

# THE EFFECT OF DIET ON CARDIOVASCULAR DISEASE AND LIPID AND LIPOPROTEIN LEVELS

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#### ABSTRACT

The role of lipids and lipoproteins as causal factors for cardiovascular disease (CVD) is well established. Dietary saturated fatty acids (SFA), which are in milk, butter, cheese, beef, lamb, pork, poultry, palm oil, and coconut oil increase LDL-C and HDL-C. The increase in LDL-C is due to a decrease in hepatic LDL clearance and an increase in LDL production secondary to a decrease in hepatic LDL receptors. Monounsaturated fatty acids (MUFA) are in olive, canola, peanut, safflower, and sesame oil, and avocados, peanut butter, and many nuts and seeds and polyunsaturated fatty acids (PUFA) are in soybean, corn, and sunflower oil, and some nuts and seeds, tofu, and soybeans. Both MUFA and PUFA lower LDL-C by increasing hepatic LDL receptor activity. Dietary cholesterol is found in egg yolks, shrimp, beef, pork, poultry, cheese, and butter and increase LDL-C but the effect is modest and varies with approximately 15-25% of individuals being hyperresponders with more robust increases. Dietary

cholesterol reduces hepatic LDL receptor activity, decreasing the clearance and increasing the production of LDL. Trans fatty acids (TFA) occur naturally in meat and dairy products and are formed during the partial hydrogenation of vegetable fat. TFA increase LDL-C and decrease HDL-C. Carbohydrates (CHO) can be divided into high-quality, for example fruits, legumes, vegetables, and whole grains, or lowquality, which include refined grains, starches, and added sugars. CHO increase TG with low quality CHO, particularly added sugars, having a more robust effect. Dietary CHO, particularly fructose, promotes hepatic de novo fatty acid synthesis leading to increased VLDL secretion. Fiber is found mostly in fruits, vegetables, whole and unrefined grains, nuts, seeds, beans, and legumes and phytosterols are naturally occurring constituents of plants and are found in vegetable oils, cereals, nuts, fruit and vegetables. Both dietary fiber and phytosterols decrease LDL-C by decreasing intestinal cholesterol absorption.

Summary of the Effect of Dietary Constituents on Lipid and Lipoproteins			
SFA	Increase LDL-C and modest increase HDL-C		
MUFA and PUFA	Decrease LDL-C		
TFA	Increase LDL-C and decrease HDL-C		
Cholesterol	Increase LDL-C		
СНО	Increase TGs particularly simple sugars		
Fiber	Decrease LDL-C		
Phytosterols	Decrease LDL-C		

With regards to CVD there are very few well conducted randomized controlled trials and most of the information is derived from observational studies that demonstrate associations. These observational have studies found that fruits. vegetables. beans/legumes, nuts/seeds, whole grains, fish, yogurt, fiber. seafood omega-3 fatty acids. and polyunsaturated fats were associated with a decreased risk of CVD while unprocessed red meats, processed meats, sugar-sweetened beverages, high glycemic load CHO, and trans-fats were associated with an increased risk of CVD. Randomized trials have shown that a Mediterranean diet reduces CVD. Based on this information current guidelines for the general population recommend 1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 2. Replacement of SFA with MUFA and PUFA 3. A reduced amount of dietary cholesterol 4. Minimizing intake of processed meats, refined CHO, and sweetened beverages and 5. Avoidance of TFA. For individuals with a high LDL-C limiting dietary SFA, TFA, and cholesterol and increasing fiber and phytosterols will help lower LDL-C while in individuals with high TG limiting low quality CHO, particularly simple sugars, and ethanol with weight loss, if indicated, will help lower TG.

## INTRODUCTION

There is a huge literature describing the effect of diet on the risk of cardiovascular disease (CVD) and this literature is often conflicting and controversial. Several well recognized investigators have discussed the limitations of the information linking various diets and dietary constituents and the risk of disease (1,2). The major problem is that almost all of the information is based on observational studies and well conducted randomized trials measuring important cardiovascular outcomes are very rare. Observational studies can demonstrate associations but do not necessarily indicate that there is a cause-and-effect relationship. Unrecognized confounding variables can result in false associations. In several instances a robust association was observed in observation trials but randomized trials failed to confirm these observations (3). For example, several observational studies showed that higher vitamin E intake from dietary sources or supplements was associated with a lower risk of CVD (4-8), but randomized controlled trials failed to demonstrate a reduction in cardiovascular events with vitamin E supplementation (9-12). Observational studies have also reported that vitamin B6, B12, or folic acid intake reduced the risk of CVD (13-15), but again randomized controlled trials failed to demonstrate a benefit of increased vitamin intake on CVD (16-19). These results point to potential deficiencies in observational studies and the need to recognize that the associations demonstrated in observational studies may not always be causal. Therefore, in this chapter, where possible, we will focus on randomized controlled trials.

Moreover, even the interpretation of the results of observational trials is often debated. For example, a 2019 meta-analysis and systematic review published in the Annals of Internal Medicine reached the conclusion that "the magnitude of association between red and processed meat consumption and all-cause mortality and adverse cardiometabolic outcomes is very small, and the evidence is of low certainty" (20). This conclusion is contrary to the recommendations of almost all dietary guidelines and as would be expected this resulted in a critique challenging this conclusion (21). There are numerous other instances where there are conflicting results and interpretations in the literature linking diet with CVD making it difficult to sort out fact from fiction.

The information pertaining to the effect of dietary manipulations on lipid and lipoprotein levels are frequently based on randomized controlled trials rather than observational studies and therefore tend to be more consistent. However, even in these studies the results are sometimes conflicting. There are many factors that could account for this variability including the heterogeneity in study settings, type of individuals studied, study designs, differences in baseline diets, adherence to the study diet, differences in types of diet or dietary composition, methods and accuracy of the methods used to measure lipid and lipoprotein levels, and many other factors.

Additionally, the clinician should recognize that the lipid response of an individual patient to dietary manipulations can vary greatly, is very modest on average (in the range of 10% reductions, typically), and in most cases will not prevent the need for lipid lowering medications. The importance of genetic differences on these responses is often under recognized by patients and providers. For example, individuals with an apo E4 allele have a more robust decrease in LDL-C in response to a decrease in dietary fat and cholesterol than subjects carrying the

apo E3 or apo E2 alleles (22). Polymorphisms in other genes have also been shown to modulate the lipid and lipoprotein response to dietary manipulations (22,23). Clinical conditions can also affect the response to diet. For example, the expected lipid and lipoprotein response to a low cholesterol, low saturated fatty acids (SFA) diet is blunted in obese individuals (24). Therefore, the effect of a specific diet can vary from individual to individual and the clinician will have to monitor a patient's response.

It should be recognized that when one increases or decreases a particular macronutrient in the diet (lipids, carbohydrates (CHO), or protein) there needs to be a reciprocal change in another macronutrient to maintain caloric balance. It can therefore be difficult to know whether the increase in a particular nutrient or a decrease in another nutrient is accounting for the observed effect (for example decreasing SFA and increasing CHO). Where possible I will try to specify which nutrient was decreased and which was increased in the studies described.

Finally, it is important to look at the effect of diet on lipids independent of weight loss. Weight loss per se can affect lipid levels resulting in a decrease in triglycerides and LDL-C and an increase in HDL-C levels (25). For a detailed discussion of the effect of weight loss on lipid levels see the chapter on obesity and dyslipidemia (25).

In this chapter we will first discuss the effect of various macronutrients, then specific foods, and finally specific diets on lipids and lipoprotein levels.

## DIETARY SATURATED FATTY ACIDS

Major sources of saturated fatty acids (SFA) in the diet are milk, butter, cheese, other dairy products, beef, lamb, pork, poultry particularly the skin, palm oil, palm kernel oil, and coconut oil (tables 1 and 3).

Table 1. Fatty Acid Composition of Foods High in Saturated Fat					
	Total Fat	SFA	MUFA	PUFA	
	grams/100 grams	grams/100 grams	grams/100 grams	grams/100 grams	
Hamburger	15.0	5.89	6.66	0.49	
Pork loin	13.3	5.23	6.19	1.20	
Chicken	12.6	3.50	4.93	2.74	
Lamb	15.1	6.90	7.00	1.20	
Whole milk*	3.9	2.5	1.0	0.1	
Gouda cheese**	30.6	20.3	7.4	0.9	
Butter***	82.2	52.1	20.9	2.8	

\*TFA = 0.1g/100g; \*\*TFA = 1.1g/100g; TFA = 2.9g/100g.

TFA= trans fatty acids, MUFA= monounsaturated fatty acids, PUFA= polyunsaturated fatty acids.

## Effect of Dietary Saturated Fatty Acids on Cardiovascular Disease

#### **OBSERVATIONAL STUDIES**

Dietary guidelines uniformly recommend reducing the intake of SFA. There are a large number of observational trials that have shown an association between dietary SFA intake and CVD (26-31). However, there are meta-analyses that have not found an association between dietary SFA intake and CVD (32-36). A possible explanation for this discordance is whether the SFA in the diet is replaced by polyunsaturated fatty acids (PUFA) vs. replaced by CHO. When SFA is replaced by PUFA there is a reduction in CVD whereas replacement with CHO has no benefit on CVD (27-29,37-39). However, replacement of SFA with high guality CHO may be beneficial (27,37,38). Additionally, in one study SFA from meat was associated with an increased risk of CVD while SFA from dairy products was associated with a decrease in CVD (40). Thus, the source of SFA may be important.

As noted above, observational studies can demonstrate an association but are not able to definitively demonstrate a causal relationship. It is therefore essential to review the results of randomized controlled trials on the effect of decreasing dietary SFA on preventing cardiovascular events.

