100 levels	– (non-HDL-C and LDL-C)	B *v.* A ↓[b]	–	– (apoA1)	6
Wong *et al.* (2014)[104] (Australia)	RCT, parallel	*n* 25 completed (12 W, 13 M), postmenopausal; aged 18–75 years, BMI >30 kg/m^2 or abdominal obesity; on average hypertriacylglycerolaemic, no CVD	Compared two diets: (A) hypoenergetic diet (measured: –24 % energy deficit) alone *v.* (B) hypoenergetic diet (measured: –20 % energy deficit) + 4 g/d Omacor (about 3·4 g/d marine *n*-3 FA, 46 % EPA, 38 % DHA). No significant differences in macronutrient intake and weight change. Dietary counselling	B *v.* A ↓[a,b] fasting apoB48 levels (production rate) B *v.* A ↓[a,b] postprandial apoB48 levels	– (non-HDL-C and LDL-C)	Both A and B ↓[a] B *v.* A ↓[b]	Both A and B ↑[a]	N/E	12
Ooi *et al.* (2012)[105] (USA)	Parallel	*n* 20 (13 W, 7 M), postmenopausal; aged >40 years; BMI about 25 kg/m^2; with mild to moderate hyperchol., no chronic disease, no lipid-lowering medication	Compared two diets: baseline Western diet followed by (A) healthy low-fish diet (measured: 0·27 g/d marine *n*-3 FA, 58 % CHO, 26 % fat, 4 % SFA, 11 % MUFA, 11 % PUFA, <0·02 % EPA, 0·1 % DHA 16 % protein) *v.* (B) healthy high-fish diet (measured: 1·23 g/d marine *n*-3 FA, 56 % CHO, 26 % fat, 5 % SFA, 12 % MUFA, 10 % PUFA, 0·2 % EPA, 0·5 % DHA 17 % protein). Stable weight. All meals were provided	B *v.* A ↓[a,b] postprandial TRL-apoB48 B *v.* A ↓ [a,b] postprandial TRL-apoB100 (production rate) A *v.* B ↓[b] postprandial LDL-apoB100 Both A and B ↓[a] postprandial LDL-apoB100	Both A and B ↓[a] postprandial LDL-C	B *v.* A ↓[a,b] postprandial TAG	A *v.* B ↓[a,b] postprandial HDL-C	Both A and B ↓[a] postprandial apoA1	24

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Davidson *et al.* (2007)[99] (USA)	RCT, parallel	*n* 254 (108 W, 146 M); aged 18–79 years; BMI about 31 kg/m^2; hypertriacylglycerolaemia, on simvastatin, LDL-C ≤ 10 % NCEP ATP III goal), no CVD, no HbA1c >8·0 %	Compared two treatments: (A) placebo *v.* (B) 4 g/d P-OM3 (3·4 g/d marine *n*-3 FA, 47 % EPA, 38 % DHA) on top of simvastatin 40 mg/d	B *v.* A ↓[b]	B *v.* A ↓[a,b] non-HDL-C B *v.* A ↓[a,b] VLDL-C – (LDL-C)	B *v.* A ↓[a,b]	B *v.* A ↑[b]	N/E	8
Bays *et al.* (2010)[100] (USA)	RCT, parallel	*n* 219 completed (103 W, 142 M enrolled); aged 18–79 years; BMI about 31 kg/m^2; with combined hyperlipidaemia on atorvastatin	Compared two treatments: (A) placebo *v.* (B) 4 g/d P-OM3 (3·4 g/d marine *n*-3 FA, 47 % EPA, 38 % DHA) on top of escalating dosages of atorvastatin (10–40 mg/d)	–	B *v.* A (10 mg) ↓[b] non-HDL-C, ↓[b] VLDL-C, ↓[b] RLP-C – (LDL-C)	B *v.* A (10 mg) ↓[b]	B *v.* A (10 mg) ↑[b]	–	16
Lee *et al.* (2012)[102] (Australia)	RCT, cross-over	*n* 11 completed (5 W, 6 M), aged 18–60 years; BMI <30 kg/m^2; hyperchol, on statins, no T2D	Compared two diets: (A) high ratio *n*-6:*n*-3 (30:1) (about 0·1 g/d marine *n*-3 FA) *v.* (B) low ratio *n*-6:*n*-3 (1·7:1) (about 2·2 g/d marine *n*-3 FA). Low ratio ↓ weight. All food provided	Both A and B ↓[a]	B ↓[a] LDL-C	–	–	Both A and B ↓[a] apoA1	4
Effects of plant-derived *n*-3 PUFA (α-linolenic acid)									
Dodin *et al.* (2005, 2008)[112,113] (Canada)	RCT, parallel	*n* 179 W, postmenopausal; aged 49–65 years; BMI about 26 kg/m^2; healthy, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: 40 g/d of (A) wheat germ (196 µg lignans, 4 g lipids, 6·9 % α-linolenic acid, 6 g dietary fibre) (measured: about 1883 kcal, about 48 % CHO, about 33 % fat, about 17 % protein) *v.* (B) flaxseed (21 mg lignans, 16 g lipids, 57 % α-linolenic acid, 11 g dietary fibre) (measured: about 1842 kcal, about 45 % CHO, about 35 % fat, about 17 % protein). Flaxseed diet: higher fat, PUFA and fibre, and lower CHO. Flaxseed ↓ weight (0·8 kg)	B *v.* A –0·05 (–0·09, 0·00)	A ↑[a] LDL-C	–	–	B *v.* A –0·10 (–0·18, –0·02) apoA1 – (apoB:apoA1)	52
Effects of *trans*-FA									
Mozaffarian & Clarke (2009)[81] (meta-analyses)	Meta-analysis	13 RCT; *n* 518; aged 32 years	Isoenergetic replacement of *trans*-FA by SFA	↓	– (LDL-C)	–	↑	↑ apoA1, ↓ apoB: apoA1	about 4·9
Vega-López *et al.* (2009)[115] (USA)	RCT, cross-over	*n* 30 W, postmenopausal; aged ≥50 years; BMI <35 kg/m^2; hyperchol, no T2D, no lipid-lowering drugs	Compared two diets: (A) high-*cis*-PUFA (maize oil; measured: 57 % CHO, 27 % fat, 0·3 % *trans*-FA, 17 % protein; measured: 2300 kcal) *v.* (B) high-*trans*-FA (partially-hydrogenated soyabean oil; measured: 57 % CHO, 25 % fat, 4·3 % *trans*-FA, 18 % protein; measured: 2312 kcal). Stable weight. All foods provided	B *v.* A ↑[b]	B *v.* A ↑[b] LDL-C B *v.* A ↑[b] VLDL-C (P = 0·052)	–	–	– (apoA1)	5
Wanders *et al.* (2010)[116] (Netherlands)	RCT, cross-over	*n* 61 (36 W, 25 M), aged 18–65 years; BMI ≤30 kg/m^2; healthy, no CVD, no T2D, no lipid-lowering drugs	Compared three diets: 7 % energy (about 20 g) of (A) high-*cis*-MUFA (oleic acid) (measured: 2532 kcal, 46 % CHO, 40 % fat, 0·2 % total *trans*-fat, 0·1 % CLA, 13 % protein), (B) industrial *trans*-FA (measured: 2568 kcal, 47 % CHO, 40 % fat, 7·5 % total *trans*-fat, 0·1 % CLA, 12 % protein), or (C) natural *trans*-FA (CLA) (measured: 2553 kcal, 46 % CHO, 40 % fat, 9·1 % total *trans*-fat, 9·0 % CLA, 13 % protein). Stable weight. Foods covering 90 % of energy needs provided	B *v.* A ↑[b] C *v.* A ↑[b] B *v.* C ↑[b]	B *v.* A ↑[b] LDL-C C *v.* A ↑[b] LDL-C B *v.* C ↑[b] LDL-C	B *v.* A ↑[b] B *v.* C ↑[b]	B *v.* A ↓[b] C *v.* A ↓[b]	N/E	3
Chardigny *et al.* (2008)[119] (France)	RCT, cross-over	*n* 40 (21 W, 19 M); aged about 28 years; BMI about 22 kg/m^2; healthy, normolipid, no lipid-lowering drugs	Compared two diets: 11–12 g/d or about 5 % energy of (A) natural *trans*-FA (measured: 1895–2155 kcal, 45–46 % CHO, 36–40 % fat, 15 % protein) *v.* (B) industrial *trans*-FA (measured: 1891–2096 kcal, 46–47 % CHO, 36–37 % fat, 15–16 % protein). Stable weight. Dietary counselling. Key sources of fat provided	B *v.* A ↓[b]	B *v.* A ↓[b] LDL-C	B *v.* A ↓[b]	B *v.* A ↓[b]	B *v.* A ↓[b] apoA1 – (apoB:apoA1)	3
Effects of MCFA									
Tremblay *et al.* (2014)[123] (Canada)	RCT, cross-over	*n* 28 M, aged about 38 years; abdominal obesity; insulin-resistant, HDL-C <1·1 mmol/l, TAG >1·7 mmol/l, no T2D, no monogenic hyperlipidaemia	Compared two diets: 20 g/d of (A) maize oil *v.* (B) MCFA oil. Stable weight. Key food provided	–	– (LDL-C and VLDL-C)	–	–	– (HDL apoA1)	4

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	Time (weeks)
Bohl *et al.* (2015)[124] (Denmark)	RCT, parallel	*n* 51 analysed (27 W, 25 M completed); 48 % men; aged ≥18 years; with abdominal obesity, no severe CVD, no T2D	Compared four diets: (A) whey protein (60 g/d) + milk fat (63 g/d) with low MCFA (measured: 6·9 g MCFA, about 2326 kcal, about 39 % CHO, about 40 % fat, about 20 % protein) *v.* (B) whey protein (60 g/d) + milk fat (63 g/d) with high MCFA (measured: 8·5 g MCFA, about 2448 kcal, about 38 % CHO, about 40 % fat, about 19 % protein) *v.* (C) casein protein (60 g/d) + milk fat (63 g/d) with low MCFA (measured: 6·9 g MCFA, about 2756 kcal, about 40 % CHO, about 40 % fat, about 19 % protein) *v.* (D) casein protein (60 g/d) + milk fat (63 g/d) with high MCFA (measured: 8·5 g MCFA, about 2392 kcal, about 39 % CHO, about 40 % fat, about 20 % protein). Treatment proteins and key fatty foods provided. Similar weight gain	– (apoB48)	N/E	–	N/E	N/E	12
Effects of high-cholesterol diet									
Cesar *et al.* (2006)[127] (Brazil)	Parallel	*n* 25 M; aged 17–22 years; aged about 24 kg/m^2; healthy, normolipid	Compared two diets: (A) low-cholesterol (0 egg yolk) (measured: 174 mg cholesterol, about 3776 kcal, about 61 % CHO, about 25 % fat, about 14 % protein) *v.* (B) high-cholesterol (three eggs per d) (measured: 804 mg cholesterol, about 4183 kcal, about 61 % CHO, about 24 % fat, about 15 % protein). All food provided	B *v.* A ↑[b]	B *v.* A ↑[b] LDL-C	–	B *v.* A ↑[b]	– (apoA1)	2·1
Pearce *et al.* (2011)[128] (Australia)	RCT, parallel	*n* 65 (36 W, 29 M); aged 20–75 years; BMI 25–40 kg/m^2; 91 % with T2D, impaired glucose tolerance or impaired fasting glucose, 42 % taking lipid medication	Compared two diets: hypoenergetic, high-protein diet with (A) low-cholesterol (measured: about 1437 kcal, 40 % CHO, 28 % fat, 228 mg cholesterol, 31 % protein) *v.* (B) high-cholesterol (two eggs/d) (measured: about 1467 kcal, 40 % CHO, 31 % fat, 590 mg cholesterol, 28 % protein). High-cholesterol diet: lower in protein, higher fat, SFA and folate intake. Similar weight loss on both diets. Dietary counselling	Both A and B ↓[a]	Both A and B ↓[a] non-HDL-C – (LDL-C)	Both A and B ↓ [a]	B *v.* A 0·09 (0·02, 0·16)	N/E	12
Effects of phytosterols									
Sialvera *et al.* (2012)[133] (Greece)	RCT, parallel	*n* 108 (48 W, 60 M); aged 30–65 years; BMI about 29 kg/m^2; with MS, no T2D, no CVD, no chronic disease	Compared two interventions: (A) control yogurt drink (measured: 2134 kcal, 39 % CHO, 43 % fat, 16 % SFA, 15 % MUFA, 5 % PUFA, 16 % protein) *v.* (B) phytosterol-enriched yogurt drink (4 g/d) (measured: 2131 kcal, 37 % CHO, 44 % fat, 16 % SFA, 15 % MUFA, 3 % PUFA, 16 % protein)	B *v.* A ↓[a,b]	B *v.* A ↓[b] LDL-C Both A and B ↓[a] LDL-C	B *v.* A ↓[a,b]	–	–	8
Shrestha *et al.* (2006)[76] (USA)	RCT, cross-over	*n* 33 (22 W, 11 M), 35–65 years, 25–35 kg/m^2, hypercholl, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: (A) placebo cookies (no psyllium/plant sterols) (measured: about 1978–2295 kcal, 41–49 % CHO, 35–41 % fat, 12–13 % SFA, 13–16 % MUFA, 7–8 % PUFA, 14–17 % protein) *v.* (B) treatment cookies (7·68 g/d psyllium soluble fibre, 2·6 g/d plant sterols) (measured: about 2006–2157 kcal, 45–50 % CHO, 36–39 % fat, 12–13 % SFA, 13–15 % MUFA, 7–9 % PUFA, 15–17 % protein). Stable weight. Cookies provided. Habitual diet	B *v.* A ↓[b]	B *v.* A ↓[b] LDL-C	–	–	N/E	4
Sola *et al.* (2012)[78] (Spain)	RCT, parallel	*n* 113 (67 W, 46 M); aged 43–65 years; BMI ≤35 kg/m^2; pre- or stage 1 hypertensive, hyperchol, ≥1 additional CVD risk factor, no T2D, no chronic disease, no lipid-lowering drugs	Compared four diets: (A) control cocoa cream (measured: about 2109 kcal, about 41 % CHO, about 41 % fat, about 10 % SFA, about 19 % MUFA, about 8 % PUFA, about 15 % protein) *v.* (B) cocoa + hazelnut (30 g/d) cream (measured: about 2064 kcal, about 40 % CHO, about 42 % fat, about 10 % SFA, about 22 % MUFA, about 6 % PUFA, about 15 % protein) *v.* (C) cocoa + hazelnuts + phytosterols (2 g/d) (measured: about 2151 kcal, about 45 % CHO, about 39 % fat, about 10 % SFA, about 19 % MUFA, about 5 %	C *v.* A ↓[a,b] apoB100 D *v.* A ↓[a,b] apoB100	C *v.* A ↓[a,b] LDL-C D *v.* A ↓[a,b] LDL-C	–	–	C *v.* A ↓[a,b] apoB: apoA1 D *v.* A ↓[a,b] apoB: apoA1 – (apoA1)	4

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	Time (weeks)
			PUFA, about 15 % protein) *v.* (D) cocoa + hazelnuts + phytosterols (2 g/d) + soluble fibre (20 g/d) (measured: about 2029 kcal, about 44 % CHO, about 41 % fat, about 10 % SFA, about 22 % MUFA, about 6 % PUFA, about 16 % protein). B higher in MUFA, B, C and D lower in PUFA (*v.* A). Stable weight						
Effects of soya proteins									
Campbell *et al.* (2010)[138] (USA)	RCT, parallel	*n* 62 W completed, postmenopausal; aged <65 years; BMI about 28 kg/m^2; hyperchol, no insulin-dependent diabetes, no lipid-lowering drugs	Compared two diets: 25 g/d of (A) casein proteins (0 mg isoflavones) (measured: 1850 kcal, about 53 % CHO, about 29 % fat, about 19 % protein) *v.* (B) soya proteins (60 mg isoflavones) (measured: 1582 kcal, about 51 % CHO, about 32 % fat, about 22 % protein). Both diets (*v.* baseline): increased weight (2 %) and higher protein. Soya diet: lower CHO. Dietary counselling. Soya products provided	Both A and B ↑[a]	– (LDL-C)	–	–	Both A and B ↓[a] apoA1	52
Santo *et al.* (2008, 2010)[143,144] (USA)	RCT, parallel	*n* 30 M; aged 18–30 years; BMI 18–26 kg/m^2; no CVD, no metabolic diseases, no lipid-lowering drugs	Compared three diets: 25 g/d of (A) isolated milk proteins (measured: 2710 kcal, 57 % CHO, 22 % fat, 20 % protein) *v.* (B) isolated isoflavone-poor soya proteins (measured: 2537 kcal, 54 % CHO, 24 % fat, 21 % protein) *v.* (C) isolated isoflavone-rich soya proteins (measured: 2360 kcal, 57 % CHO, 23 % fat, 20 % protein). All diets ↑ weight (1 %), protein intake (*v.* baseline). Isoflavone-poor soya protein: lower PUFA (*v.* milk). Treatment proteins provided	–	– (LDL-C)	B ↑[a] postprandial TAG – (fasting TAG)	A, B and C ↑[a]	A, B and C ↑[a] apoA1	4
McVeigh *et al.* (2006)[145] (Canada)	RCT, cross-over	*n* 35 M; aged 20–40 years; BMI 19–29 kg/m^2; healthy, no disease, no medication	Compared three diets: (A) isolated milk proteins (measured: 2564 kcal, about 52 % CHO, about 29 % fat, about 19 % protein) *v.* (B) isolated low-isoflavone soya proteins (1·64 mg isoflavones) (measured: 2536 kcal, about 50 % CHO, about 30 % fat, about 19 % protein) *v.* (C) isolated high-isoflavone soya proteins (61·7 mg isoflavones) (measured: 2587 kcal, about 51 % CHO, about 30 % fat, about 19 % protein). All three diets (*v.* baseline): higher in protein and Ca, lower in fat. Stable weight. Dietary counselling. Treatment proteins provided	–	– (non-HDL-C and LDL-C)	–	–	B *v.* A ↓[b] apoB:apoA1 C *v.* A ↓ [b] apoB: apoA1 – (apoA1)	8·1
Maki *et al.* (2010)[139] (USA)	RCT, parallel	*n* 58 (32 W, 26 M); aged 18–79 years; BMI about 28 kg/m^2; moderately hyperchol, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: 25 g/d of (A) isolated milk proteins (with high Ca content) (measured: about 1955 kcal, about 48 % CHO, about 30 % fat, about 19 % protein) *v.* (B) isolated soya proteins (measured: about 1765 kcal, about 54 % CHO, about 26 % fat, about 20 % protein). Both diets: lower fat (*v.* baseline). Soya protein: lower cholesterol, Ca and Mg; lower K intake (*v.* baseline). Milk protein: higher protein (*v.* baseline). Soya protein slightly decreased weight (1 %). Treatment proteins provided	B *v.* A ↓[a,b]	Both A and B ↓[a] LDL-C B *v.* A ↓[b] non-HDL-C Both A and B ↓[a] non-HDL-C	–	–	B *v.* A ↓[a,b] apoA1	4
Chen *et al.* (2005)[140] (Taiwan)	RCT, parallel	*n* 37 (27 W, 10 M); aged about 62 years; BMI about 23 kg/m^2; hyperlipid and normolipid, on haemodialysis, no T2D, no lipid-lowering drugs	Compared two diets: 30 g/d of (A) isolated milk proteins (measured: 32–33 kcal/kg, 49–50 % CHO, 1·2 g/kg protein, 35 % fat) *v.* (B) isolated soya proteins (measured: 32 kcal/kg, 49–50 % CHO, 1·2 g/kg protein, 35–36 % fat). Stable weight. Dietary counselling. Treatment proteins provided	B *v.* A ↓[a,b] in hyperlipid subjects only	B *v.* A ↓ [a,b] non-HDL-C B ↓[a] LDL-C in hyperlipid subjects only	B *v.* A ↓[a,b] in hyperlipid subjects only	B ↑[a] in hyperlipid subjects only	– (apoA1)	12
Chen *et al.* (2006)[141] (Taiwan)	RCT, parallel	*n* 26 (7 W, 19 M); aged about 59 years; BMI about 23 kg/m^2; hyperchol, with haemodialysis, no T2D, no lipid-lowering drugs	Compared two diets: 30 g/d of (A) isolated milk proteins (0 mg isoflavones) (measured: about 32 kcal/kg, 52 % CHO, 1·2 g/kg protein, 35 % fat) *v.* (B) isolated soya proteins (36 mg isoflavones) (measured: about 32 kcal/kg, 52 % CHO, 1·2 g/kg protein, 35 % fat). Both diets (*v.* baseline): lower SFA and cholesterol. Stable weight. Dietary counselling. Treatment proteins provided	B *v.* A ↓[a,b]	B *v.* A ↓[a,b] non-HDL-C B ↓[a] LDL-C	–	–	– (apoA1)	12

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Pipe *et al.* (2009)[146] (Canada)	RCT, cross-over	*n* 29 (13 W, 16 M), postmenopausal women; aged >19 years; BMI ≤35 kg/m^2; diet-controlled T2D, no lipid-lowering drugs	Compared two diets: beverages containing 40 g/d of (A) isolated milk proteins (0 mg isoflavones) (measured: about 2139 kcal, 237 g CHO, 79 g fat, 120 g protein) *v.* (B) isolated soya proteins (88 mg isoflavones) (measured: about 2055 kcal, 230 g CHO, 73 g fat, 119 g protein). Both diets (*v.* baseline): higher protein and Ca. Soya diet: lower SFA. Stable weight. Dietary counselling. Treatment proteins provided	–	B *v.* A ↓[b] LDL-C – (non-HDL-C)	–	–	B *v.* A ↓[b] apoB: apoA1 – (apoA1)	8·1
Kwak *et al.* (2012)[147] (South Korea)	RCT, parallel	*n* 64 (37 W, 27 M); aged 19–65 years; BMI ≥23 kg/m^2; no chronic disease, no CVD, no T2D	Compared two treatments: (A) placebo (casein, 3·9 g/d) (measured: 2472 kcal, 62 % CHO, 22 % fat, 17 % protein) *v.* (B) black soya peptide supplement (4·5 g/d) (measured: 2518 kcal, 62 % CHO, 22 % fat, 17 % protein). Test group reduced weight (no adjustment)	A ↓[a]	– (LDL-C)	–	Both A and B ↑[a]	– (apoA1)	12
Effects of cowpea proteins									
Frota *et al.* (2015)[151] (Brazil)	RCT, cross-over	*n* 38 (32 W, 6 M), postmenopausal; aged 30–70 years; BMI ≤35 kg/m^2; mild or moderately hyperchol, no CHD, no T2D, no lipid-lowering drugs	Compared two diets: 25 g/d of (A) casein (measured: 1370 kcal, about 50 % CHO, about 23 % fat, about 26 % protein) *v.* (B) cowpea protein isolate (measured: 1400 kcal, about 52 % CHO, about 22 % fat, about 26 % protein). Stable weight. Treatment proteins provided	B *v.* A ↓[a,b]	B *v.* A ↓[a,b] non-HDL-C B *v.* A ↓[a,b] LDL-C	–	B *v.* A ↑[a,b]	– (apoA1)	6
Effects of whey proteins									
Bohl *et al.* (2015)[124] (Denmark)	RCT, parallel	*n* 51 analysed (27 W, 25 M completed), 48 % men; aged ≥18 years; with abdominal obesity, no severe CVD, no T2D	Compared four diets: (A) whey protein (60 g/d) + milk fat (63 g/d) with low MCFA (measured: 6·9 g MCFA, about 2326 kcal, about 39 % CHO, about 40 % fat, about 20 % protein) *v.* (B) whey protein (60 g/d) + milk fat (63 g/d) with high MCFA (measured: 8·5 g MCFA, about 2448 kcal, about 38 % CHO, about 40 % fat, about 19 % protein) *v.* (C) casein protein (60 g/d) + milk fat (63 g/d) with low MCFA (measured: 6·9 g MCFA, about 2756 kcal, about 40 % CHO, about 40 % fat, about 19 % protein) *v.* (D) casein protein (60 g/d) + milk fat (63 g/d) with high MCFA (measured: 8·5 g MCFA, about 2392 kcal, about 39 % CHO, about 40 % fat, about 20 % protein). Treatment proteins and key fatty foods provided. Similar weight gain	– (fasting apoB48) A + B *v.* C + D ↓[b] postprandial apoB48	N/E	–	N/E	N/E	12
Effects of alcohol									
Volcik *et al.* (2008)[154] (USA)	Cross-sect.	*n* 8932 (4904 W, 4028 M, 6410 white, 2522 African-American); aged 45–64 years; no cholesterol-lowering drugs	Compared categories of ROH consumption: (A) low-moderate (men ≤210 g/week (= 3 glasses/d), women ≤105 g/week) *v.* (B) heavy (men >210 g/week, women >105 g/week) *v.* (C) never drinkers	A-wine *v.* C associated with ↓ apoB (white females)	A-wine *v.* C associated with ↓ LDL-C (white females) B-beer *v.* C associated with ↓ LDL-C (women)	A-wine *v.* C associated with ↓ TAG (white females) B *v.* C associated with ↑ TAG (African American)	A *v.* C associated with ↑ HDL-C B *v.* C associated with ↑ HDL-C	A *v.* C associated with ↑ apoA1 B *v.* C associated with ↑ apoA1	–
Tognon *et al.* (2012)[155] (Sweden)	Cross-sect.	*n* 2907 (1537 W, 1370 M); aged 25–74 years; 15 % BMI ≥30 kg/m^2, no statins	Calculation of total ethanol intake from a FFQ. Adjusted for BMI and nine factors	10 g/d ethanol associated with ↓ apoB in women	N/E	N/E	10 g/d ethanol associated with ↑ HDL-C	10 g/d ethanol associated with ↑ apoA1, ↓ apoB: apoA1	–
Liangpunsakul *et al.* (2010)[156] (USA)	Cross-sect.	*n* 8708 (5761 W, 2947 M); aged about 44 years; BMI about 26 kg/m^2	Four categories of ROH consumption: 0, <1, 1–2 and >2 drinks/d. No indication of types of ROH	Higher ROH associated with ↓ apoB	N/E	N/E	N/E	Higher ROH associated with ↑ apoA1	–
Simonsson *et al.* (2007)[157] (Sweden)	Cross-sect.	*n* 636 W, postmenopausal; aged 64 years; BMI about 27 kg/m^2; some T2D, no CVD, no lipid-lowering drugs in non-diabetics	Compared tertiles of ethanol intake: (A) 0–2·45 *v.* (B) 2·56–8·5 *v.* (C) 8·9–46·3 g/d (corresponding to 0, 0–1, 1–5 glasses/d). No distinction of types of ROH	–	N/E	N/E	N/E	C *v.* A associated with ↑ apoA1 C *v.* A associated with ↓ apoB: apoA1	–