#### RANDOMIZED CONTROLLED OUTCOME TRIALS

This section will review the major randomized trials analyzing the effect of decreasing SFA intake on preventing CVD. Studies with very few participants, few cardiovascular events, or very short-term studies will not be included. It is important to note that many of these studies were carried out in the 1950's and 1960's when the diagnosis and treatment of CVD was very primitive compared to current standards. Also, typical diets were much different (higher in SFA) and mean plasma cholesterol levels were higher. Lastly, the methodology of these studies was not up to the current standards by which randomized controlled trials are performed (small number of patients, often not blinded, inadequate statistical power, non-specific endpoints, etc.). Thus, the accuracy of these trials and the relevancy of these older studies to current times is uncertain.

In a study from England initiated in 1957, 252 men under the age of sixty-five who recently

had a myocardial infarction were assigned to a low-fat diet or usual diet (41). The low-fat diet was limited to 40 grams per day of fat with decreases in butter and meat. The intake of fat during the trial was approximately 100-120 grams per day in the usual diet group and slightly greater than 40 grams per day in the low-fat diet group. At the time of the study the typical diet was high in SFA so a decrease in total fat would have resulted in a significant decrease in SFA. During the trial serum cholesterol levels were in the 240mg/dL range in the usual diet group and 220mg/dL in the lowfat diet group. There were no differences between the two groups in cardiovascular events during the 5 years of the trial. To see a reduction in cardiovascular events with the modest reduction in serum cholesterol levels this study would have required a much larger number of participants.

The Oslo Diet-Heart Study randomized men under 65 years of age with a history of a myocardial infarction to a diet low in SFA and cholesterol, and high in PUFA (n=206) or their usual diet (n=206) (42). Cholesterol levels were approximately 295mg/dL and decreased to approximately 240mg/dL in the patients on the low SFA diet with minimal changes in the control group. After 5 years major cardiovascular events and cardiovascular mortality were reduced in the group on the low SFA diet (Events- 61 low SFA group vs. 81 control group).

The Medical Research Council soya-bean trial randomized men under 60 years of age with a recent myocardial infarction to continue their usual diet (n=194) or a diet low in SFA and containing 85 grams of soya-bean oil daily (PUFA) (n=199) (43). The low SFA diet lowered cholesterol from 272 to 213mg/dL (22% decrease) while in the controls, cholesterol decreased from 273 to 259mg/dL (6% decrease). The primary outcome was first relapse (myocardial infarction, angina, sudden death). After 4 years, 62 of 199 in the soybean oil group had a recurrent coronary event compared with 74 of 194 in the usual diet group; the difference, -18% (95% CI, -38 to 7), was not statistically significant but given the small number of participants was suggestive of benefit.

The Los Angeles Veterans Administration Center study randomized 422 men to the conventional control diet and 424 to the experimental diet low in SFA and cholesterol and enriched in PUFA (44,45). 30% of the

men had CVD. The baseline plasma cholesterol was 233mg/dL and on treatment there was a 13% decrease in the experimental diet compared to controls. Over 8 years the primary endpoint of myocardial infarction and sudden death from ischemia were reduced in the experimental diet group (control 67 vs experimental diet 45). The difference in the primary end point of the study-sudden death or myocardial infarction was not statistically significant but when these data were pooled with those for cerebral infarction and other secondary end points, the totals were 96 in the control group and 66 in the experimental group; P=0.01. Fatal atherosclerotic events occurred in 70 patients in the control group and 48 in the experimental group (P<0.05). For all primary and secondary end points the incidence rates were 47.7% and 31.3% for the control and experimental groups respectively (P= 0.02).

The Finnish Mental Hospital Study was carried out in two mental hospitals. One hospital was switched to a diet low in SFA and cholesterol and relatively high in PUFA, while the other hospital continued the usual hospital diet (46-48). After 6 years the type of diet was reversed in each hospital. The individuals in this study were hospitalized men between 34 to 64 years of age and women age 44 to 64 years. During the study individuals were removed from the study and others added to the study cohort. The serum cholesterol level on the usual diet was 268mg/dL while on the low SFA diet the serum cholesterol level was 226mg/dL. The incidence of CVD was consistently much lower during the low SFA diet periods than during the normal-diet periods but detailed comparisons are difficult due to the lack of randomization of individuals and the adding and removal of individuals during the study leading to only 36% of the men and 20.6% of the women completing both periods of the study. Nevertheless, this study provides evidence of the benefit of a diet low in SFA and cholesterol and enriched in PUFA.

The Sydney Diet Heart Study was a randomized controlled trial conducted from 1966 to 1973 that evaluated the effects of increasing linoleic acid from

safflower oil (PUFA ~ 15% of calories) in place of SFA (<10% of calories) in men aged 30-59 years with a history of coronary artery disease (49). Participants were randomized to the dietary intervention group (n=221) or a control group with no specific dietary instruction (n=237). Baseline cholesterol levels were ~280mg/dL and decreased to 267mg/dL in the control group and 244mg/dL in the diet intervention group. Compared with the control group, the intervention group had an increased risk of all-cause mortality (17.6% v 11.8%; P=0.051), cardiovascular mortality (17.2% v 11.0%; P=0.037), and mortality from coronary heart disease (16.3% v 10.1%; P=0.036) over the 5 years of the trial. The reason for the increase in mortality is not clear but the safflower oil margarine substitute for animal fats may have contained trans fatty acids, which could have increased CVD.

The DART trial was a multicenter trial in men less than 70 years of age with a diagnosis of an acute myocardial infarction (50). There were several different dietary approaches used in this trial but the one of interest reduced fat intake to 30% of total energy and increased the PUFA/SFA ratio to 1.0 (n=1018) vs. no advice (n=1015). The fat advice group reduced SFA from 15% to 11% of total calories, increased PUFA from 7% to 9%, and increased carbohydrate intake from 44% to 46%. Cholesterol levels were reduced by 3.6% (baseline 252mg/dL) in the diet advice group. During the 2-year trial the number of cardiovascular events were similar in the diet group vs. no advice group.

The Minnesota Coronary Survey was a 4.5-year, randomized trial that was conducted in six Minnesota state mental hospitals and one nursing home and included 4,393 men and 4,664 women (51). The trial compared the effects of the usual diet (18% SFA, 5% PUFA, 16% monounsaturated fatty acid (MUFA), 446 mg dietary cholesterol per day) versus a low SFA and cholesterol treatment diet (9% SFA, 15% PUFA, 14% MUFA, 166 mg dietary cholesterol per day). The mean duration of time on the diets was 384 days, with 1,568

subjects consuming the diet for over 2 years. The baseline serum cholesterol level was 207 mg/dL, falling to 175 mg/dL in the treatment group and 203 mg/dL in the control group. No differences between the treatment and control groups were observed for cardiovascular events, cardiovascular deaths, or total mortality, perhaps due to the relatively short duration of this study.

The Women's Health Initiative trial randomized 19,541 postmenopausal women 50-79 years of age to the diet intervention group and 29,294 women to usual dietary advice (52). The goal in the diet intervention group was to reduce total fat intake to 20% of calories and increase intake of vegetables/fruits to 5 servings/day and grains to at least 6 servings/day. Fat intake decreased by 8.2% of energy intake in the intervention vs the comparison group, with small decreases in SFA (2.9%), MUFA (3.3%), and PUFA (1.5%) with increased consumption of vegetables, fruits, and grains. LDL-C levels were reduced by 3.55 mg/dL in the intervention group while levels of HDL-C and TGs were not significantly different in the intervention vs comparison groups. The dietary intervention did not significantly decrease CVD. In fact, in the women with pre-existing CVD there was an increase in cardiovascular events with diet therapy.

## Summary of Dietary Randomized Controlled Trials

In reviewing these randomized controlled trials, it appears that the dietary studies that produce a longterm decrease in plasma cholesterol levels resulted in a reduction in cardiovascular events (Oslo Diet-Heart Study, soya-bean trial, Los Angeles Veterans Administration Center, Finnish Mental Hospital Study) while the dietary studies that did not produce a longterm decrease in plasma cholesterol levels failed to demonstrate a reduction in CVD. The baseline plasma cholesterol levels in the positive studies tended to be high and allowed for a robust cholesterol lowering with dietary manipulation. Additionally, as will presented in the next section the greater the reduction in SFA in the diet the greater the decrease in TC and LDL-C levels and many of the positive studies were carried out in an era when the content of SFA in the diet was high. Additionally, studies in non-human primates have also demonstrated that reducing SFA intake reduces atherosclerosis (53,54).

These results correspond very nicely with the large number of trials demonstrating that using a variety of different pharmacologic agents that lower plasma cholesterol levels results in a decrease in cardiovascular events (55). In an analysis comparing cholesterol lowering with diet vs. drug therapy it was observed that a similar decrease in cardiovascular events occurred adjusting for the magnitude of cholesterol lowering (56). Thus, it would appear that diets that decrease dietary SFA and thereby lead to a significant decrease in plasma cholesterol levels for an extended period of time have benefits on CVD with the caveat that there is not an increase in other nutrients that will adversely affect other parameters thereby negating the beneficial effects of decreasing SFA. For example, an increase in dietary simple sugars for SFA could lead to an increase in TG levels with negative effects.

#### REVERSAL OF ATHEROSCLEROSIS TRIALS

Two studies have examined the effect of decreasing dietary SFA on atherosclerotic lesions.