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Naissides *et al.* (2006)[160] (Australia)	RCT, parallel	*n* 45 W completed, postmenopausal; aged 50–70 years; BMI about 26 kg/m^2; hyperchol, no T2D, no lipid-lowering drugs	Compared three diets: (A) 400 ml/d of water (measured: about 2315 kcal, 42 % CHO, 39 % fat, 19 % protein) *v.* (B) dealcoholised red wine (measured: about 2049 kcal, 42 % CHO, 39 % fat, 19 % protein) *v.* (C) red wine (about three glasses) (measured: about 2218 kcal, 49 % CHO, 33 % fat, 18 % protein). Drinks provided	–	C *v.* A ↓[b] LDL-C	–	C *v.* A ↑[b] HDL-C	N/E	6
Tomé-Carneiro *et al.* (2012)[163] (Spain)	RCT, parallel	*n* 75 (41 W, 34 M); aged 18–80 years; BMI about 31 kg/m^2; statin-treated subjects with T2D or hyperchol and one additional risk factor, no CVD	Compared three treatments: one capsule (350 mg) per d of (A) placebo *v.* (B) resveratrol-enriched (8 mg) grape extract (Stilvid) *v.* (C) grape extract (similar polyphenolic content but no resveratrol)	B ↓[a]	Both B and C ↓[a] LDL-C – (non-HDL-C)	–	–	N/E	26
Effects of specific foods									
Jenkins *et al.* (2011)[172] (Canada)	RCT, parallel	*n* 117 (39 W, 78 M), postmenopausal; aged about 62 years; BMI about 29 kg/m^2; with T2D, no CVD	Compared three treatments: 24 % energy as (A) mixed nuts (75 g/d) (measured: 2024 kcal, 39 % CHO, 41 % fat, 19 % MUFA, 9 % SFA, 9 % PUFA, 18 % protein), (B) muffins (whole-wheat, no sugar added) (measured: 1871 kcal, 44 % CHO, 35 % fat, 11 % MUFA, 11 % SFA, 9 % PUFA, 19 % protein), or (C) half portions of both (measured: 2028 kcal, 39 % fat, 41 % CHO, 16 % MUFA, 10 % SFA, 9 % PUFA, 19 % protein). Stable weight. Key foods provided	A and C *v.* B ↓[b]	A and C *v.* B ↓[b] LDL-C	–	–	A and C *v.* B ↓[b] apoB:apoA1 – (apoA1)	12
Wu *et al.* (2014)[173] (Germany)	RCT cross-over	*n* 40 (30 W, 10 M); aged ≥50 years; BMI <35 kg/m^2; healthy, normolipid, no T2D, no systemic disease, no lipid-lowering drugs	Compared two diets: (A) Western-type control diet (measured: 2013 kcal, 49 % CHO, 33 % fat, 11 % MUFA, 14 % SFA, 5 % PUFA, 16 % protein) *v.* (B) walnut-enriched diet (43 g/d) (measured: 2067 kcal, 44 % CHO, 39 % fat, 11 % MUFA, 12 % SFA, 14 % PUFA, 15 % protein). Walnut diet: higher in fat, PUFA and α-linolenic acid, lower in SFA, protein, CHO and cholesterol. Walnuts provided. Dietary counselling. Stable weight	B –0·048 (–0·082, –0·014)	B –0·07 (–0·14, 0·00) non-HDL-C – (LDL-C or VLDL-C)	–	–	N/E	8
Tey *et al.* (2011)[174] (New Zealand)	RCT, cross-over	*n* 46 (27 W, 19 M); aged 25–64 years; BMI about 26 kg/m^2; mildly hyperchol, no chronic disease, no lipid-lowering drugs	Compared three diets: 30 g of (A) ground (measured: about 2000 kcal, 41 % CHO, 36 % fat, 15 % MUFA, 11 % SFA, 6 % PUFA, 19 % protein) *v.* (B) sliced (measured: about 2012 kcal, 43 % CHO, 35 % fat, 15 % MUFA, 11 % SFA, 5 % PUFA, 18 % protein) *v.* (C) whole (measured: about 2163 kcal, 42 % CHO, 34 % fat, 14 % MUFA, 12 % SFA, 5 % PUFA, 18 % protein) hazelnuts. In replacement of high-SFA snacks. All diets (*v.* baseline): higher in vitamin E, fat and MUFA, lower in CHO. Stable weight	A, B and C ↓[a] apoB100	A, B and C ↓[a] LDL-C	–	A, B and C ↑[a] HDL-C	A, B and C ↓[a] apoB:apoA1 – (apoA1)	4
Sola *et al.* (2012)[78] (Spain)	RCT, parallel	*n* 113 (67 W, 46 M); aged 43–65 years; BMI ≤35 kg/m^2; pre- or stage 1 hypertensive, hyperchol, ≥1 additional CVD risk factor, no T2D, no chronic disease, no lipid-lowering drugs	Compared four diets: (A) control cocoa cream (measured: about 2109 kcal, about 41 % CHO, about 41 % fat, about 10 % SFA, about 19 % MUFA, about 8 % PUFA, about 15 % protein) *v.* (B) cocoa + hazelnut (30 g/d) cream (measured: about 2064 kcal, about 40 % CHO, about 42 % fat, about 10 % SFA, about 22 % MUFA, about 6 % PUFA, about 15 % protein) *v.* (C) cocoa + hazelnuts + phytosterols (2 g/d) (measured: about 2151 kcal, about 45 % CHO, about 39 % fat, about 10 % SFA, about 19 % MUFA, about 5 % PUFA, about 15 % protein) *v.* (D) cocoa + hazelnuts + phytosterols + soluble fibre (20 g/d) (measured: about 2029 kcal, about 44 % CHO, about 41 % fat, about 10 % SFA, about 22 % MUFA, about 6 % PUFA, about 16 % protein). B higher in MUFA, B, C and D lower in PUFA (*v.* A). Stable weight	C *v.* A ↓[a,b] apoB100 D *v.* A ↓[a,b] apoB100	C *v.* A ↓[a,b] LDL-C D *v.* A ↓[a,b] LDL-C	–	–	C *v.* A ↓[a,b] apoB: apoA1 D *v.* A ↓[a,b] apoB: apoA1 – (apoA1)	4

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Welty *et al.* (2007)[178] (USA)	RCT, cross-over	*n* 60 W completed, postmenopausal; aged about 60 years; BMI about 27 kg/m^2; normotensive and hypertensive, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: healthy diet (planned: 55 % CHO, 30 % fat, 15 % protein) including 25 g/d of proteins from (A) non-soya products (measured: 1399–1465 kcal) *v.* (B) soya nuts (101 mg/d isoflavones) (measured: 1554–1869 kcal). Soya diet: lower in fat and SFA in all women; higher in PUFA and protein, lower in CHO in normotensive women. Stable weight. Dietary counselling. Nuts provided	B *v.* A ↓[b] in hypertensive women only	B *v.* A ↓[b] LDL-C in hypertensive women only	–	–	N/E	8
Tabibi *et al.* (2010)[179] (Iran)	RCT, parallel	*n* 36 (18 W, 18 M); aged 18–83 years; BMI about 26 kg/m^2; peritoneal dialysis patients	Compared two diets: (A) control diet (measured: 1060 kcal, about 53 % CHO, about 34 % fat, about 15 % protein) *v.* (B) 28 g/d textured soya flour (14 g of soya protein, in replacement of 60 g of meat) (measured: 1071 kcal, about 56 % CHO, about 30 % fat, about 16 % protein). Soya diet: higher in fibre. Stable weight	– (apoB100)	– (LDL-C)	–	–	Both A and B ↓[a] apoA1	8
Back *et al.* (2011)[180] (South Korea)	RCT, parallel	*n* 55 analysed (49 W, 11 M enrolled); aged 19–65 years; BMI ≥23 kg/m^2; no disease	Compared two treatments: (A) placebo *v.* (B) 26 g/d dried chungkookjang (fermented soyabean). No significant differences in macronutrient intake. Stable weight	B *v.* A ↓[a,b]	– (LDL-C)	–	–	– (apoA1 or apoB:apoA1)	12
Tovar *et al.* (2014)[182] (Sweden)	RCT cross-over	*n* 46 W; aged 50–73 years; BMI 25–33 kg/m^2; healthy, no T2D, mild hyperchol, no medication	Compared two diets: (A) control diet (planned: 2140 kcal, 53 % CHO, 31 % fat, 16 % protein) *v.* (B) whole-grain barley and legume-rich diet (lower glycaemic index and higher prebiotics) (planned: 2130 kcal, 53 % CHO, 31 % fat, 16 % protein). Equivalence in fibre. Stable weight. Menus and key foods provided	B *v.* A ↓[a,b]	Both A and B ↓[a] LDL-C B *v.* A ↓[b] LDL-C	–	Both A and B ↓[a]	Both A and B ↓[a] – (apoB:apoA1)	4
Giacco *et al.* (2014)[183] (Italy)	RCT, parallel	*n* 54 (31 W, 23 M); aged 40–65 years; BMI about 32 kg/m^2; with MS, no T2D, no chronic diseases, no lipid-lowering drugs	Compared two diets: (A) refined (measured: 1929 kcal, 55 % CHO, 28 % fat, 17 % protein) *v.* (B) whole-grain cereal products diet (measured: 2058 kcal, 52 % CHO, 30 % fat, 18 % protein). Both diets (*v.* baseline): higher CHO, lower fat and cholesterol intake. Whole-grain diet: higher fibre, PUFA, and protein and lower MUFA, and SFA (*v.* baseline). Stable weight. Test products provided	–	– (LDL-C)	B *v.* A ↓[a,b] postprandial TAG	–	N/E	12
Drouin-Chartier *et al.* (2015)[184] (Canada)	RCT, cross-over	*n* 27 W completed, postmenopausal; aged <70 years; BMI about 32 kg/m^2; with abdominal obesity, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: (A) NCEP without milk or other dairy (measured: 2307 kcal, 56 % CHO, 29 % fat, 9 % SFA, 17 % protein) *v.* (B) NCEP diet with 3·2 servings/d of 2 % fat milk (20 % of energy) (measured: 2320 kcal, 56 % CHO, 30 % fat, 10 % SFA, 17 % protein). All meals provided. Milk diet higher in Ca and vitamin D. Adjusted for weight loss in both groups	A ↓[a] (apoB) – (VLDL apoB) B *v.* A ↓[b] VLDL apoB fractional catabolic rate (*n* 9)	– (LDL-C and VLDL-C)	–	Both A and B ↓[a]	Both A and B ↓[a] apoA1	6
Conway *et al.* (2013)[185] (Canada)	RCT, cross-over	*n* 34 (19 W, 15 M); aged 18–65 years; BMI ≤35 kg/m^2; LDL-C <5·0 mmol/l, no CVD and low risk, no T2D, no lipid-lowering drugs	Compared two treatments: 45 g/d of (A) placebo using dairy ingredients (about 35 mg phospholipids) *v.* (B) buttermilk (about 188 mg phospholipids). Difference in buttermilk milk fat globule membrane components (minor proteins and phospholipids). Stable weight	–	– (LDL-C)	B *v.* A ↓[b]	–	N/E	4
Gammon *et al.* (2014)[186] (New Zealand)	RCT, cross-over	*n* 70 M; aged 27–73 years; BMI about 27 kg/m^2; hyperchol, low (CRP <1 mg/l) *v.* medium (CRP 1–3 mg/l) inflammatory group, no chronic disease, no CVD, no T2D, no lipid-lowering drugs	Compared two diets: (A) healthy diet alone (measured: about 2060–2157 kcal, 49–50 % CHO, 27–28 % fat, 20 % protein) *v.* (B) healthy diet + two green kiwifruit/d (measured: about 2251–2272 kcal, 48–49 % CHO, 28–30 % fat, 19–20 % protein). Kiwifruit diet: higher in vitamins C and E Stable weight. Dietary counselling	–	– (LDL-C)	–	B *v.* A ↑[a,b] (in medium inflammatory group only)	B ↑[a] apoA1 B ↓[a] apoB: apoA1 (both in medium inflammatory group only)	4
Shidfar *et al.* (2011)[187] (Iran)	Pros	*n* 32 M completed; aged 40–60 years; BMI <30 kg/m^2; with T2D, no CVD, no lipid-lowering drugs	200 g/d raw tomato (measured: 1433 kcal, 138 g CHO, 35 g fat, 38 g protein). Stable weight	–	N/E	N/E	N/E	↑[a] apoA1	8

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	Time (weeks)
Mahdavi-Roshan *et al.* (2013) [188] (Iran)	RCT, parallel	*n* 56 completed (13 W, 43 M); aged 25–75 years; BMI ≤ 30 kg/m^2; with severe coronary artery disease, no T2D	Compared two treatments: (A) placebo (measured: 2451 kcal, about 57 % CHO, about 27 % fat, about 18 % protein) *v.* (B) garlic powder tablets (2·4 g/d allicin) (measured: 2566 kcal, about 57 % CHO, about 27 % fat, about 18 % protein). Stable weight	–	– (LDL-C)	–	–	– (apoA1)	13
Effects of Mediterranean diet									
Sola *et al.* (2011)[190] (Spain)	RCT, parallel	*n* 551 (308 W, 243 M); aged 55–80 years; BMI about 30 kg/m^2; at high risk for CVD, 54 % diabetes, 46 % lipid-lowering drugs, no CVD	Compared three diets: (A) control (measured: 2230 kcal, 45 % CHO, 35 % fat, 9 % SFA, 17 % MUFA, 6 % PUFA, 18 % protein) *v.* (B) Med diet + virgin olive oil (*ad libitum*) (measured: 2356 kcal, 45 % CHO, 35 % fat, 9 % SFA, 17 % MUFA, 6 % PUFA, 18 % protein) *v.* (C) Med diet + nuts (30 g/d) (measured: 2538 kcal, 39 % CHO, 41 % fat, 9 % SFA, 19 % MUFA, 10 % PUFA, 18 % protein). Dietary counselling. Olive oil/nuts provided	B *v.* A –0·029 (–0·056, –0·001)	B *v.* A –0·14 (–0·29, –0·00) non-HDL-C C *v.* A –0·20 (–0·35, –0·06) non-HDL-C Both B and C ↓[a] LDL-C	C *v.* A –0·159 (–0·279, –0·038)	B *v.* A 0·054 (0·023, 0·083) C *v.* A 0·031 (0·000, 0·062)	B *v.* A 0·033 (0·008, 0·058) apoA1 B *v.* A –0·03 (–0·05, –0·01) apoB:apoA1	13
Defoort *et al.* (2011)[191] and Vincent-Baudr *et al.* (2005)[192] (France)	RCT, parallel	*n* 135 (83 W, 52 M); aged 22–70 years; BMI about 28 kg/m^2; with moderate CVD risk, no lipid-lowering drugs	Compared two diets: (A) control (measured: about 1532 kcal, 45 % CHO, 34 % fat, 10 % SFA, 13 % MUFA, 6 % PUFA, 21 % protein) *v.* (B) Med diet (measured: about 1501 kcal, 46 % CHO, 35 % fat, 10 % SFA, 16 % MUFA, 6 % PUFA, 20 % protein). Med diet (*v.* baseline): higher fibre. Similar weight loss. Dietary counselling	B *v.* A ↓[a,b] postprandial apoB48 – (fasting apoB48)	N/E	B ↓[a] fasting TAG – (postprandial TAG)	N/E	N/E	13
Van Dijk (2012)[85] and Bos (2010)[86] (Netherlands)	Controlled, parallel	*n* 49 (27 W, 22 M); aged 45–60 years; BMI ≥25 kg/m^2, with abdominal obesity, healthy, no T2D, no lipid-lowering drugs	Compared three diets: (A) Western-type high-SFA diet (measured: about 2556 kcal, 47 % CHO, 37 % fat, 19 % SFA, 11 % MUFA, 5 % PUFA, 14 % protein) *v.* (B) Western-type high-MUFA diet (measured: about 2484 kcal, 46 % CHO, 40 % fat, 11 % SFA, 20 % MUFA, 7 % PUFA, 11 % protein) *v.* (C) Med-type high-MUFA diet (measured: about 2460 kcal, 41 % CHO, 40 % fat, 11 % SFA, 21 % MUFA, 7 % PUFA, 15 % protein). Similar weight loss. Food provided (90 % of energy intake)	B *v.* A –0·10 (–0·17, –0·03) C *v.* A –0·15 (–0·21, –0·09)	B *v.* A –0·38 (–0·65, –0·11) LDL-C C ↓[a] LDL-C	Both B and C ↓[a]	–	N/E	8
Bedard *et al.* (2012)[193] (Canada)	Pros	*n* 69 (32 W, 37 M); aged 25–50 years; BMI about 29 kg/m^2; mild hyperchol + one criterion of MS, premenopausal, no CVD, no T2D, no lipid-lowering drugs	Med diet (measured: 46 % CHO, 32 % fat, 7 % SFA, 18 % MUFA, 5 % PUFA, 17 % protein). All food provided. Greater weight loss in men. Adjusted for weight change	↓[a]	↓[a] LDL-C	–	–	↓[a] apoA1	4
Richard *et al.* (2011, 2014)[194,195] (Canada)	Pros	*n* 19 M; aged 24–62 years; BMI about 32 kg/m^2; with MS, no CVD, no T2D, no lipid-lowering drugs	Compared three diet phases: (A) isoenergetic North American (measured: 3148 kcal, 48 % CHO, 34 % fat, 13 % SFA, 13 % MUFA, 5 % PUFA, 17 % protein), followed by (B) isoenergetic Med (measured: 3170 kcal, 50 % CHO, 32 % fat, 7 % SFA, 18 % MUFA, 5 % PUFA, 17 % protein), then followed by (C) hypoenergetic Med diet (measured: 2865 kcal, 50 % CHO, 32 % fat, 7 % SFA, 18 % MUFA, 5 % PUFA, 17 % protein). Med diet higher in ROH and fibre, lower in TFA. Food provided	B and C *v.* A ↓[b] C *v.* B ↓[b] B and C *v.* A ↑[b] LDL-apoB FCR	B and C *v.* A ↓[b] LDL-C	C *v.* B and A ↓[b]	–	B *v.* A ↓[b] apoA1	5 weeks (isoenergetic diet), 20 weeks (hypoenergetic diet)
Sotos-Prieto *et al.* (2014)[196] (England)	Cross-sect.	*n* 20 986 (about 11479 W, 9507 M); aged 40–49 years; BMI about 26 kg/m^2	Compared three levels of adherence to the Med diet: (A) low *v.* (B) medium *v.* (C) high adherence, according to the Relative Mediterranean Diet Score. High score for high consumption of vegetables, legumes, fruits, nuts, cereals, fish, seafood, olive oil and moderate consumption of ROH and high score for low consumption of meat and dairy products. Adjusted for BMI and nine factors	–	–	C *v.* A associated with ↓ TAG	C *v.* A associated with ↑ HDL-C	C *v.* A associated with ↑ apoA1, ↓ apoB: apoA1	–

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					Time (weeks)
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	
Beltaifa *et al.* (2011)[197] (Tunisia)	Pros	*n* 26 W; aged 20–50 years; BMI ≥30 kg/m^2; no CVD, no T2D	Compared two treatments: (A) hypoenergetic Med diet (planned: 25–30 % energy deficit, 50–55 % CHO, <30 % fat) alone *v.* (B) added to walk–run transition speed training. Dietary counselling	–	B *v.* A ↓[b] LDL-C	Both A and B ↓[a]	B *v.* A ↑[b] HDL-C	– (apoA1)	26
Effects of vegetarian diet									
Zhang *et al.* (2013)[198] (China)	Cross-sect.	*n* 296 M; aged ≥21 years; BMI about 24 kg/m^2; vegetarian monks *v.* omnivore workers, 2 % diabetes	Compared two diets: (A) omnivorous (measured: 2364 kcal, 57 % CHO, 28 % fat, 15 % protein) *v.* (B) vegetarians (measured: 1775 kcal, 60 % CHO, 29 % fat, 12 % protein) (lower in protein, SFA and cholesterol, higher in CHO and PUFA). Adjusted for BMI	B *v.* A associated with ↓ apoB	B *v.* A associated with ↓ LDL-C	B *v.* A associated with ↓ TAG (NS when adjusted for BMI)	B *v.* A associated with ↓ HDL-C	B *v.* A associated with ↓ apoA1	–
Bradbury *et al.* (2014)[199] (Europe)	Cross-sect.	*n* 1694 (1023 W, 671 M); aged 20–90 years; BMI about 23 kg/m^2; no CVD	Compared four diets: (A) meat eaters (measured: about 1946–2211 kcal, 48–49 % CHO, 31–32 % fat, 16–17 % protein) *v.* (B) fish eaters (no meat) (measured: about 1816–2161 kcal, 50–52 % CHO, 30–31 % fat, 14–15 % protein) *v.* (C) vegetarians (no meat or fish) (measured: about 1898–2177 kcal, 51–53 % CHO, 30–31 % fat, 13–14 % protein) *v.* (D) vegans (no meat, fish, dairy products or eggs) (measured: about 1692–1912 kcal, 54–55 % CHO, 29 % fat, 13 % protein). All adjusted for BMI and three other factors	C *v.* A associated with ↓ apoB D *v.* A associated with ↓ apoB	C *v.* A associated with ↓ non-HDL-C (men only) D *v.* A associated with ↓ non-HDL-C	N/E	C *v.* A associated with ↓ HDL-C (women only) D *v.* A associated with ↓ HDL-C (women only)	D *v.* A associated with ↓ apoA1 (women only) D *v.* A associated with ↓ apoB:apoA1 (men only)	–
Karelis *et al.* (2010)[200] (Finland)	Cross-sect.	*n* 62 W; aged about 47 years; BMI about 23 kg/m^2; omnivores *v.* vegetarians, no CVD/T2D	Compared two diets: (A) omnivorous (measured: 1832 kcal, 60 % CHO, 21 % fat, 19 % protein) *v.* (B) vegetarians (measured: 1823 kcal, 65 % CHO, 19 % fat, 16 % protein). Vegetarian diet: higher in CHO and fibre, lower in protein, fat, MUFA and cholesterol. Lower BMI in vegetarians	B *v.* A associated with ↓ apoB (NS when adjusted for BMI)	N/E	N/E	N/E	B *v.* A associated with ↑ apoA1 (even when adjusted for BMI) and ↓ apoB:apoA1 (NS when adjusted for BMI)	–
Effects of Nordic diet									
Uusitupa *et al.* (2013)[204] (Finland, Sweden, Denmark, Iceland)	RCT, parallel	*n* 166 completed (126 W, 63 M enrolled); aged 30–65 years; BMI 27–40 kg/m^2; two other criteria for MS, no T2D, no chronic disease	Compared two diets: (A) control diet (measured: about 2041 kcal, 45 % CHO, 35 % fat, 16 % protein) *v.* (B) Nordic diet (high fruits, berries, vegetables, whole grains, rapeseed oil, fish, low-fat dairy products, low sugar-sweetened products) (measured: about 2042 kcal, 47 % CHO, 32 % fat, 18 % protein). Nordic diet: higher in CHO, protein, PUFA, α-linolenic acid, EPA, DHA, fibre, β-carotene, vitamins C and E, K and Mg, lower in fat, SFA, cholesterol, Na and ROH. Stable weight. Dietary counselling. Key foods provided	–	B −0·18 (−0·35, −0·01) non-HDL-C – (LDL-C)	–	–	B −0·04 (−0·07, −0·00) apoB:apoA1 – (apoA1)	18–24
Adamsson *et al.* (2011)[203] (Sweden)	RCT, parallel	*n* 86 (54 W, 32 M); aged 25–65 years; BMI 20–31 kg/m^2; healthy, mildly hyperchol (LDL-C ≥3·5 mmol/l), no lipid-lowering drugs	Compared two diets: *ad libitum* (A) control Western diet (measured: 2457 kcal, 46 % CHO, 34 % fat, 17 % protein) *v.* (B) Nordic diet (more fruits, berries, vegetables, legumes (soya), whole grains (oats, barley, psyllium), rapeseed oil, nuts (almonds), fish and low-fat milk products, less added sugars) (measured: 1989 kcal, 52 % CHO, 27 % fat, 19 % protein). Nordic diet (*v.* baseline): higher in protein, CHO, fibre and PUFA, lower in fat, SFA, cholesterol and Na. All food provided. Adjusted for weight loss	B −0·25 (−0·31, −0·19)	B −0·93 (−1·19, −0·67) LDL-C	–	B −0·19 (−0·28, −0·10)	B −0·22 (−0·29, −0·15) apoA1 B −0·06 (−0·11, −0·01) apoB:apoA1	6