The St Thomas' Atherosclerosis Regression Study (STARS) determined the effect of decreasing dietary saturated fat in the diet (n=26) vs. usual diet (n=24) in men less than 66 years of age with a plasma cholesterol greater than 234mg/dL referred for coronary angiography to investigate angina pectoris or other findings suggestive of coronary heart disease (57). In the diet group total fat intake was reduced to 27% of dietary energy, saturated fatty acid content to 8-10% of dietary energy, and dietary cholesterol to 100 mg/1000 kcal; omega-6 and omega-3 polyunsaturated fatty acids were increased to 8% of dietary energy, and plant-derived soluble fiber intake was increased to the equivalent of 3-6 g polygalacturonate/1000 kcal. During the trial LDL-C levels were 163mg/dL in the diet intervention group vs.182mg/dL in the usual diet group. Additionally, TGs decreased in the diet intervention group (206mg/dL to 165mg/dl) with no change in TG levels in the usual diet group. After approximately 3 years coronary angiography revealed that the percentage of patients who showed progression of coronary narrowing was significantly reduced by the dietary intervention (usual diet 46% vs, dietary intervention 15%), whereas the percentage who showed an increase in luminal diameter rose significantly (usual diet 4% vs. dietary intervention 38%). While the number of cardiovascular events was small, they were significantly reduced in the dietary intervention group (usual diet 36% vs dietary intervention 11%; p< 0.05). Finally, the improvement in angiographic appearance correlated with LDL-C levels.

The Lifestyle Heart Trial was a one year randomized, controlled trial to determine whether lifestyle changes affect coronary atherosclerosis in patients with angiographically documented coronary artery disease (58). Patients were assigned to the lifestyle group (low-fat vegetarian diet, stopping smoking, stress management training, and moderate exercise) (n= 22) or a usual-care control group (n=19). The lifestyle diet contained approximately 10% of calories as fat PUFA/SFA ratio greater than 1), 15-20% protein, and 70-75% predominantly complex carbohydrates. Cholesterol intake was limited to 5 mg/day or less. In the lifestyle group LDL-C decreased from 153mg/dL to 96mg/dl (37% decrease) whereas in the usual care group LDL-C decreased from 168mg/dL to 159mg/dL. Patients in the lifestyle group reported a 91% decrease in the frequency of angina, a 42% decrease in the duration of angina, and a 28% decrease in the severity of angina. In contrast, patients in the usual care group reported a 165% increase in the frequency of angina, a 95% increase in the duration of angina, and a 39% increase in the severity of angina. In the lifestyle group regression of coronary atherosclerosis occurred in 18 of the 22 patients (82%) whereas in the

usual care group progression of coronary atherosclerosis occurred in 10 of 19 patients (53%).

These two regression trials provide strong support for the results observed in the randomized cardiovascular outcome studies described above i.e., that lowering LDL-C levels by decreasing dietary SFA can reduce atherosclerosis and cardiovascular events.

## Effect of Dietary Saturated Fatty Acids on Lipid Levels

It should be recognized that when one increases or decreases a particular macronutrient in the diet there needs to be a reciprocal change in another macronutrient to maintain caloric balance.

The effect of substituting PUFA, MUFA, or carbohydrates (CHO) for SFA is shown in table 1. Note

that this table shows the effect of replacing 5% of energy from SFA for the indicated dietary component. Thus, going from a diet where 15% of the calories is from SFA to a diet where 10% of the calories is from SFA is estimated to lower LDL-C levels from 6 to 9mg/dL depending on which dietary component replaces the SFA. To keep this decrease in LDL-C in perspective it is estimated that a 40mg/dL decrease in LDL-C induced by statin therapy will result in an approximate 20% decrease in cardiovascular events over a 5 year period of time but the lifetime benefits of a 10 mg/dL decrease in LDL-C due to genetic variants will result in a 16-18% decrease in cardiovascular events (59). The effect on TGs is dependent on the dietary component replacing SFA with CHO resulting in a large increase in TG levels. One should note that there is also a decrease in HDL-C with replacement of SFA (table 2).

Table 2. Effect of Decreasing Dietary Saturated Fatty Acids on Lipid Levels					
Dietary Component         LDL-C (mg/dL)         TGs (mg/dL)         HDL-C (mg/dL)					
PUFA	-9.0	-2.0	-1.0		
MUFA	-6.5	+1.0	-6.0		
СНО	-6.0	+9.5	-2.0		

PUFA- polyunsaturated fatty acids; MUFA- monounsaturated fatty acids; CHO- carbohydrates. Effects on lipoprotein lipids of replacing 5% of energy from SFA with the 5% of energy from the specified dietary component. Table adapted from references (26,60).

SFA in the diet predominantly increases LDL-C levels, predominantly larger, cholesterol-enriched LDL, with modest increases in HDL-C (60,61). As expected, Apo B and apo AI levels also increase (60). These effects are observed in both men and women (60). The effect of a decrease or increase in SFA intake on lipids and lipoproteins is linear with a consistent effect on serum lipids and lipoproteins across a wide range of SFA intakes (60). Of note the effects of decreasing SFA intake was observed even when the SFA intake was already less than 10% of the daily energy intake. Most studies have suggested that replacement of SFA with carbohydrate or unsaturated fat modestly increases Lp(a) but the results have varied from study to study with replacement of SFA with unsaturated fat from

particular food sources such as nuts showing no increase in Lp(a) (62).

Individual SFA have diverse biological and cholesterol-raising effects with chain length of SFA playing an important role in determining the effect on lipid and lipoprotein levels. The most commonly consumed SFA are palmitic acid (16:0; major source: vegetable oil, dairy, and meat), stearic acid (18:0; meat, dairy, and chocolate), myristic acid (14:0; dairy and tropical oil, particularly coconut oil) and lauric acid (12:0; dairy and tropical oil). A meta-analysis of 60 controlled trials by Mensink et al. reported an increase in LDL-C and HDL-C concentrations by isocaloric replacement of carbohydrates with palmitic, myristic,

and lauric acids (63). As expected, apolipoprotein B and A-I also increase (60,64). Myristic and palmitic acids increased LDL-C and HDL-C levels to a similar extent, whereas lauric acid had the largest LDL-C- and HDL-C-raising effect (63,65). Stearic acid did not increase LDL-C levels (63,65). The lack of an association between stearic acid and changes in LDL-C levels has been linked to a slower and/or less efficient absorption as well as desaturation of stearic acid to oleic acid (66). Compared with carbohydrates, an increased intake of lauric, myristic, palmitic or stearic acid lowered TG levels (63,65). For a specific individual many factors including lifestyle factors such as overall dietary composition and physical activity, clinical conditions such as obesity, insulin resistance and hypertriglyceridemia, as well as genetic factors may modify these responses.

#### MECHANISM FOR THE INCREASE IN LDL-C

Dietary SFA have been shown to decrease hepatic LDL receptor activity, protein, and mRNA levels and this results in a decrease in the clearance of circulating LDL leading to increased LDL-C levels (67,68). Additionally, the decrease in LDL receptors could result in an increase in the conversion of intermediate density lipoproteins to LDL rather than clearance by the liver (i.e., LDL production is enhanced).

SFA have been shown to decrease the formation of cholesterol esters, a reaction catalyzed by the enzyme acyl CoA:cholesterol acyltransferase (ACAT) (68).

Free cholesterol in the endoplasmic reticulum is the primary regulator of the activation of sterol receptor binding protein (SREBP), which translocates to the nucleus and enhances the transcription of the LDL receptor (69). Elevated levels of cholesterol in the endoplasmic reticulum prevents the activation of SREBP (69). When free cholesterol is esterified into cholesterol esters it no longer prevents the activation of SREBP and the up-regulation LDL receptor expression. Thus, SFA by decreasing the formation of cholesterol esters and increasing free cholesterol may lead to the down-regulation of LDL receptor expression (68).

## DIETARY MONOUNSATURATED AND POLYUNSATURATED FATTY ACIDS

Olive oil, canola oil, peanut oil, safflower oil, sesame oil, avocados, peanut butter, and many nuts and seeds are major sources of MUFA (table 3). Soybean oil, corn oil, sunflower oil, some nuts and seeds such as walnuts and sunflower seeds, tofu, and soybeans are major sources of PUFA (table 3). Omega-3-fatty acids, eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), are mostly found in fish and other seafood, while another omega-3 fatty acid, alpha-linolenic acid (ALA, 18:3) is found mostly in nuts and seeds such as walnuts, flaxseed, and some vegetable oils such as soybean and canola oils. The body is capable of converting ALA into EPA and DHA but the conversion rates are low.

Table 3. Fat Composition of Oils, Lard, Butter, and Margarine				
Type of Oil	SFA (%)	MUFA (%)	PUFA (%)	
Corn oil	13.6	28.97	57.43	
Safflower oil (linoleic)	6.51	15.1	78.4	
Canola oil	7.46	64.1	28.49	
Almond oil	8.59	73.19	18.22	
Olive oil	14.19	74.99	10.82	
Soybean oil	16.27	23.69	60.0	
Sesame oil	14.85	41.53	43.62	
Sunflower oil (linoleic)	10.79	20.42	68.8	
Avocado oil	12.1	73.8	14.11	
Peanut oil	17.77	48.58	33.65	
Palm oil	51.57	38.7	9.73	
Coconut oil	91.92	6.16	1.91	
Lard	41.1	47.23	11.73	
Butter	68.1	27.87	4.0	
Margarine (soft)	20	47	33	
Margarine (hard)	80	14	6	

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## Effect of Dietary Monounsaturated and Polyunsaturated Fatty Acids on Cardiovascular Disease

#### MONOUNSATURATED FATTY ACIDS

Many meta-analyses, but not all, have failed to demonstrate that MUFA intake reduces cardiovascular events (29,33,35,70). However, one meta-analysis and the Nurses' Health Study and Health Professionals Follow-Up Study, two very large observational studies, found that MUFA when delivered from plant sources was protective but MUFA from other sources was not protective from developing cardiovascular events (71,72).

The PREDIMED a randomized controlled outcome trial employing a Mediterranean diet (increased MUFA) reduced the incidence of major CVD (73-75). In this multicenter trial, carried out in Spain, over 7,000 individuals at high risk for developing CVD were randomized to three diets (primary prevention trial). A Mediterranean diet supplemented with extra-virgin

olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet. In the patients assigned to the Mediterranean diets there was 29% decrease in the primary composite end point (myocardial infarction, stroke, and death from CVD), which was primarily due to a decrease in strokes. The Mediterranean diet resulted in a small but significant increase in HDL-C levels and a small decrease in both LDL-C and TG levels (76). The changes in lipids were unlikely to account for the beneficial effects of the Mediterranean diet on CVD.

The Lyon Diet Heart Study randomized 584 patients who had a myocardial infarction within 6 months to a Mediterranean type diet vs usual diet (77,78). The oils recommended for salads and food preparation were rapeseed and olive oils exclusively. Additionally, they were also supplied with a rapeseed (canola) oil-based margarine. There was a marked reduction in events in the group of patients randomized to the Mediterranean diet (cardiac death and nonfatal myocardial infarction rate was 4.07 per 100 patient years in the control diet vs.1.24 in the Mediterranean diet; p<0.0001). Lipid levels were similar in both groups in this trial (77).

The CORDIOPREV study was a single center randomized trial that compared a Mediterranean diet to a low-fat diet in 1,002 patients with cardiovascular disease (79). The Mediterranean diet contained a minimum of 35% of the calories as fat (22% monounsaturated fatty acids, 6% polyunsaturated fatty acids, and <10% saturated fat), 15% proteins, and a maximum of 50% carbohydrates while the lowfat diet contained less than 30% of total fat (<10% saturated fat, 12-14% monounsaturated fatty acids, and 6-8% polyunsaturated fatty acids), 15% protein, and a minimum of 55% carbohydrates. The risk of an ASCVD event was reduced by approximately 25-30% in the Mediterranean diet group. Whether these diets differed in their effects on fasting lipid levels has not been reported.

The results of these three randomized trials indicate that a Mediterranean diet enriched in plant MUFA reduce the risk of CVD. It is likely that the beneficial effects of the Mediterranean diet on CVD is mediated by multiple mechanisms with alterations in lipid levels making only a minor contribution. It should be noted that in addition to an increase in MUFA the diet also includes low to moderate red wine consumption, high consumption of whole grains and cereals, low consumption of fish, and meat products, increased consumption of fish, and moderate consumption of milk and dairy products. As in many dietary studies it is difficult to change a single variable and therefore the interpretation of which factor or factors account for the benefits is difficult to untangle.

#### POLYUNSATURATED FATTY ACIDS

Recent meta-analyses of the effect of PUFA on cardiovascular events in observational studies have demonstrated either no effect or a modestly lower risk of CVD and mortality (80-84). Randomized trials are described in the section on saturated fats and CVD and describe the results of replacing SFA with PUFA. It appears that dietary PUFA has a neutral effect on CVD except in the circumstances where it replaces SFA and results in a sustained decrease in plasma cholesterol levels leading to a decrease in cardiovascular events.

## OMEGA-3-FATTY ACIDS

As discussed in detail in the chapter entitled "Triglyceride Lowering Drugs" numerous randomized controlled trials of the effect of low dose omega-3-fatty acids (approximately ≤1 gram/day) on CVD have been published and the bulk of the evidence indicates no benefit (85). The effect of pharmacologic doses of omega-3-fatty acids (≥1.8 grams/day) on cardiovascular outcomes is discussed in the chapter entitled "Triglyceride Lowering Drugs" (85).

## Effect of Dietary Monounsaturated and Polyunsaturated Fatty Acids on Lipid Levels

Table 4 shows the effect of substituting PUFA or MUFA for carbohydrates on LDL-C, HDL-C, and TG levels. Both PUFA and MUFA decrease LDL-C and TGs but PUFA induces a greater decrease (60). Both PUFA and MUFA increase HDL-C levels (60).

Table 4. Effect of Decreasing Dietary Carbohydrate on Lipid Levels					
Dietary ComponentLDL-C (mg/dL)TGs (mg/dL)HDL-C (mg/dL)					
PUFA	-4.3	-9.2	1.2		
MUFA	-1.8	-6.6	1.6		

PUFA- polyunsaturated fatty acids; MUFA- monounsaturated fatty acids; Effects on lipoprotein lipids of replacing 5% of energy from carbohydrates with the 5% of energy from the specified dietary component. Table adapted from reference (60). In a meta-analysis of 14 studies no significant differences in TC, LDL-C, or HDL-C levels were observed when diets high in MUFA or PUFA were compared directly (86). TG levels were modestly but consistently lower on the diets high in PUFA (P = .05) (86).

While high dose omega-3-fatty acids (3-4 grams/day) lower TG levels, lower doses (≤1 gram/day) have minimal effects on lipid levels (85).

## MECHANISM FOR THE DECREASE IN LDL-C

Unsaturated fatty acids increase hepatic LDL receptor activity, protein, and mRNA abundance, which will increase the clearance of LDL from the circulation (67,68). Unsaturated fatty acids are a preferred substrate for ACAT and thereby result in an increase in cholesterol ester formation and a decrease in free cholesterol in the liver (68). A decrease in hepatic free cholesterol will result in the up-regulation of LDL receptor expression leading to a decrease in LDL-C levels. PUFA also increase membrane fluidity leading to an increase in the ability of LDL receptors to bind LDL (67). Additionally, the increase in LDL receptors could result in a decrease in the conversion of intermediate density lipoproteins (IDL) to LDL due to increased uptake of IDL by the liver (i.e., LDL production is decreased).

## DIETARY TRANS FATTY ACIDS

The two major sources of dietary trans fatty acids (TFA) are those that occur naturally in meat and dairy products as a result of anaerobic bacterial fermentation in ruminant animals and those formed during the partial hydrogenation of vegetable fat (the fatty acids in vegetable oils have cis double bonds) (87). Partial hydrogenation and the formation of TFA converts the liquid vegetable oil into a solid form at room temperature allowing for ease of use in food products and increased shelf life (87,88). TFA acids were widely used in baked products, packaged snack

foods, margarines, and crackers (88). With the recognition of the adverse effects of TFA the use of partial hydrogenated oils in food products has markedly diminished World-wide and in the US is no longer allowed.

## Effect of Trans Fatty Acids on Cardiovascular Disease

A meta-analysis by de Souza and colleagues of 5 studies with 70,864 participants found that the relative risk of coronary heart disease mortality disease was increased with dietary TFA (1.28; p=0.003) (34). Similarly, the relative risk of coronary heart disease was also increased (1.21; p<0,001) (34). Another meta-analysis by Chowdhury and colleagues of 5 studies with 155,270 participants found that the relative risk of coronary events was increased with higher intake of TFA (RR 1.16; CI 1.06-1.27) (33). It has been estimated that a 2 percent increase in energy intake from TFA was associated with a 23 percent increase in the incidence of coronary heart disease (88). Thus, observational studies have consistently demonstrated that an increase in dietary TFA increase the risk of CVD. Clearly it would not be ethical to carry out randomized trials of the effect of TFA acids on CVD.

## Effect of Trans Fatty Acids on Lipid Levels

The effect of replacing SFA, MUFA or PUFA with TFA acids is shown in table 5. TFA increase LDL-C levels and decrease HDL-C levels. Of note TFA increase LDL-C even when substituting for SFA. There appears to be a nearly linear relationship between TFA intake and LDL-C concentration, but this relationship does not seem to exist between TFA intake and HDL-C (89). HDL-C seems to be lowered significantly by TFA only when intake is >2% to 4% of the total energy intake (89). TFA also increases TG and Lp(a) levels (88). Additionally, dietary TFA increases small dense LDL and the increase correlates with the quantity of TFA in the diet (90).



Table 5. Effect on Lipids of Replacing Various Fatty Acids with Trans Fatty Acids				
Dietary ComponentLDL-C (mg/dL)HDL-C (mg/dL)				
SFA	2.0	-2.0		
PUFA	11.5	-1.3		
MUFA	9.5	-1.5		

SFA- saturated fatty acids; PUFA- polyunsaturated fatty acids; MUFA- monounsaturated fatty acids. All results are statistically significant (P<0.05) except the increase in LDL-C with SFA replacement. Effects on lipoprotein lipids of replacing 5% of energy from various fatty acids with 5% of the energy from TFA. Table adapted from reference (88).

Replacing carbohydrates with TFA results in an increase in LDL-C and apo B and no change in HDL-C, apo AI, or TG levels (63).

#### RUMINANT TRANS FATTY ACID

A key question now that TFA derived from partial hydrogenation of vegetable fat in the diet have been markedly reduced is whether ruminant derived TFA which are present in milk, butter, cheese, and beef have harmful effects similar to industrial created TFA. It is important to note that ruminant derived TFA have a different composition with ruminant TFA being enriched in vaccenic acid, which is the predominant TFA, and conjugated linoleic acid (89,91). Also the quantities of ruminant TFA ingested is much lower than the quantities of industrial TFA ingested (89). In an analysis of a large number of studies of the effect of ruminant and industrial TFA on lipid levels it was observed that the effect of ruminant TFA on LDL-C and HDL-C was similar but slightly less than that of industrial TFA (the difference was not significant) (91). Whether the low quantities of ruminant TFA in the diet will influence the risk of CVD is unknown (89) but a meta-analysis of 4 observational trials did not find a link between ruminant-TFA intake (increments ranging from 0.5 to 1.9 g/day) and the risk of CHD (RR=0.92; CI 0.76-1.11; P=0.36) (92). Another meta-analysis

also did not find a link between ruminant TFA and CVD (34).