Table 1. *Continued*

Reference and country	Study design	Population†	Dietary interventions‡	Plasma effects§					
				apoB (g/l)	Non-HDL-C (mmol/l)‖	TAG (mmol/l)¶	HDL-C (mmol/l)	apoA1 (g/l) or apoB:apoA1	Time (weeks)
Effects of DASH diet									
Valente *et al.* (2011)[45] (USA)	RCT, parallel	*n* 27 (16 W, 11 M), 41 % men; aged 60–75 years; BMI 25–40 kg/m^2	Compared two diets: (A) DASH hypoenergetic diet (measured: 1530 kcal) *v.* (B) DASH hypoenergetic diet (measured: 1641 kcal) + RT (40 min × 3 d/week). DASH diet ↓ fat-free mass, but not weight. DASH diet + RT ↓ fat mass and weight. Dietary counselling	B *v.* A ↓[b]	– (LDL-C)	B *v.* A ↓[b]	–	– (apoA1)	10
Hodson *et al.* (2010)[205] (UK)	Controlled parallel	*n* 27 (11 W, 16 M); aged 25–60 years; BMI 20–40 kg/m^2; no T2D, no metabolic disease, no lipid-lowering drugs	Compared two diets: (A) habitual *v.* (B) DASH diet. DASH diet: Higher in protein, CHO and NSP, lower in fat, SFA and Na. Slight weight loss in DASH group (0·9 kg). Dietary counselling. No-salt fats provided	B ↓[a]	B *v.* A ↓[a,b] LDL-C	–	B ↓[a]	N/E	4·3
Effects of Palaeolithic diet									
Ryberg *et al.* (2013)[208] (Sweden)	Pros	*n* 10 W, postmenopausal; BMI 28–35 kg/m^2; healthy, no CVD, no T2D, no lipid-lowering drugs	*Ad libitum* Palaeolithic diet (measured: 1888 kcal, 25 % CHO, 44 % fat, 28 % protein). Included lean meat, fish, fruit, vegetables, eggs and nuts. Excluded dairy and cereal products, beans, refined fats and sugar, added salt. Higher protein, fat, MUFA, PUFA, cholesterol, lower CHO, sucrose, SFA. Weight loss (5 %). Menus and prepared meals provided	↓[a]	↓[a] LDL-C	↓[a]	↓[a]	↓[a] apoA1 – (apoB:apoA1)	5

↓, Significant decrease in the plasma parameter examined; ↑, significant increase in the plasma parameter examined; –, no significant effect; AMR101, eicosapentaenoic acid ethyl ester; CHO, carbohydrates; CLA, conjugated linoleic acid; cross-sect., cross-sectional study; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; dyslipid, dyslipidaemic; FA, fatty acids; FCR, fractional catabolic rate; HbA1c, glycated Hb; HDL-C, HDL-cholesterol; HFCS, high-fructose corn syrup; hyperchol, hypercholesterolaemic; hyperlipid, hyperlipidaemic; LDL-C, LDL-cholesterol; M, men; MCFA, medium-chain fatty acids; Med, Mediterranean; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; N/E, not examined; non-HDL-C, non-HDL-cholesterol; normolipid, normolipidaemic; MS, metabolic syndrome; P-OM3, prescription omega-3-acid ethyl esters; Pros, prospective intervention study; RCT, randomised controlled trial; Ref, reference; RESMENA, Reduction of the Metabolic Syndrome in Navarra-Spain; RLP, remnant-like particles; ROH, alcohol; RT, resistance training; T2D, type 2 diabetes; TRL, TAG-rich lipoproteins; VAT, visceral adipose tissue; VLDL-C, VLDL-cholesterol; W, women.[a] Significant effect *v.* baseline; [b] significant effect *v.* control, placebo or other test diets. For cross-sectional studies, the effects were based on differences in group means. When more than two diets were compared, each diet was labelled by a letter to indicate the diets compared.

* The Table summarises the effects of each dietary component or intervention presented in the horizontal subtitles on plasma concentrations of apoB and other lipoprotein-related parameters.

† *n* Represents the number of subjects analysed in each study for plasma apoB, except when indicated as either enrolled or completed.

‡ Percentage macronutrient represents percentage of total daily energy intake of each nutrient. Percentages of energy intake from macronutrients were estimated, when necessary, using Atwater coefficients (4 kcal/g for carbohydrates and protein, 9 kcal/g for lipids). To convert energy intake to kJ, multiply by 4·184.

§ When enough data were provided, the effect size was calculated as a 95 % CI based on the change during the intervention in comparison with control, placebo or other test diets.

‖ Non-HDL-C refers to non-HDL-C, LDL-C and/or VLDL-C depending on the data provided in each paper. To convert cholesterol concentrations to mg/dl, multiply by 38·67.

¶ To convert TAG concentrations to mg/dl, multiply by 88·57.

Table 2. Summary of the effects of dietary components and healthy dietary patterns on plasma apoB and lipoprotein parameters based on the original human studies examined in the present review

Dietary factor	ApoB	Non-HDL-C*	TAG	HDL-C	ApoA1 or apoB:apoA1
Energy					
Hypoenergetic diet-induced weight loss†	↓	↔	↓	↔	↔
Carbohydrates					
Moderate-CHO/high-fat diet†	↓	↔	↓	↑	↔
Very low-CHO/high-fat diet	↔	↑ LDL-C	↓	↑	↔
Fructose (*v.* glucose)	↔	↔	↔	↔	↔
Soluble fibre: psyllium‡§	↓	↓ LDL-C	↔	↔	↔
Soluble fibre: α-cyclodextrin	↔	↔	↔	↔	N/E
Lipids					
Low-SFA/high-MUFA diet†‖	↓	↓ LDL-C	↔	↓	↔
Low-SFA/high-PUFA diet†‖	↓	↓ LDL-C	↔	↓	↔
Low-MUFA/high-PUFA diet†‖	↔	↓ LDL-C	↔	↔	↔
Marine-derived *n*-3 PUFA (EPA and DHA)†§	↓	↔	↓	↔	↔
Plant-derived *n*-3 PUFA (α-linolenic acid)	↔	↔	↔	↔	↔
Trans-FA (no effect of industrial *v.* natural)†‖	↑	↔	↔	↓	↓ apoA1, ↑ apoB:apoA1
Medium-chain FA (pure oil or dietary)	↔	↔	↔	↔	↔
Cholesterol	↔	↔	↔	↔	↔
Phytosterols‡§	↓	↓ LDL-C	↔	↔	↔
Proteins					
Soya proteins (*v.* milk proteins or casein)	↔	↔	↔	↔	↔
Cowpea proteins (*v.* casein)	↔	↔	↔	↔	↔
Whey proteins (*v.* casein)	↔	N/E	↔	N/E	N/E
Alcohol					
Moderate alcohol consumption (highlighted was red wine)	↓¶	↔	↔	↑¶	↑ apoA1¶
Specific foods					
Nuts‡	↓	↔	↔	↔	↔
Soya products, barley, legumes, whole grains, milk fat, buttermilk, kiwifruit, tomato, garlic powder	↔	↔	↔	↔	↔
Healthy dietary patterns					
Mediterranean diet‡	↓	↓ LDL-C	↓	↔	↔
Vegetarian diet	↓¶	↔	↔	↓¶	↓ apoA1¶, ↓ apoB:apoA1
Nordic diet	↔	↔	↔	↔	↔
DASH diet	↔	↔	↔	↔	↔
Palaeolithic diet	↔	↔	↔	↔	↔

Non-HDL-C, non-HDL-cholesterol; HDL-C, HDL-cholesterol; ↓, majority of the studies reviewed (>50 %) reported a decrease; ↔, lack of effect, controversial findings (<50 % in agreement) or insufficient data (≤2 studies); CHO, carbohydrates; ↑, majority of the studies reviewed (>50 %) reported an increase; LDL-C, LDL-cholesterol; N/E, not examined; FA, fatty acids; DASH, Dietary Approaches to Stop Hypertension; VLDL-C, VLDL-cholesterol; RCT, randomised controlled trial.
* Non-HDL-C includes non-HDL-C, LDL-C and/or VLDL-C depending on the data provided.
† Marks the dietary component or pattern with consistent effect based on >3 RCT.
‡ Marks the dietary component or pattern with consistent effect based on 2–3 RCT.
§ Effects examined in subjects with the metabolic syndrome and/or dyslipidaemia only.
‖ Includes conclusions reported in a previous meta-analysis.
¶ Evidence derived from cross-sectional studies and association analysis.

Simple sugars. The American Heart Association recently issued a strict recommendation to limit the intake of added sugars to 630 and 420 kJ/d (150 and 100 kcal/d) for men and women, respectively (about 6–7 % of total energy)[68]. The Dietary Intake Reference for Canadians remains more permissive with a maximal intake of ≤25 % of total energy[51]. However, neither guideline distinguishes between the types of simple sugars. Compared with glucose, fructose intake is known to be a poor stimulant of insulin secretion due to the low expression of its receptor, GLUT5, in the pancreas[69]. A high-fructose diet decreases hepatic insulin sensitivity and raises *de novo* lipogenesis and plasma TAG, effects which hinder hepatic degradation of apoB and enhance VLDL secretion[70].

Human research on the differential effects of fructose and glucose on plasma apoB is limited to two non-RCT studies (55 % CHO, 30 % fat and 15 % protein), small sample size (*n* 7–48) and short duration (2–10 weeks) (Table 1). Nevertheless, their results are consistent with present knowledge on the negative effects of fructose metabolism on plasma apoB and postprandial TAG[69,71]. In addition, increased fasting glucose and decreased postprandial insulin secretion were also reported in one study with fructose *v.* glucose intake[69]. Notably, however, both studies used 25 % of energy from fructose alone[69,71], which may not represent usual intake. More RCT are needed to determine the effect of habitual fructose intake on plasma apoB, apoB:apoA1 and other lipoprotein-related parameters.

Dietary fibres. Epidemiological and clinical studies suggest that high intake of dietary fibre is associated with reduced risk of T2D and CVD[72]. Soluble fibres, such as psyllium, reduce the reabsorption of bile acids, thus increasing cholesterol excretion[73]. Moreover, in guinea-pigs, psyllium was reported to decrease the secretion of VLDL particles and their conversion to LDL, and to enhance VLDL and LDL apoB turnover by increasing hepatic LDL receptor expression[74]. Soluble fibre

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consumption up to 10–25 g/d is recommended for hypercholesterolaemic patients by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[75] as it consistently lowers LDL-C[76–79]. It has, however, little, if any, effect on plasma TAG and HDL-C[76–79].

Human research examining the effect of dietary fibres on plasma apoB is limited to four RCT, the results of which are, however, promising (Table 1). One RCT reported that psyllium soluble fibre (7·68 g/d), in combination with plant sterols (2·6 g/d), decreased plasma apoB in subjects with hypercholesterolaemia[76] due to reduction in intermediate-density lipoprotein and LDL numbers. Interestingly, there was also a reduction in small HDL particles possibly adding to the anti-atherogenic effects of this diet. Similarly, cocoa cream enriched with hazelnuts, phytosterols (2 g/d) and soluble fibre (20 g/d) reduced plasma apoB100 and LDL-C compared with a control cocoa cream in hypertensive and hypercholesterolaemic subjects[78]. Concordant results were drawn from another RCT where the addition of Metamucil (11 g/d psyllium soluble fibre) to simvastatin therapy (10 mg, cholesterol-lowering agent) had a similar hypocholesterolaemic effect as a higher dose of simvastatin (20 mg)[77]. Soluble fibres also include α-cyclodextrin, which is derived from maize and is known to form a complex with dietary fat, reducing its bioavailability. In contrast to psyllium, no effect of α-cyclodextrin intake was observed on plasma apoB in one RCT on healthy subjects despite lower plasma LDL-C[79].

Thus, in all three out of four RCT conducted on dyslipidaemic subjects (*n* 214 in total) and ranging from 4 to 8 weeks, the intake of soluble fibre (about 8–20 g psyllium) on a dietary background of 44–50 % CHO, 36–41 % fat and 15–17 % protein reduced plasma apoB and LDL-C but did not affect TAG[76–79]. Less consistent or no data exist for VLDL-C, HDL-C, apoA1 and apoB:apoA1 (note that the macronutrient composition of these diets fits within the range reported to reduce plasma apoB in the Abstract and Conclusion). More RCT are needed to examine the independent effects of the quantity and/or types of soluble fibres on plasma apoB and apoB:apoA1.

Lipids

MUFA and PUFA v. *SFA*. High intake of SFA is known to increase plasma total, LDL-C and HDL-C and to be associated with a higher risk of cardiometabolic disease compared with the intake of unsaturated fats[54]. Current FAO/WHO guidelines limit SFA intake to less than 10 % of total energy, with the remaining fat sources as PUFA (6–11 %) or MUFA[80]. Notably, the higher limit of PUFA at <11 % was set as the risk for lipid peroxidation may increase with higher intake, particularly when tocopherol (vitamin E) intake is low[80].