## MECHANISM FOR THE LIPID EFFECTS OF TRANS FATTY ACIDS

The mechanism for the increase in LDL-C levels by dietary TFA is thought to be due to decreased LDL-Apo B catabolism without a change in LDL-Apo B production (87,93). The decrease in HDL-C induced by TFA has been attributed to an increase in HDL Apo A-I catabolism without a significant change in HDL apoA-1 production rate (87,93). Additionally, TFA increases CETP activity which could increase the transfer of cholesterol esters from HDL to LDL thereby contributing to the decreased HDL-C levels and increased LDL-C levels (94).

#### **DIETARY CHOLESTEROL**

The primary food sources of dietary cholesterol are egg yolks, shrimp, beef, pork, poultry, cheese, and butter with the top five food sources being eggs and mixed egg dishes, chicken, beef, burgers, and cheese (table 6) (95). In the US the typical cholesterol intake varies from 50 to 400mg per day with a mean of 293 mg/day (348 mg/day for men and 242 mg/day for women) (96).

Table 6. Cholesterol Content of Food			
Food	mg per 100 grams		
Egg	373		
Butter	215		
Shrimp	125		
Cheese	108		
Beef	90		
Chicken	88		
Pork	80		
Ice Cream	47		

## Effect of Dietary Cholesterol on Cardiovascular Disease

In reviews of prospective observational studies an association between dietary cholesterol and CVD has not been clearly demonstrated with some studies reporting an association and others no association (97,98). Most of these studies did not adjust for the amount and types of fatty acids consumed, which could influence the results as foods containing large amounts of cholesterol are also rich in SFA. Dietary cholesterol was not associated with cardiovascular risk among >80,000 nurses and 43,000 male health care professionals after adjusting for energy intake, PUFA, trans fatty acid, and SFA intake (99,100).

Most foods that contain cholesterol also contain significant amounts of SFA. An exception are eggs which contain significant amounts of cholesterol and only small amounts of SFA (95). It is therefore of interest to examine the effect of egg consumption on CVD. In an analysis of 7 cohort studies no association between egg intake and coronary heart disease was observed and egg intake may be associated with a reduced risk of stroke (101). A recent meta-analysis of 23 prospective studies with 1,415,839 individuals and a median follow-up of 12.28 years also found that increased consumption of eggs was not associated with increased risk of CVD (102). Other meta-analyses and reviews have also not demonstrated a consistent link between eggs and CVD (98,103-105). However, a recent very large meta-analysis with 3,601,401

participants with 255,479 events showed that the consumption of 1 additional 50-g egg daily was associated with a very small increase in CVD risk (pooled relative risk, 1.04; 95% CI 1.00-1.08) (106). Thus, eggs have either no effect or a very small effect on CVD that can be seen only in very large studies.

There appears to be no randomized studies of the effect of decreasing cholesterol intake on CVD. Do recognize that the studies of decreasing dietary SFA intake described earlier also result in a decrease in cholesterol intake. Thus, at this time there is very limited data linking dietary cholesterol intake with an increased risk of CVD.

## Effect of Dietary Cholesterol on Lipid Levels

In a meta-analysis of fifty-five studies with 2,652 subjects the predicted change in LDL-C levels for an increase of 100 mg dietary cholesterol per day adjusted for dietary fatty acids ranged from 1.90mg/dL to 4.58 mg/dL depending upon the model employed (107). An increase of 200mg dietary cholesterol per day increased LDL-C levels from 3.80mg/dL to 6.96mg/dL. It should be noted that the effect of dietary cholesterol levels is greater the higher the LDL-C level (107). For a baseline LDL-C level of 100, 125, 150, and 175 mg/dL the predicted increase in LDL-C for a change in dietary cholesterol of 100mg is 2.7, 3.6, 4.6, and 5.5 mg/dL respectively (107). While the absolute increase is greater if the LDL-C level is higher the percentage increase is similar. Moreover, cholesterol

feeding does not alter number of LDL particles – instead it increases the cholesterol content of the LDL particles leading to the formation of large buoyant LDL (108).

The effect of dietary cholesterol on HDL-C levels differs in males and females. In men an increase of 100mg of dietary cholesterol results in a 0.30 to 1.44mg/dL decrease in HDL-C levels while in women this results in a 0.50 to 1.61 increase in HDL-C levels (107). Dietary cholesterol does not impact TG or VLDL cholesterol levels (97).

Approximately 15-25% of the population have an increased response to dietary cholesterol with greater increases in LDL-C levels (i.e., sensitive or hyperresponders), while the majority respond minimally (i.e., non-sensitive or hypo-responders) (109). An intake of 100 mg/day dietary cholesterol leads to a 3-4-fold difference in LDL-C concentration between hyper- and hypo-responders (an increase of 2.84 mg/dL vs. 0.76 mg/dL (110). The mechanism for the increase in cholesterol absorption in hyper-responders is unknown. On average 50% (typical range 40-60%) of dietary cholesterol is absorbed but this varies from person to person (111). A high-cholesterol diet leads to significant increases in non-HDL-C levels in insulinsensitive individuals but not in lean or obese insulinresistant subjects whereas HDL-C levels increased in all 3 groups (112). The above observations demonstrate the variable response of lipid and lipoprotein levels that can occur in response to dietary manipulations and emphasize how the response of an individual can be variable.

#### MECHANISM FOR THE INCREASE IN LDL-C

The increase in LDL-C levels by dietary cholesterol is due to a decrease in hepatic LDL receptors (111). Cholesterol absorbed by the small intestine is packaged into chylomicrons which deliver dietary cholesterol to the liver (111). This increases hepatic cholesterol levels which down-regulates the expression of LDL receptors leading to a decrease in the clearance of LDL from the circulation (111). Additionally, the decrease in LDL receptors could result in an increase in the conversion of intermediate density lipoproteins to LDL rather than clearance by the liver (i.e., LDL production is enhanced).

#### DIETARY CARBOHYDRATES

Carbohydrates (CHO) can be divided into high-quality CHO, for example fruits, legumes, vegetables, and whole grains, or low-quality CHO, which include refined grains (such as white bread, white rice, cereal, crackers, and bakery desserts), starches (potatoes), and added sugars (sugar-sweetened beverages, candy). The high-quality CHO are typically enriched in fiber and have a low glycemic index/glycemic load (i.e., are slowly absorbed and thus do not rapidly increase plasma glucose levels). The low-quality CHO have a high glycemic index and load and rapidly increase plasma glucose levels.

## Effect of Dietary Carbohydrates on Cardiovascular Disease

## **OBSERVATIONAL STUDIES**

When SFA is replaced by CHO there is no reduction in CVD whereas replacement of SFA with high quality CHO may be beneficial (27,37,38). A study by Jakobsen and colleagues found that replacing SFA with CHO with a low-glycemic index value is associated with a lower risk of myocardial infarction whereas replacing SFA with CHO with a high-glycemic index values is associated with a higher risk of myocardial infarction (113). Meta-analyses and reviews of the association of glycemic index with CVD have varied with some showing an association of low glycemic index with CVD and others reporting no link (114,115). Two very large studies found that a diet with a high glycemic index was associated with an increased risk of cardiovascular disease (116,117). It should be noted that in the largest study the relative risk for CVD was relatively modest (RR 1.15; 95% CI 1.11-1.19) (117). An increase in cardiovascular morbidity and mortality was associated with an increase in added sugar intake (118-121). Hazard ratios were 1.30 (95% CI- 1.09-1.55) and 2.75 (95% CI-1.40-5.42), respectively, comparing participants who consumed 10.0% to 24.9% or 25.0% or more calories from added sugar with those who consumed less than 10.0% of calories from added sugar (118). Additionally, in the Health Professionals Follow-up Study participants in the top quartile of sugar-sweetened beverage intake had a 20% higher relative risk of coronary heart disease than those in the bottom quartile (RR=1.20; 95% CI- 1.09-1.33) after adjustment for multiple risk factors (122).

#### RANDOMIZED CONTROLLED TRIALS

Three of the randomized trials described above in the SFA and CVD section provide information on the role of CHO on CVD. The British Medical Research Council studied 252 men after a myocardial infarction aiming to reduce total fat from 41% to 22% of calories and maintaining total fat at 41% in the control group (41). The type of fat was similar in the high- and lowfat groups, mainly saturated fat from dairy products and meat. It is likely that the decrease in fat calories was substituted by an increase in CHO calories. The type of CHO that replaced the SFA was not specified but the authors indicated that there was a marked increase in sugar intake in the low- fat diet group. There was no difference between the two groups in cardiovascular events during the 5 years of the trial. The DART study decreased SFA which were substituted with PUFA and CHO (50). During the 2year trial cardiovascular events were similar in the decreased SFA vs. PUFA and CHO group. Finally, the Women's Health Initiative trial randomized 19,541 postmenopausal women 50-79 years of age to the diet intervention group and 29,294 women to usual dietary advice (52). The goal in the diet intervention group was to reduce total fat intake to 20% of calories and increase intake of vegetables/fruits to 5 servings/day and grains to at least 6 servings/day (i.e., CHO). Fat intake decreased by 8.2% of energy intake in the intervention vs the comparison group, with small decreases in SFA (2.9%), MUFA (3.3%), and PUFA (1.5%) fat with increased consumption of CHO. The dietary intervention did not significantly decrease CVD even though the CHO recommended was high quality CHO. These randomized studies do not provide support for a benefit of substituting CHO for fat in reducing CVD. Of particular note is the Women's Health Initiative which decreased fat intake and increased high quality CHO and observed no cardiovascular benefits in contrast to the results of observational studies.

#### Effect of Dietary Carbohydrates on Lipids

Replacing SFA, MUFA, or PUFA with CHO results in an increase in TGs and a decrease in HDL-C levels (60,63). Replacing SFA with CHO results in a decrease in LDL-C while replacing MUFA or PUFA with CHO results in an increase in LDL-C (see tables 2 and 4) (60,63). In addition, dietary CHO increases the quantity of small dense LDL particles (123). The consumption of moderate amounts of fructose or sucrose (40-80 grams/day) in healthy young men was sufficient to increase small dense LDL levels (124). The effect of increasing dietary CHO on Lp(a) levels has been variable (62).

Conversely, decreasing CHO in the diet and adding fat results in an increase in LDL-C and HDL-C levels and a decrease in TG levels (125). In a meta-analysis of eleven randomized controlled trials with 1,369 participants comparing low fat/high CHO diet to high fat/low CHO diet it was found that the high fat/low CHO led to an increase in LDL-cholesterol (6.24mg/dL; 95 % CI 0.12- 12.9) and HDL-C (5.46mg/dL; 95% CI 3.51-7.41) compared with subjects on the low fat/high CHO diets (126). The high fat/low CHO decreased TG levels (-22.9mg/dL; 95 % CI -13.4- -32.6 (126). Another meta-analysis of 23 randomized controlled trials also found that a high fat/low CHO diet increased LDL-C and HDL-C levels and decreased TG levels (127). These studies nicely demonstrates that a high fat diet will increase LDL-C and HDL-C levels while a

high CHO diet will increase TG levels and decrease HDL-C levels.

### COMPARISON OF DIFFERENT CARBOHYDRATES ON LIPIDS

A meta-analysis of twenty-eight randomized controlled trials comparing low- with high glycemic index diets (1,272 participants) reported that low glycemic index diets significantly decreased LDL-C levels by 6.2 mg/dL; P < 0.0001) with no effect on HDL-C or TGs (128). The decrease in LDL-C was related to the amount of fiber and/or phytosterols in the low glycemic diet (see Fiber and Plant Sterols/Stanols section below).

High fructose corn syrup (HFCS) has become a major source of fructose intake (HFCS made for beverages contains 55% fructose and 45% glucose). Because sucrose and HFCS are major contributors to total CHO intake there has been interest in the effect of fructose, glucose, and sucrose on lipid levels. In a comparison of isocalorically substituting starch for glucose, fructose, or sucrose there were no difference in TG levels but there was a decrease in LDL-C (approximately 7.8mg/dL) (129).

A meta-analysis by Te Morenga and colleagues examined the effect of the addition of sugar on lipid levels. In studies where energy intake was isocaloric, sugar intake increased TG levels by 11.7mg/dL, LDL- C by 6.6mg/dL, and HDL-C by 0.8mg/dL (130). In a similar meta-analysis by Fattore and colleagues an isocaloric substitution of free sugars for complex CHO increased TGs by 8.3mg/dL, LDL-C by 7.1mg/dL, and HDL-C by 1.3mg/dL (131). The increase in TG and LDL-C levels were larger in the trials where greater amounts of free sugar were employed.

In a meta-analysis of adding fructose to the diet there was no significant effect on fasting TG levels at dietary fructose < 100 grams per day but at higher amounts fructose increased fasting TG levels (132). Fructose is more likely to have adverse effects on lipids when intake is high and/or when caloric excess is present. For example, in young healthy individuals, a 2-week intervention with 25% of energy requirements as HFCS or fructose sweetened beverages resulted in significant increases in fasting LDL-C, small dense LDL particles, non-HDL-C, apo B, and HDL-C and postprandial TGs (133). High quantities of glucose did not affect LDL-C, non-HDL-C, Apo B, HDL-C, or postprandial TG levels but did increase fasting TG levels (133).

Thus, the effect of CHO on lipids can vary depending upon the particular type of CHO studied (table 7). In the case of glycemic index (complex CHO) and starch vs sugar some of the difference in lipid response could be due to other dietary constituents (i.e., fiber, phytosterols).

Table 7. Summary of the Effect of Different Carbohydrates on Lipid and Lipoproteins			
Comparisons	Effect on Lipids and Lipoproteins		
Low GI vs. High GI	High GI increases LDL-C		
Sugar vs. Starch	Sugar increases LDL-C		
Sugar vs. Complex CHO	Sugar increases LDL-C and TGs		
Fructose vs. Glucose	Fructose increases LDL-C and HDL-C and postprandial TGs		

Sugar- sucrose, glucose, or fructose



#### MECHANISM OF THE EFFECTS OF CARBOHYDRATES ON LIPIDS

Dietary CHO promote hepatic de novo fatty acid synthesis by providing substrate for fatty acid synthesis (Figure 1). This is particularly the case when there is caloric excess. Additionally, the glucose provided by dietary CHO stimulates insulin secretion which also increases hepatic fatty acid synthesis. The increase in fatty acid synthesis in the liver enhances TG synthesis which promotes VLDL formation and secretion leading to an increase in plasma TG levels.



Figure 1. Carbohydrates stimulate VLDL production by stimulating de novo fatty acid synthesis.

Fructose is more potent at increasing de novo fatty acid synthesis than glucose. Small quantities of fructose in the diet are metabolized in the small intestine to glucose and organic acids and do not affect systemic metabolism while high quantities of fructose can escape intestinal metabolism and are delivered to the liver (134). In the liver fructose but not glucose activates SREBP1c and ChREBP leading to the increased expression of the genes that synthesize fatty acids stimulating hepatic lipogenesis (134,135). Additionally, fructose metabolism in the liver is not inhibited providing an unlimited supply of fructose carbons for lipogenesis. In contrast, the first steps in glucose metabolism can be inhibited and thus the utilization of glucose for lipogenesis is regulated (134). In addition, fructose inhibits fatty acid oxidation whereas glucose does not (135). These differences in the metabolism of fructose and glucose in the liver explain the increased ability of fructose to stimulate hepatic lipogenesis and the enhanced formation and secretion of VLDL. In the addition to increased VLDL production fructose does not stimulate the secretion of insulin, which plays a key role in stimulating lipoprotein lipase activity and the clearance of TG rich lipoproteins. The failure of dietary fructose to induce an increase in lipoprotein lipase activity may lead to a decrease in the clearance of TG rich lipoproteins compared to dietary glucose, which stimulates insulin secretion.

The elevation in TG rich lipoproteins in turn may have effects on other lipoproteins (25) (Figure 2).

Specifically, cholesterol ester transfer protein (CETP) mediates the equimolar exchange of TGs from TG rich VLDL and chylomicrons for cholesterol from LDL and HDL (25). The increase in TG rich lipoproteins per se leads to an increase in CETP mediated exchange, increasing the TG content and decreasing the cholesterol content of both LDL and HDL particles. This CETP-mediated exchange underlies the commonly observed reciprocal relationship of low HDL-C levels when TG levels are high and the increase in HDL-C when TG levels decrease. The TG on LDL and HDL are then hydrolyzed by hepatic lipase and lipoprotein lipase leading to the production of small dense LDL and small HDL particles.



Figure 2. The effect of hypertriglyceridemia on LDL and HDL.

#### **DIETARY PROTEIN**

## Effect of Dietary Protein on Cardiovascular Disease

In a meta-analysis of 10 studies with 425,781 participants intake of plant protein was associated with

a decrease in cardiovascular mortality (136). Other meta-analyses have also found that intake of plant proteins was associated with a lower risk of cardiovascular mortality (137-139). In some but not all studies animal protein intake increased the risk of cardiovascular mortality (136-139). The differences in outcomes observed between plant and animal proteins could be due to increased intake of SFA with animal proteins and increased fiber and phytosterol intake with plant proteins.

### **Effect of Dietary Protein on Lipids**

Because a high protein diet is often associated with an increase in SFA intake it is important to control for this variable in determining the effect of dietary protein on lipid levels. In a meta-analysis of a high vs. low protein diets in individuals on a low-fat diet no difference in LDL-C, HDL-C, or TG levels were observed (140). In another meta-analysis of 24 trials with 1,063 participants that compared isocaloric diets matched for fat intake but with differences in protein and CHO intakes no differences in LDL-C and HDL-C levels were observed but TG levels were decreased in the high protein diet group (-20.2mg/dL) (141). Greater weight loss and decreased CHO intake in the high protein diet group likely contributed to the decrease in TGs. In a meta-analysis where fat intake was not controlled the high protein diet was associated with an increase in HDL-C levels and a decrease in TG levels (142). It is obviously difficult to determine the effect of dietary protein on lipid levels as other dietary constituents are changing (SFA, CHO) and secondary effects induced by changes in protein intake (weight loss) could influence lipid levels.

#### **DIETARY FIBER**

Dietary fiber are non-digestible carbohydrates including non-starch polysaccharides, cellulose, pectins, hydrocolloids, fructo-oligosaccharides and lignin. Fiber is found mostly in fruits, vegetables, whole grains, nuts, seeds, psyllium seeds, beans, and legumes. There are two main types of dietary fiber; soluble and insoluble. The main sources of soluble fiber are fruits and vegetables and insoluble fiber are cereals and whole-grain products. Most high fiber foods contain both soluble and insoluble fiber. A summary of the fiber content of some foods is shown in tables 8-11.