A meta-analysis on twenty-five RCT[81] together with four more recent RCT and a controlled parallel trial confirmed that decreasing SFA intake by increasing MUFA intake lowers plasma apoB and LDL-C, but are less consistent in regards to plasma TAG, HDL-C, apoA1 and apoB:apoA1[62,82–86] (Table 1). In the largest RCT on 548 individuals at high risk of the metabolic syndrome, 24 weeks on a high-MUFA diet (16 %) decreased plasma apoB compared with an isoenergetic diet with high-SFA (16 %) on a similar moderate-CHO (about 42–45 %) and -fat (36–38 %) backgrounds[82]. Of note, however, an even greater effect of a combination of low fat (26–28 %) and low SFA (8–9 %) was observed on plasma apoB in that study that counterbalanced the effect of higher CHO (about 51–52 %), suggesting that lowering SFA intake is key[82]. Similar effects were also observed in eighty-five dyslipidaemic subjects at risk for T2D within high-CHO diets, where a high-CHO (55 %)/low-fat (29 %)/low-SFA (8 %) diet did not increase plasma apoB when compared with a lower-CHO (49 %)/high-fat (36 %)/high-SFA (16 %) diet with similar MUFA (16 and 14 %) and PUFA (6 %) backgrounds[83], underlying the effects of low SFA. This further underscores the need for head-to-head comparison between the specific effects of CHO, SFA and MUFA on plasma apoB. The beneficial effects of replacing SFA by MUFA were also observed in healthy men following a moderate-CHO diet (31 %)[62], in healthy subjects following a high-CHO diet (48 %)[84], in subjects at risk for T2D following a high-CHO diet (49 %)[83], and in healthy abdominally obese subjects following moderate- to high-CHO diets (41 and 46 % CHO; 95 % CI −0·09, −0·21 and −0·03, −0·17 g apoB/l, respectively)[85,86]. Finally, in the same meta-analysis by Mozaffarian & Clarke[81] on twenty-five RCT, while isoenergetic replacement of SFA by PUFA reduced plasma apoB, LDL-C and HDL-C, and induced a greater reduction in LDL-C than MUFA, the two types of unsaturated FA had similar effects on plasma apoB. This is also in line with another RCT on hypercholesterolaemic subjects[87]. No additional studies were found on the effect on PUFA on plasma apoB except for those examined in the section on *n*-3 PUFA.

A recent review on lipoprotein kinetics in humans suggests that the intake of SFA increases the pool size of LDL-apoB100 particles by decreasing their fractional catabolic rate[30]. SFA may also be linked to cardiometabolic risk through the activation of inflammatory cascades via Toll-like receptors 2 and 4 and the NF-κB-dependent pathway in murine and human cells, as reviewed[88]. This is believed to promote systemic inflammation and insulin resistance, both of which are known to reduce insulin-mediated degradation of apoB by the liver and TRL clearance by adipose tissue[70,89]. SFA can also amplify lipopolysaccharide response by promoting the generation of ceramides that activate protein kinase C–ζ and mitogen-activated protein kinases in monocytes[90,91]. Reducing SFA intake is associated with an increase in the expression of LDL receptors on mononuclear cells in humans, promoting LDL uptake[89,92]. It should be noted, however, that the association of SFA intake with chronic inflammation in humans remains controversial and may be dependent on the inflammatory marker examined[93,94]. A recent systemic analysis reported that, while positive associations were found between SFA intake with soluble intercellular adhesion molecule-1 and IL-6, no significant association or insufficient data were found with other markers such as E-selectin, TNFα and C-reactive protein[93].

In summary, in four RCT and one controlled parallel trial examined in the present review including 737 healthy or dyslipidaemic subjects, a consistent beneficial effect of reducing SFA intake (from 19 % to 8 %) by increasing MUFA intake (from 10 % to 21 %) was observed on plasma apoB and LDL-C using diets

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composed of 31–51% CHO, 26–40% fat and 11–32% protein[62,82–86]. These findings support an earlier meta-analysis published to date[81]. Plasma HDL-C was reduced with these diets, probably a reflection of the reduction in plasma cholesterol, while less consistent or insufficient data exist for VLDL-C, TAG, apoA1 and apoB:apoA1 in these studies[62,82–86]. Of note, in addition to the six diets in the section on CHO (Carbohydrates section), the macronutrient composition of the five studies examined here were used to generate the summary of the isoenergetic diets observed to reduce plasma apoB (reported in the Abstract and Conclusion).

Marine- and plant-derived n-3 *PUFA*. Fish oil and *n*-3 FA found in fish oil, EPA and DHA, have been reported to improve dyslipidaemia, inflammation, insulin resistance and hepatic steatosis in mice and humans[95,96]. The American Heart Association recommends fish consumption, at least two servings per week, or fish oil supplementation to reduce the risk of CVD[97]. Similarly, the Canadian Cardiovascular Society Guidelines indicates that the intake of *n*-3 FA (2–4 g/d of both EPA and DHA), under a physician's care, can lower plasma TAG by 25–30% in patients with hypertriacylglycerolaemia[1]. Increasing *n*-3 FA intake decreases plasma TAG and frequently VLDL-C, but rarely affects LDL-C and HDL-C[98–104].

Reduction in plasma apoB and TAG has been reported by all four RCT and one parallel trial reviewed using marine-derived *n*-3 FA supplementation (3·2 and 3·4 g/d of EPA:DHA at a 1·2:1 ratio[99,103,104] or 4 g/d EPA alone[98]) or high fish intake (1·1–1·7 g *n*-3 FA/d)[101,105], for 6–24 weeks in hyperlipidaemic subjects not taking hypolipidaemic agents (Table 1). Less consistent effects have been reported for LDL-C, VLDL-C, non-HDL-C and HDL-C and insufficient data exist for apoA1 or apoB:apoA1 in these studies. When added to statins (i.e. cholesterol-lowering agents), P-OM3 (prescription omega-3-acid ethyl esters; 3·4 g/d; EPA:DHA at a 1·2:1 ratio) further decreased plasma apoB in hyperlipidaemic patients, when simvastatin (40 mg; *n* 254)[99] not atorvastatin (10–40 mg/d; *n* 219)[100] was used. However, it is reported that atorvastatin induces a greater reduction in plasma apoB than simvastatin[106,107], which may limit additional benefits of the *n*-3 FA. Using a cross-over design, modulating the ratio of *n*-6:*n*-3 in a diet supplemented with 2·2 g/d marine-derived *n*-3 FA had no effect on plasma apoB in eleven hypercholesterolaemic subjects on statin treatment[102].

Kinetics studies have demonstrated that the reduction in plasma TAG and apoB by *n*-3 FA in human subjects is mainly due to the reduction in the production rate of apoB100 and apoB48 TRL[103–105], as recently reviewed[30–32]. When combined with weight loss, *n*-3 FA induce a greater reduction in fasting apoB48 production rate and postprandial apoB48 concentrations[104]. As secretion of TRL-TAG and TRL-apoB are closely linked, decreased TRL apoB100 secretion may be due to the inhibition of enzymes involved in TAG synthesis such as diacylglycerol acyltransferase and FA synthase, suppression of sterol regulatory element binding protein-1c gene transcription, and activation of β-oxidation[105,108]. In addition, both *n*-3 FA and *n*-6 PUFA favour hepatic apoB degradation in the post-endoplasmic reticulum pre-secretory proteolysis pathway through reactive oxygen species-induced autophagy[109].

Observational studies also support that higher intakes of plant-derived *n*-3 FA (α-linolenic acid), but not plasma levels[110], are significantly associated with moderately lower risk of CVD[97,110]. The use of vegetable oils is encouraged to increase the intake of α-linolenic acid up to 0·6–1·2% of total energy, the acceptable macronutrient distribution range established by the Institute of Medicine[111]. While few studies have examined the effect of plant-derived *n*-3 FA on apoB, a recent RCT on 179 healthy postmenopausal women reported that the intake of 40 g/d of flaxseeds with high α-linolenic acid compared with an equal amount of wheat germ had a small but modest benefit on plasma apoB (95% CI –0·00, –0·09 g/l; Table 1)[112,113]. However, the conversion of plant- into marine-derived *n*-3 FA is at less than 1%[114] and the mechanism by which α-linolenic acid benefits cardiometabolic health in humans may not involve plasma lipids and apoB.

In summary, for all four RCT and one parallel study conducted mostly on hyperlipidaemic subjects (*n* 411 in total) and ranging from 6 to 24 weeks, the intake of marine-derived *n*-3 FA, from oily fish (1·1–1·7 g/d) or supplementation (3·2–3·4 g/d EPA and DHA or 4 g/d EPA alone) reduced plasma apoB and TAG with less consistent benefits or insufficient data on the other lipids[98,101,103–105]. Insufficient data also exist for the additional benefit of *n*-3 FA in combination with statins (two RCT; *n* 473) (note that not all studies reported the macronutrient or FA composition of the background diets to provide their summary). More RCT examining the additional effects of *n*-3 FA in combination with hypolipidaemic agents on plasma apoB and the apoB:apoA1 ratio are needed.

Trans-*fatty acids*. A higher consumption of *trans*-FA from industrial partially hydrogenated fats, a characteristic of the Western diet with high intake of processed food, is associated with higher risk of CVD[31]. Isoenergetic substitution of *trans*-FA by SFA reduces plasma apoB and apoB:apoA1 and increases HDL-C and apoA1, as reported in a meta-analysis of thirteen trials[81]. Only two more recent RCT were found, in both of which decreasing *trans*-FA (from 7·5 and 4·3% to <0·5%) by increasing *cis*-PUFA[115] or *cis*-MUFA[116] also led to a decrease in plasma apoB. *Trans*-FA increase the pool size of LDL apoB100 by decreasing their fractional catabolic rate, but have no effect on VLDL apoB100[30].

Trans-FA can also be produced naturally during the bio-hydrogenation of dietary PUFA by anaerobic bacteria in the rumen, and thus exist in small amounts (about 2–5%) in meat and dairy products derived from ruminants[117]. Contradictory findings exist regarding the impact of natural *trans*-FA on CVD risk; while observational studies found no association[118], a cross-over trial reported that a diet high in conjugated linoleic acids and naturally occurring double-bonds increased plasma apoB and LDL-C and decreased HDL-C compared with a high-MUFA diet[116]. Contradictory findings also exist as to whether industrial *trans*-FA have a higher[116] or a lower[119] impact on plasma apoB than natural *trans*-FA. However, sex-specific effects of natural *trans*-FA on increasing plasma LDL-C, HDL-C, apoB and apoA1 in women but not in men have been reported and may need to be accounted for in future studies[119].

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Of importance to note is that, in 2007, Health Canada recommended that the content of *trans*-FA in vegetable oils and soft, spreadable margarines should be limited to 2% of the total fat, while that of all other foods including ingredients sold to restaurants should be limited to 5%. It also gave the food industry a 2-year window to achieve these recommendations[120]. This strategy appears to have achieved a positive impact, as the Canadian consumption of *trans*-FA has declined by 40% over the past decade (from 8·4 to 4·9 g/d)[120]. Moreover, in June 2015, the US Food and Drug Administration removed partially hydrogenated oils, the main source of artificial *trans*-FA in processed foods, from the 'generally recognized as safe' list and gave food manufacturers 3 years to remove them from their products[121]. The current recommendation to promote cardiovascular health by both the American[52] and the Canadian[51] guidelines is to reduce *trans*-FA to the least possible. This is also in line with the recommendation of the WHO of <1% of total energy per d[120]. Thus, while plasma apoB was increased in the two RCT examined, the amounts of *trans*-FA used (4·3% or about 11 g/d[115] and 7·5% or about 20 g/d[116]) are unlikely to represent current habitual intake.

Medium-chain fatty acids. Medium-chain FA (MCFA) contain 6–12 carbons. Unlike long-chain FA, MCFA are usually absorbed directly into the portal circulation without the need for being incorporated in the chylomicron particles. Accordingly, oil made from MCFA is prescribed to treat patients with familial hyperchylomicronaemia[122].

Only two studies with limited sample size (*n* 28 and 51) and duration (4 and 12 weeks) were reported on the effect of MCFA on plasma apoB in human subjects. Nevertheless, both studies reported no effect of high MCFA intake, as pure oil (20 g/d) or milk fat (8·5 *v.* 6·9 g/d), on fasting or postprandial plasma apoB, TAG, LDL-C, VLDL-C or apoA1[123,124] in subjects with abdominal obesity alone[124] or with secondary hypertriacylglycerolaemia[123]. No data were reported on plasma apoB:apoA1 in either study. These findings are also in line with the lack of an effect of MCFA on apoB reported in a recent review on the effect of dietary FA on lipoprotein metabolism[30]. As MCFA are suggested to increase fat oxidation[125], more RCT comparing different types and higher doses of MCFA (with attention to possible gastrointestinal symptoms) or in combination with weight-loss intervention may be needed.