Table 8. Fiber Content of Selected Vegetables					
Vegetables	Serving	Total Fiber/	Soluble Fiber/	Insoluble Fiber/	
	Size	Serving (g)	Serving (g)	Serving (g)	
Cooked vegetables					
Turnip	1⁄2 cup	4.8	1.7	3.1	
Peas, green, frozen	1⁄2 cup	4.3	1.3	3.0	
Okra, frozen	<sup>1</sup> / <sub>2</sub> cup	4.1	1.0	3.1	
Potato, sweet, flesh	<sup>1</sup> / <sub>2</sub> cup	4.0	1.8	2.2	
Brussels sprouts	<sup>1</sup> / <sub>2</sub> cup	3.8	2.0	1.8	
Asparagus	<sup>1</sup> / <sub>2</sub> cup	2.8	1.7	1.1	
Kale	<sup>1</sup> / <sub>2</sub> cup	2.5	0.7	1.8	
Broccoli	<sup>1</sup> / <sub>2</sub> cup	2.4	1.2	1.2	
Carrots, sliced	1⁄2 cup	2.0	1.1	0.9	
Green beans, canned	<sup>1</sup> / <sub>2</sub> cup	2.0	0.5	1.5	
Beets, flesh only	<sup>1</sup> / <sub>2</sub> cup	1.8	0.8	1.0	
Tomato sauce	<sup>1</sup> / <sub>2</sub> cup	1.7	0.8	0.9	

Corn, whole, canned	<sup>1</sup> / <sub>2</sub> cup	1.6	0.2	1.4
Spinach	<sup>1</sup> / <sub>2</sub> cup	1.6	0.5	1.1
Cauliflower	<sup>1</sup> / <sub>2</sub> cup	1.0	0.4	0.6
Turnip	<sup>1</sup> / <sub>2</sub> cup	4.8	1.7	3.1
Raw vegetables		·		
Carrots, fresh	1, 7 ½ in. long	2.3	1.1	1.2
Celery, fresh	1 cup chopped	1.7	0.7	1.0
Onion, fresh	<sup>1</sup> / <sub>2</sub> cup chopped	1.7	0.9	0.8
Pepper, green, fresh	1 cup chopped	1.7	0.7	1.0
Cabbage, red	1 cup	1.5	0.6	0.9
Tomato, fresh	1 medium	1.0	0.1	0.9
Mushrooms, fresh	1 cup pieces	0.8	0.1	0.7
Cucumber, fresh	1 cup	0.5	0.2	0.3
Lettuce, iceberg	1 cup	0.5	0.1	0.4

Adapted from Anderson JW. Plant Fiber in Foods. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

Table 9. Fiber Content of Selected Legumes				
Legumes (cooked)	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Kidney beans, light red	½ cup	7.9	2	5.9
Navy beans	½ cup	6.5	2.2	4.3
Black beans	½ cup	6.1	2.4	3.7
Pinto beans	½ cup	6.1	1.4	4.7
Lentils	½ cup	5.2	0.6	4.6
Black-eyed peas	½ cup	4.7	0.5	4.2
Chick peas, dried	½ cup	4.3	1.3	3
Lima beans	½ cup	4.3	1.1	3.2

Adapted from Anderson JW. Plant Fiber in Foods. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

Table 10. Fiber Content of Selected Fruits				
Fruits	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Apricots, fresh w/skin	4	3.5	1.8	1.7
Raspberries, fresh	1 cup	3.3	0.9	2.4
Figs, dried	1 1/2	3	1.4	1.6
Mango, fresh	½ small	2.9	1.7	1.2
Orange, fresh	1 small	2.9	1.8	1.1
Pear, fresh, w/skin	1/2 large	2.9	1.1	1.8
Apple, red, fresh w/skin	1 small	2.8	1	1.8
Strawberries, fresh	1 ¼ cup	2.8	1.1	1.7
Plum, red, fresh	2 medium	2.4	1.1	1.3
Applesauce, canned	½ cup	2	0.7	1.3
Apricots, dried	7 halves	2	1.1	0.9
Peach, fresh, w/skin	1 medium	2	1	1
Kiwifruit, fresh	1 large	1.7	0.7	1
Prunes, dried	3 medium	1.7	1	0.7
Grapefruit, fresh	1⁄2 medium	1.6	1.1	0.5
Blueberries, fresh	¾ cup	1.4	0.3	1.1
Cherries, black, fresh	12 large	1.3	0.6	0.7
Banana, fresh	1⁄2 small	1.1	0.3	0.8
Melon, cantaloupe	1 cup cubed	1.1	0.3	0.8
Watermelon	1 ¼ cup cubed	0.6	0.4	0.2
Grapes, fresh w/skin	15 small	0.5	0.2	0.3
Raisins, dried	2 tbsp	0.4	0.2	0.2

Adapted from Anderson JW. Plant Fiber in Foods. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

Table 11. Fiber Content of Grains				
Food	Serving Size	Total Fiber/ Serving (g)	Soluble Fiber/ Serving (g)	Insoluble Fiber/ Serving (g)
Wheat bran	½ cup	12.3	1.0	2.7
Barley, pearled, cooked	½ cup	3.0	0.8	2.2
Oatmeal, dry	⅓ cup	2.7	1.4	11.3
Bread, pumpernickel	1 slice	2.7	1.2	1.5
Wheat flakes	¾ cup	2.3	0.4	1.9
Bread, rye	1 slice	1.8	0.8	1.0
Bread, whole wheat	1 slice	1.5	0.3	1.2
Rice, white, cooked	½ cup	0.8	trace	0.8
Bread, white	1 slice	0.6	0.3	0.3

Adapted from Anderson JW. Plant Fiber in Foods. 2nd ed. HCF Nutrition Research Foundation Inc, PO Box 22124, Lexington, KY 40522, 1990.

#### Effect of Dietary Fiber on Cardiovascular Disease

Several meta-analyses have demonstrated that an increase in total fiber, soluble fiber, and insoluble fiber are associated with a decrease in cardiovascular events (143-148). The greater the intake of fiber the greater the reduction in risk of cardiovascular events.

## Effect of Dietary Fiber on Lipids

In a meta-analysis of randomized controlled trials the effect of fiber on lipid levels was evaluated (149). Increased dietary fiber decreased total cholesterol (TC) (-7.8mg/dL; 95% CI -13.3 to -2.3), LDL-C (-5.5mg/dL; 95% CI -8.6 to -2.3), and HDL-C levels (-1.17mg/dL; 95% CI -2.34 to -0.39) (149,150), There was no change in TG levels. A meta-analysis of randomized controlled studies of whole-grain foods vs non-whole-grain foods found that the whole-grain diet lowered LDL-C (-3.51mg/dL; P < 0.01) and TC levels (-4.68mg/dL; P < 0.001) compared with the non-whole grain foods (151). HDL-C and TG levels were not significantly altered by the whole grain diet. Moreover,

3.4 g of psyllium (Metamucil), a soluble fiber, decreased LDL-C with no significant effects on HDL-C or TGs (152,153). In a meta-analysis of 28 randomized trials psyllium lowered LDL by 12.9mg/dL (P < 0.00001) (154). A mean reduction in LDL-C concentrations of about 1.1 mg/dL can be expected for each g of water-soluble fiber in the diet (155,156).

#### MECHANISM OF EFFECT OF FIBER ON LDL-C

Fiber is thought to decrease cholesterol absorption by the small intestine (157,158). This leads to a decrease in cholesterol content of chylomicrons and a reduction in the delivery of cholesterol to the liver. The decrease in cholesterol in the liver upregulates LDL receptors resulting in a decrease in plasma LDL-C levels. Fiber may also decrease small intestinal absorption of bile acids which will lead to the increased utilization of hepatic cholesterol for the synthesis of bile acids (159). This will also decrease hepatic cholesterol levels inducing an increase in the expression of LDL receptors lowering plasma LDL-C levels. Finally, colonic fermentation of dietary fiber with production of short-chain fatty acids, such as acetate, propionate, and butyrate, is postulated to inhibit hepatic cholesterol synthesis contributing to a decrease in LDL-C levels (159).

## PLANT STEROLS AND STANOLS (PHYTOSTEROLS)

Plant sterols and plant stanols (phytosterols) are naturally occurring constituents of plants and are found in vegetable oils, such as corn oil, soybean oil, and rapeseed oil and cereals, nuts, fruits, and vegetables. The intake of plant sterols and stanols is about 200–400 mg/day. The most commonly occurring phytosterols in the human diet are  $\beta$ -sitosterol, campesterol, and stigmasterol. Higher intakes can be achieved by consuming a vegetable-based diets such as a vegetarian diet (400-800mg/day) or by consuming food products enriched with plant sterols or stanols (for example margarines or yogurt). If using foods enriched in phytosterols it is best to take them with main meals to enhance their effectiveness. High doses of phytosterols can affect the absorption of fat-soluble vitamins. The plant sterol and stanol content of different foods is shown in table 12.