Dietary cholesterol. The impact of dietary cholesterol on plasma lipids and CVD risk remains controversial. To reduce the risk of CVD, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends limiting the intake of dietary cholesterol to 200 mg/d for subjects with hyperlipidaemia[75]. However, the recent American Heart Association/American College of Cardiology guidelines to reduce CVD concluded that there is insufficient evidence to determine whether lowering cholesterol intake reduces LDL-C[126]. Studies examining the specific effect of cholesterol on plasma apoB are also scarce and limited in size[127,128]. Consumption of a high-cholesterol diet (804 mg/d; three eggs/d) in twenty-five normolipidaemic healthy young men increased plasma LDL-C, HDL-C and apoB, without affecting plasma TAG, apoA1 and Lp(a) compared with a low-cholesterol diet[127]. In contrast in patients with T2D or prediabetes (42% on lipid-lowering medications), consumption of a high- or low-cholesterol (590 *v.* 228 mg/d)/hypoenergetic/high-protein diet led to similar reductions in weight and plasma apoB, non-HDL-C, TAG, glucose, and insulin and blood pressure, whereas only the high-cholesterol diet led to an increase in HDL-C[128]. However, weight loss and improved insulin sensitivity on both diets may have masked the effects of high cholesterol *per se* on plasma apoB. More RCT are needed to determine the independent effect of dietary cholesterol on plasma apoB and apoB:apoA1.

Phytosterols. Phytosterols are plant-derived steroid compounds similar in structure and function to cholesterol[129]. Current recommendations for hyperlipidaemic patients[75] include 2 g/d of phytosterols, which is known to reduce LDL-C[130,131]. Dietary sources of phytosterols include vegetable oils, cereals and nuts and provide about 300 mg/d, as reported in a British population[132]. Only three RCT explored the effects of phytosterol-enriched foods in subjects with the metabolic syndrome[133], hypertension and/or hypercholesterolaemia (*n* 254 in total)[76,78]. All three RCT reported a consistent improvement in plasma apoB and LDL-C when phytosterols were added to a yogurt drink (4 g/d)[133], a cocoa–hazelnut cream (2 g/d)[78] or in combination with soluble fibres (7·68 g/d psyllium and 2·6 g/d phytosterols[76]). It is thus not possible to isolate an independent effect of phytosterol alone in these RCT. Of note, the background dietary composition of the phytosterol-enriched diets was 37–50% CHO, 36–44% fat and 15–17% proteins, which is within the range observed to reduce plasma apoB (reported in the Abstract and Conclusion). More studies are needed to confirm the effect of phytosterols *per se* on plasma apoB and other lipids.

Proteins

Soya proteins. Following the publication of a meta-analysis supporting the negative association of soya protein intake with plasma cholesterol[134], the US Food and Drug Administration permitted the food industry to claim that '25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease'[135]. Soya proteins are reported to increase the clearance of apoB-lipoproteins by enhancing the synthesis of bile acid, increasing LDL receptor activity, and reducing hepatic particle secretion[136,137]. On the other hand, increased insulin growth factor binding protein-3 has also been reported with soya protein intake, which suggests reduced bioavailability of insulin growth factor-1 and increased CVD risk[138].

Eight RCT explored the impact of isolated soya proteins, in comparison with isolated milk proteins, on plasma apoB and lipids and their findings are inconsistent. Replacement of isolated milk proteins by isolated soya proteins (25–30 g/d) reduced plasma apoB, LDL-C and non-HDL-C in hypercholesterolaemic or hyperlipidaemic patients without[139] or with haemodialysis[140,141], but had no effect on plasma LDL-C or apoB in normolipidaemic subjects[140]. However, accumulation of isoflavones due to lack of renal excretion and unavailability of isoflavones for dialysis have been reported, which may limit the applicability of the results[142].

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In contrast, no benefits on plasma apoB were reported in healthy men[143–145] or patients with diet-controlled T2D[146] consuming isolated soya proteins in comparison with isolated milk proteins, nor in healthy subjects supplemented with black soya peptide in comparison with casein[147]. On the other hand, an RCT in hypercholesterolaemic postmenopausal women reported an increase in plasma apoB, which was, however, accompanied by an increase in weight with both soya and casein proteins[138].

It should be noted, however, that an interaction was identified between plasma apoB and equol urinary excretion status[146]. Equol is a type of isoflavone produced endogenously in the intestine, which not all humans have the ability to synthesise[148,149]. It has a greater oestrogen receptor-binding affinity and antioxidant capacity than other types of isoflavones. This may add to the inter-subject variability in the response to isoflavones. Moreover, as isoflavones are known to bind oestrogen receptors[150], sex differences may also need to be explored. In addition to isoflavones, soya protein isolates contain other components such as saponins, phytic acid and trypsin inhibitors, which are biologically active molecules that may influence lipid profile[136]. While the specific effect of isoflavones on plasma apoB and lipids is yet to be demonstrated[143–145], that of the other components have not yet been examined.

Finally, the effect of non-soya protein was also examined in one RCT in comparison with casein protein in thirty-eight hypercholesterolaemic subjects. The intake of 25 g/d of cowpea protein isolate was reported to decrease plasma apoB, non-HDL-C and LDL-C and to increase plasma HDL-C[151].

In summary, inconsistent findings were observed in eight RCT (*n* 341; 4–52 weeks) examining the effect of replacing isolated milk proteins or casein with soya proteins on plasma apoB and lipids[138–147]. However, three out of the four RCT conducted with 121 hyperlipidaemic subjects reported a decrease in plasma apoB and LDL-C with the intake of 25–30 g/d isolated soya protein over 4–12 weeks. More RCT are needed to confirm whether the effects of soya proteins are specific to subjects with hyperlipidaemia, are restricted to a specific soya protein component (i.e. isoflavones) or include other non-soya legume proteins.

Whey proteins. Milk proteins comprise a soluble fraction named whey and an insoluble fraction named casein[152]. Whey proteins are recognised as immunomodulators, antioxidants and nutrient carriers (FA, retinol and Fe). Studies on the effect of whey proteins on lipid metabolism are scarce. However, consumption of 60 g/d whey protein, compared with an equal amount of casein, on a similar background diet of milk fat (63 g/d) with low or high MCFA reduced postprandial apoB48 in fifty-one subjects with abdominal obesity, an effect that remained significant after adjustment for age, sex, blood pressure, statin intake and weight change[124]. More RCT are needed to explore the effect of whey protein *v.* casein or other types of proteins on lipoprotein profile in healthy and hyperlipidaemic subjects.

Alcohol

The Canadian Low-Risk Alcohol Drinking Guidelines recommend moderate alcohol consumption, defined as less than fifteen drinks for men and ten drinks for women per week[153]. The protective effect of alcohol consumption, ranging from low to high, on plasma HDL-C was reported in the Atherosclerosis Risk in Communities (ARIC) cross-sectional study in 8932 middle-aged subjects[154]. In contrast, only low-to-moderate alcohol consumption (about 1·5 drinks/d), compared with lack of, was associated with a lower plasma apoB and TAG in that study, and the effect was limited to wine drinkers who were also white women[154]. In another cross-sectional study in 2907 Swedish adults, total ethanol intake (about one drink/d) correlated with lower plasma apoB in women only and higher HDL in all subjects after adjustment for multiple confounders[155]. In the larger Third National Health and Nutrition Examination Survey (NHANES III) study on 8708 adults, plasma apoB decreased across the quartiles of higher alcohol consumption (>2 and 1–2 drinks/d), although no adjustment was made for potential confounders such as the types of alcohol or sex[156]. In contrast, in a smaller cross-sectional study on 636 postmenopausal women, alcohol consumption was not associated with plasma apoB *per se* but with a lower plasma apoB:apoA1 ratio[157].

Heavy alcohol consumption promotes alcoholic fatty liver disease, elevated hepatic apoB mRNA and higher plasma TAG[158,159]. This may explain why in the ARIC study, heavy alcohol consumption (>210 g/week or about >3 glasses/d for men, >105 g/week or about >1·5 glasses/d for women) did not have beneficial association with plasma apoB[154]. Moreover, a J-shaped relationship has been described in regards to plasma TAG, where low-moderate alcohol consumption is associated with lower plasma TAG while heavy alcohol consumption is associated with higher plasma TAG[159]. A similar relationship may exist in regards to plasma apoB.

Only two studies employed an RCT design to examine the effect of alcohol or grape extract on plasma apoB. In one RCT, daily consumption of red wine (about three glasses), though not dealcoholised red wine, reduced fasting plasma LDL-C and increased HDL-C, but had no effect on plasma apoB in forty-five postmenopausal women[160]. This is in contrast to *in vitro* findings where incubation of HepG2 cells[161] or Caco-2 intestinal cells[162] with either red wine or dealcoholised red wine, but not ethanol, reduced apoB100 synthesis and apoB48 secretions, respectively. Of note, red wine may provide a greater health benefit compared with other alcoholic beverages due to its high resveratrol content, a polyphenol recognised for its cardioprotective properties. In another RCT, resveratrol-enriched (8 mg) grape extract reduced plasma apoB and oxidised LDL without any effect on plasma TAG or HDL-C in statin-treated patients[163]. Finally, the few studies that examined the effect of alcohol on apoA1 (four studies) and apoB:apoA1 (two studies) reported a benefit on these parameters.

Thus, most evidence to date on the association of alcohol consumption with reduced plasma apoB is derived from three out of four cross-sectional population studies (20 547 in total[154–157]), while the available RCT on forty-five women reported no effect[160]. More research employing the RCT design is needed to explore the role of the quantity and the type of alcohol consumed on the regulation of plasma apoB,

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apoB:apoA1 and other lipoprotein-related parameters in healthy and hyperlipidaemic subjects.

Effects of micronutrients on plasma apoB

In line with their antioxidant properties that combat oxidative stress involved in the pathogenesis of T2D, high dietary intake of vitamins A, C and E and Mg have been associated with lower risk of diabetes[164,165]. Moreover, a protective role for a higher intake of vitamin D on the development of the metabolic syndrome has been reported in association studies[166,167]. However, interventional studies using these micronutrients reported conflicting results[164,168] and none addressed plasma apoB. Much more research is needed in this area.

Effects of specific foods and healthy dietary patterns on plasma apoB

Studying the effect of healthy food items and dietary patterns is essential and may have a greater benefit on atherogenic apoB-lipoproteins than the individual components described above. This is due to their high complexity, possible nutrient interactions and presence of other non-nutritive bioactive components such as phytochemicals. Moreover, the effects of nutrients that may remain unidentified are also considered.

Specific foods

Nuts contain a high amount of fat of favourable FA composition, which would be expected to reduce plasma apoB. These food items are low in SFA and have almost half of their total fat content in the form of MUFA, except for walnuts that are predominantly composed of PUFA[169]. Nuts are also rich in fibre, several vitamins and minerals and phytochemicals including phenols (particularly walnuts), phytosterols, proanthocyanidins and carotenoids[170]. High intake of such phytochemical-rich foods has been associated with lower risk for abdominal obesity and hypertriacylglycerolaemia[171].

Three RCT reported that the consumption of mixed nuts (75 g/d or half a portion in 117 T2D subjects)[172], walnuts (43 g/d in forty healthy subjects)[173] or hazelnuts (30 g/d in forty-six hypercholesterolaemic subjects)[174] reduces plasma apoB, with no effect on TAG and inconsistent effects on the other lipoprotein parameters. In contrast, one RCT reported no effect of hazelnuts (30 g/d) when added to a cocoa cream alone, and a decrease in plasma apoB100 and LDL-C when combined with phytosterols and soluble fibre[78]. Of note, these studies used a background diet of 39–45 % CHO, 34–41 % fat, 15–19 % protein, 11–22 % MUFA, 9–12 % SFA and 5–14 % PUFA, which is within the ranges observed to reduce plasma apoB (summarised in the Abstract and Conclusion). More RCT are needed to confirm the effect of nuts on plasma apoB and other lipoprotein parameters.

Higher consumption of soya nuts and products is believed to favour a lower incidence of CVD in the Asian compared with the Western population[175–177]. However, results are inconsistent in regards to the effects of different soya products on plasma apoB. Consumption of soya nuts instead of equal amounts of non-soya products was reported to reduce plasma apoB and LDL-C in hypertensive, though not normotensive, postmenopausal women[178]. In contrast, no improvement in plasma apoB was reported in subjects on peritoneal dialysis with the consumption of soya flour that provided more soya proteins and fibres compared with a control meat diet[179]. On the other hand, fermented soyabean reduced plasma apoB, though not lipids, in healthy subjects[180]; however, fermentation of isoflavones is known to increase their bioavailability by carrying out their conversion from glycones to bioactive aglycones[181].

Studies examining the effects of whole-grain- and legume-rich diets on plasma apoB are scarce and inconsistent. In one RCT in forty-six healthy women, a diet rich in whole-grain barley and legumes reduced plasma apoB and LDL-C in comparison with a diet with equivalent macronutrients and fibres[182]. In another study, no effects of mixed whole-grain cereal products on plasma apoB were reported in fifty-four subjects with the metabolic syndrome[183]. However, these specific foods contain prebiotics such as dietary fibre, resistant starch, α-galactosides and β-glucans, as well as polyphenols and phenolic acids, all of which can be used as substrates for colonic fermentation. The subsequent production of SCFA and their influence on lipid metabolism deserve further studies.

Other specific food items explored in regards to their effects on plasma apoB include: partially skimmed 2 % fat milk (3·2 servings/d) in twenty-seven postmenopausal women with abdominal obesity[184], buttermilk (45 g/d) in thirty-four subjects with low risk of CVD[185], kiwifruit (two per d) in seventy men with hypercholesterolaemia[186], raw tomato (200 g/d) in thirty-two men with T2D[187], and garlic powder (2·4 g/d allicin) in fifty-six subjects with severe coronary artery disease[188]. None of these foods had an effect on plasma apoB, and had only a minor, if any, effect on the other plasma lipoprotein parameters.

Mediterranean diet

The Mediterranean diet (Med diet) captured the interest of many scientists in the early 1960s because of longer life expectancy and lower prevalence of CVD observed in Greece and southern Italy[189]. These populations have a high consumption of fruits, vegetables, cereal products, potatoes, beans, nuts and seeds, use olive oil as the principal source of fat, have frequent intake of fish and sea products, moderate intake of wine, dairy products, poultry and eggs, and low intake of red meat and sweets. This dietary pattern translates into a diet that is moderate in alcohol, CHO and fat content, low in SFA and cholesterol, and high in MUFA, *n*-3 PUFA and fibre, all of which promote a lower plasma apoB. In addition to its high nutritional quality, a Med diet may reduce plasma apoB as it supports weight loss secondary to its low energy density and high satiety effect.

Of the seven studies examining the effect of a Med diet on plasma apoB, only two employed an RCT design. They reported a decrease in fasting plasma apoB (95 % CI –0·001, –0·056 g/l[190]) or postprandial apoB48[191,192] on 13 weeks of a Med diet (45–46 % CHO, 35 % fat, and 18–20 % protein, 9–10 % SFA, 16–17 % MUFA, 6 % PUFA) in a total of 686 subjects at risk

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for CVD. A reduction in plasma TAG was also induced with both diets, while insufficient data exist for the other lipoprotein parameters. Notably, the high-MUFA/low-SFA content of the Med diet appears to play a major role. In a controlled parallel trial, a Western-type diet (46 % CHO, 40 % fat, 11 % protein) also reduced plasma apoB, LDL-C and TAG when MUFA intake was increased (11 to 20 %) and that of SFA was reduced (19 to 11 %) in abdominally obese subjects, and to a similar extent as a Med diet (average –0·10 *v.* –0·15 g/l, respectively)[85,86]. Results from two prospective intervention studies also support a favourable impact on plasma apoB and LDL-C, independent of weight loss[193–195], which was attributed to increased LDL-apoB fractional catabolic rate[194,195]. Similarly, a large cross-sectional study (*n* 20 986) reported an association between a Med diet score and lower apoB:apoA1 and TAG and higher HDL-C, even after adjustment for BMI and nine other confounders[196]. The impact of a hypoenergetic Med diet as a weight-loss intervention is less clear; prospective intervention studies found either a reduction of[194,195], or no impact on[197], plasma apoB. However, the first population was in nineteen men with the metabolic syndrome[194,195], while the other was in twenty-six healthy women[197]. Thus the heterogeneity and small sample size of the populations examined probably affected the outcomes.

In summary, two RCT and three intervention studies reported the reduction in plasma apoB, LDL-C and TAG using a Med dietary pattern (41–50 % CHO, 32–40 % fat, 15–20 % protein, 16–21 % MUFA, 7–11 % SFA, 5–7 % PUFA) over 4–13 weeks in a total of 823 subjects, the majority of whom (>94 %) were at risk for CVD[85,86,190–195]. Of note, the composition of these Med diets used fits within the macronutrient ranges observed to reduce plasma apoB (summarised in the Abstract and Conclusion). Furthermore, a large cross-sectional study also reported that higher adherence to a Med diet is associated with lower plasma apoB:apoA1 and TAG and higher HDL-C in 20 986 British subjects. More RCT are needed to confirm the beneficial effect of a weight-maintenance or a hypoenergetic Med diet on plasma apoB, apoB:apoA1 in comparison with other lipoprotein parameters in healthy and hyperlipidaemic subjects.

Vegetarian diet

Vegetarian diets are associated with lower plasma cholesterol and prevalence of CVD and T2D[198]. Vegetarian diets exclude meat, poultry and/or fish, while vegan diets exclude all animal products, resulting in lower SFA and cholesterol and higher MUFA, PUFA and fibre intake, which is expected to reduce plasma apoB. While this hypothesis is yet to be proven by RCT, three cross-sectional studies on vegetarian/vegan diets reported lower plasma apoB in Europeans (*n* 1694)[199] and Buddhist monks (men) (*n* 296)[198], even after adjustment for confounders such as BMI, while adjustment for BMI in sixty-two women eliminates their significance[200]. Vegetarian diets were also associated with lower HDL-C and apoA1 after adjustment for many confounders, probably secondary to their higher CHO content compared with the omnivorous control diets in these studies[198,199]. They were also associated with lower apoB:apoA1 in men[200], while their association with lower apoB:apoA1 in women was eliminated after adjustment for BMI[200]. These findings need to be confirmed by RCT.

Moreover, indole-3-carbinol, which is produced from the breakdown of the glucosinolate glucobrassicin found at relatively high levels in cruciferous vegetables such as broccoli, cabbage, and cauliflower was reported to reduce apoB production in HepG2 cells[201]. Human studies are lacking and the role of the vegetarian diet and its components needs to be explored.

Nordic diet

Consumption of traditional Nordic foods has been associated with lower total mortality[202]. Though limited, two recent RCT using Nordic diets that mainly included higher intake of wholegrain products, berries, fruits, vegetables, rapeseed oil, fish and low-fat dairy products, and lower intake of sugar-sweetened products, reported a reduction in either plasma apoB (95 % CI –0·19, –0·31 g/l)[203] or apoB:apoA1 ratio (95 % CI –0·01, –0·11 g/l)[203,204] in subjects with hypercholesterolaemia or the metabolic syndrome. A less consistent effect was observed for LDL-C, HDL-C and apoA1, while no effect was reported for plasma TAG. The beneficial effects of Nordic diets may be attributed to higher intakes of fibre and PUFA and a lower intake of SFA[203,204]. Other dietary benefits include increased micronutrient intake (β-carotene, vitamin C, vitamin E, K, Mg) and/or decreased cholesterol and Na intake; although the specific effects of these nutrients on plasma apoB remain unclear. More RCT are needed to explore the effects of a Nordic diet on weight loss or maintenance in various populations.

Dietary Approaches to Stop Hypertension diet

The Dietary Approaches to Stop Hypertension (DASH) encourage higher intake of fruit and vegetables, whole-grain cereals, low-fat dairy products and nuts, and lower intake of salt, refined CHO and SFA. Two trials, one of which was a RCT, reported that a DASH diet led to a reduction in plasma apoB with variable effects on plasma lipids[45,205]. However, the impact of reduced Na intake *per se* on plasma apoB is rarely explored. One study that examined this reported no effect of a 7 d low-Na diet on plasma apoB, LDL-C and TAG with a decrease in HDL-C in normotensive men[206]. More RCT are also needed exploring the effects of a DASH diet on plasma apoB.

Palaeolithic diet

During the Palaeolithic period, our ancestors lived as hunter–gatherers, eating wild animal-source foods (lean meats, fish, eggs, no dairy) and uncultivated plant-source foods (fruits, vegetables, nuts, no cereal grains and legumes)[207]. This period was followed by agriculture (predominantly of cereals) and animal domestication and more recently, by the industrial revolution (refined fats and sugar, added salt), which introduced major dietary changes. One hypothesis states that time was insufficient for evolutionary adaptation and that a Palaeolithic diet would optimise our metabolism and reduce risk of contemporary chronic diseases. The only study that examined this hypothesis only included ten women with a short duration (5 weeks), not allowing any solid conclusion. Nevertheless, this

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study reported a reduction in plasma apoB, LDL-C, TAG, HDL-C, together with weight loss, in ten postmenopausal women following an *ad libitum* Palaeolithic diet[208], which may be related to the high MUFA and PUFA and low CHO and SFA content of this diet. More RCT are needed exploring the effects of a Palaeolithic diet in comparison with a Western diet or healthy dietary patterns on plasma apoB and other lipoprotein parameters in various populations.

Conclusion

We analysed eighty-seven recent original studies published within the past 10 years on the concomitant modulation of plasma apoB and other lipoprotein parameters by nutritional components and dietary patterns. When an effect of a dietary component or pattern was reported by the majority of ≥3 interventional studies, the effect was indicated as significant in Table 2. Effects derived from association studies were also highlighted.

Consistent data from seven studies, three of which were RCT, in a total of 335 overweight and obese healthy or hyperlipidaemic subjects indicated that plasma apoB was reduced with hypoenergetic diet-induced weight loss of 6 to 12 %, using diets composed of 5440–7110 kJ (1300–1700 kcal/d), 34–50 % CHO, 27–39 % fat, and 18–24 % protein[41–47]. Eleven interventional studies, eight of which were RCT, compared macronutrients in isoenergetic diets in a total of 1189 healthy or hyperlipidaemic subjects. These were the studies that compared the effects of different amounts of CHO (see the Carbohydrates section[56,59–63]) or replacing SFA by MUFA (see the MUFA and PUFA *v.* SFA section[62,82–86]). The diets that reduced plasma apoB over 3–24 weeks were composed of 26–51 % CHO, 26–46 % fat, 11–32 % protein, 10–27 % MUFA, 5–14 % PUFA and 7–13 % SFA. Notably, among these diets, those that used higher CHO also used higher MUFA and/or lower SFA; thus it is not clear which of these macronutrients has the largest effect on plasma apoB. Nevertheless, replacement of CHO in high- or moderate-CHO diet by MUFA, not SFA, decreased plasma apoB. Few studies were found comparing the effect of MUFA *v.* PUFA on plasma apoB; however, this may be due to the recent meta-analysis reporting the lack of difference between these two types of unsaturated FA[81].

Five studies, including four RCT, reported that the intake of marine-source *n*-3 FA from natural fish sources (1·1–1·7 g/d) or supplementation (3·2–3·4 g/d, EPA:DHA, 1·2:1 or 4 g/d EPA alone) decreased plasma apoB[98,101,103–105]. This was examined mostly in hyperlipidaemic subjects (*n* 411). Additional effects of *n*-3 FA (3·4 g/l) on plasma apoB was reported with simvastatin[99], but not with atorvastatin[100]. While fewer RCT exist (three or four per component), they indicate that enriching the diet with soluble fibre such as psyllium (about 8–20 g/d)[76–79], phytosterols (about 2–4 g/d)[76,78,133] or nuts (30–75 g/d)[172–174] decreases plasma apoB (examined only in hyperlipidaemic subjects for psyllium and phytosterol). A high intake of *trans*-FA (4·3–9·1 %)[115,116] has been reported to increase plasma apoB. However, with the worldwide recommendation to reduce *trans*-FA intake to <1 %, it is unlikely that these elevated doses represent usual consumption. While inconsistent data were found in eight RCT regarding the replacement of milk proteins with soya proteins (25–30 g/d)[138–147], the effect of soya protein may be specific to patients with hyperlipidaemia. Differential regulation of plasma apoB and TAG *v.* non-HDL-C, LDL-C and VLDL-C by weight loss, moderate CHO and high *n*-3 FA intake was noted, as these appear to benefit plasma apoB and TAG only.

Solid evidence from five studies[85,86,190–195], including two RCT[190–192], in a total of 823 subjects mostly at risk for CVD indicates that following an isoenergetic Med diet decreases plasma apoB, LDL-C and TAG. Cross-sectional studies suggest that alcohol consumption[154–157] and vegetarian diets[198–200] are associated with lower plasma apoB in 20 547 and 2052 subjects, respectively. However, RCT are lacking to confirm these observations and clarify the quantities and types of alcohol with the biggest effect of plasma apoB. Few other studies examined the regulation of the plasma apoB:apoA1 ratio; thus findings were insufficient. No effect or insufficient data were found using specific dietary components (MCFA as oil or in dietary items, fructose *v.* glucose, α-cyclodextrin *v.* psyllium fibre, plant-derived PUFA α-linolenic acid, whey or cowpea protein), dietary patterns (DASH, Nordic or Palaeolithic diet), food items (soya products, barley, legumes, whole grains, buttermilk, milk fat, kiwifruit, tomato, garlic powder) and vitamins and minerals. Future RCT need to explore the effects of these dietary components and patterns on plasma apoB and apoB:apoA1, and confirm the beneficial roles of soya protein, moderate alcohol intake, and vegetarian diets in healthy and hyperlipidaemic subjects during weight-loss or weight-maintenance interventions.

In summary, the healthy dietary pattern with the strongest reported evidence to reduce plasma apoB is a Mediterranean diet. This is probably because it encompasses the overall macronutrient composition (moderate CHO and fat, high *n*-3 FA, MUFA and PUFA, low SFA, and moderate alcohol) and dietary components (high psyllium, phytosterols and nuts) individually observed to reduce plasma apoB in the present review. It is this overall dietary pattern of a Mediterranean diet, rather than its individual components, that needs to be encouraged for optimal nutritional management of hyperapoB and for reducing the risk of CVD and T2D in humans.

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