Table 12. Plant Sterol and Stanol Contents in Different Foods			
Food item	Plant Sterols	Plant Stanols	
	(mg/100 g)	(mg/100 g)	
Vegetable oils			
Corn oil	686-952	23-33	
Rapeseed oil (canola oil)	250-767	2-12	
Soybean oil	221-328	7	
Sunflower oil	263-376	4	
Olive oil	144-193	0.3-4	
Palm oil	60-78	Traces	
Cereals	-	-	
Corn	66-178	-	
Rye	71-113	12-22	
Wheat	45-83	17	
Barley	80	2	
Millet	77	-	
Rice	72	3	
Oats	35-61	1	
Vegetables	•		
Broccoli	39	2	
Cauliflower	18-40	Traces	
Carrot	12-16	Traces	
Lettuce	9-17	0.5	
Potato	7	0.6	

Tomato	7	1	
Fruits and berries			
Avocado	75	0.5	
Passion fruit	44	Not detected	
Raspberry	27	0.2	
Orange	24	Not detected	
Apple	12-18	0.8	
Banana	12-16	Not detected	

Adapted from Piironen V and Lampi AM (160)

## Effect of Phytosterols on Cardiovascular Disease

There is minimal data on the effect of phytosterols on cardiovascular events. From the effect on LDL-C levels one would anticipate that phytosterols would reduce CVD.

## Effect of Phytosterols on Lipids

Plant sterols or plant stanols at a dose of 3 grams per day lowers LDL-C by approximately 12% (161). Higher doses do not dramatically further lower LDL-C levels and lower doses have less effect on LDL-C (for example 2 grams/day lowers LDL-C by 8%) (161). HDL-C levels are not affected by plant sterols or stanols but TG levels decrease modestly (~6%) with a greater absolute reduction in individuals with high TG level (percent change is the same) (162). To achieve these high doses consuming food products enriched is phytosterols is necessary.

### MECHANISM OF EFFECT OF PHYTOSTEROLS ON LDL-C

Plant sterols or plant stanols reduce LDL-C levels by competing with cholesterol for incorporation into micelles in the gastrointestinal tract, resulting in decreased cholesterol absorption (163). This leads to the decreased delivery of cholesterol to the liver and the up-regulation of LDL-receptor expression lowering LDL-C levels.

## SUMMARY OF THE EFFECT OF DIETARY CONSTITUENTS ON LIPID LEVELS

A summary of the major effects of dietary constituents on lipid levels is shown in table 13, typically under isocaloric feeding conditions in short-term feeding studies. Dietary SFA, TFA, and cholesterol increase LDL-C levels whereas CHO increases TG levels. MUFA, PUFA, fiber and phytosterols decrease LDL-C and TFA decrease HDL-C levels.

Table 13. Summary of the Effect of Dietary Constituents on Lipid and Lipoproteins			
SFA	Increase LDL-C and modest increase HDL-C		
MUFA and PUFA	Decrease LDL-C		
TFA	Increase LDL-C and decrease HDL-C		
Cholesterol	Increase LDL-C		
СНО	Increase TGs, increase greater with simple sugars particularly fructose		
Fiber	Decrease LDL-C		
Phytosterols	Decrease LDL-C		



## EFFECT OF SPECIFIC FOODS ON CARDIOVASCULAR DISEASE

There are a large number of observational trials linking various foods with either an increased or decreased risk of CVD. A large meta-analysis by Micha et al reported that fruits, vegetables, beans/legumes, nuts/seeds, whole grains, fish, yogurt, fiber, seafood omega-3 fatty acids, polyunsaturated fats, and potassium were associated with a decreased risk of CVD while unprocessed red meats, processed meats, sugar-sweetened beverages, and sodium were associated with an increased risk of CVD (164). A similar meta-analysis by Bechthold et al found that whole grains, vegetables and fruits, nuts, and fish consumption were associated with a decrease in CVD while red meat, processed meat, and sugar sweetened beverage consumption was associated with an increase in CVD (165). Note, as discussed in the introduction, observational studies have limitations and cannot be assumed to indicate cause and effect. Additional one can find other meta-analyses that reach different conclusions than the results described above. For example, a meta-analysis by Zeraatkar et al and a meta-analysis by Vernooij et al reached the conclusion that meat and processed meat were not associated with a significant increase in CVD (20,166). Thus, one needs recognize that while these studies can suggest beneficial and harmful effects of eating certain foods more definitive studies are required to be certain. For a detailed analysis of the limitations of observational dietary studies see articles by Ioannidis and Nissen (1,2).

Only a single randomized trial has examined the effect of specific foods on CVD events. The DART trial randomized men with an acute myocardial infarction to at least two weekly portions (200-400 g) of fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, or trout) (n=1015) or no dietary advice (n=1018) (50). After approximately 2 years total mortality was significantly lower (RR 0.71; CI 0.54-0.93) in the fish advice group than in the no fish advice group, due to a reduction in ischemic heart disease deaths. There were no significant differences in ischemic heart disease events (RR 0.84; CI 0.66-1.07). In a separate portion of the DART trial there was also a group of men with an acute myocardial infarction randomized to increased intake of cereal fiber (18 grams/day) (n=1017) vs. no dietary advice (n=1016). No reduction in cardiovascular events was seen in the cereal fiber group.

Clearly addition randomized trials are required to determine the true benefits of specific foods on cardiovascular events.

#### EFFECT OF SPECIFIC FOODS ON LIPID LEVELS

In contrast to the paucity of randomized controlled trials on the effect of specific foods on cardiovascular disease there are an abundance of studies on the effect of specific foods on lipid and lipoprotein levels. Given the large number of studies in many instances I will cite the results of meta-analyses to provide the reader with the typical effects that are observed. It should be noted that the effect of specific foods on lipid and lipoprotein levels tend to be small and therefore the results can be inconsistent from study to study.

#### **Nuts and Seeds**

The most consumed edible tree nuts are almonds, hazelnuts, walnuts, pistachios, pine nuts, cashews, pecans, macadamias, and Brazil nuts. Peanuts are botanically groundnuts or legumes, and are widely considered to be part of the nut food group. Nuts are generally consumed as snacks (fresh or roasted), in spreads (peanut butter, almond paste), or as oils or baked goods. Seeds come in all different sizes, shapes and colors. Popular seeds include flax, pumpkin, sunflower, chia, sesame, and mustard seeds.

Nuts and seeds are rich in MUFAs, such as oleic acid and in PUFAs, such as linoleic acid and alpha-linolenic acid (ALA). They also contain small amounts of SFA. Almonds, cashews, hazelnuts, pistachios and macadamian nuts have a high MUFA content (>50%) content when compared with other nuts. For other nuts (e.g., Brazil nuts, pine nuts, and walnuts) the PUFA content is high (>50%), while peanuts and pecans have been found to contain relatively high levels of both MUFA and PUFA (table 14). Nuts are a good source of dietary fiber, ranging from 4-11 g/100 g and phytosterols.

Table 14. Nutrient Composition of Nuts				
Nuts	PUFA (g/100 g)	MUFA (g/100 g)	SFA (g/100 g)	Fiber (g/100 g)
Walnuts	47.2	8.9	6.1	6.7
Peanuts	15.6	24.4	6.3	8.8
Pistachios	13.7	23.8	5.6	10.3
Almonds	12.3	31.6	3.8	12.5
Hazelnuts	7.9	45.7	4.5	9.7
Cashews	7.8	23.8	7.8	3.3
Pecans	21.6	40.8	6.2	9.6
Macadamias	1.5	58.9	12.1	8.6

Consumption of nuts and seeds lower TC and LDL-C levels in healthy subjects or patients with moderate hypercholesterolemia (167-172). Nuts had no significant or minimal effect on increasing HDL-C. The benefits of nuts and seeds vary depending on the type, nutrient composition, and quantity of nuts and seeds consumed. Studies have noted that the estimated cholesterol lowering effect of nuts was greater in individuals with higher initial values of LDL-C and in those with a lower baseline BMI (169).

Walnuts: A meta-analysis on the effect of walnuts on lipid levels that included 365 participants showed a decrease in LDL-C (9.2 mg/dL), while HDL-C or TG were not significantly affected (173). In another meta-analysis that analyzed 1,059 participants with a walnut enriched diet LDL-C was lowered by 5.5 mg/dL (174).

Almonds: A meta-analysis of 15 studies with 534 participants found that almonds decreased LDL

cholesterol (5.8 mg/dL; 95% CI: -9.91, -1.75 mg/dL) and apo B (6.67 mg/dL; 95% CI: -12.63, -0.72 mg/dL) (175). Triglycerides, apo A1, and lipoprotein (a) showed no differences.

Pistachio nuts: A meta-analysis of twelve randomized studies reported that pistachio nuts decreased LDL-C -3.82 mg/dL (95% CI, -5.49 to -2.16) and TG -11.19 mg/dL (95% CI, -14.21 to -8.17) levels without effecting HDL-C levels (176).

A meta-analysis by Houston et al analyzed the effect of a variety of different nuts on lipid levels (table 15) (177). They found that in general nuts lowered LDL-C and minimally lowered TG levels but had no effect on HDL-C levels. A meta-analysis found that whole flaxseed reduced TC and LDL-C by 6 and 8 mg/dL, respectively (178). Thus, both nuts and seeds lower LDL-C levels.



Table 15. Effect of Nuts on Lipid Levels				
	Number of	Number of	Effect estimate (mmol/L)	
	analyses	participants	95% CI	
LDL Cholesterol				
Almond	32	2439	-0.15 [-0.22, -0.08]	
Brazil nut	4	307	-0.30 [-0.70, 0.11]	
Cashew nut	3	432	0.02 [-0.12, 0.16]	
Hazelnut	6	374	-0.01 [-0.15, 0.12]	
Macadamia	6	410	-0.11 [-0.27, 0.04]	
Mixed nuts	10	791	0.04 [-0.06, 0.14]	
Peanut	10	1021	0.08 [-0.04, 0.20]	
Pecan	6	295	-0.23 [-0.46, 0.00]	
Pistachio	12	736	-0.15 [-0.30, 0.00]	
Walnut	35	2582	-0.12 [-0.18, -0.06]	
Triglycerides				
Almond	32	2439	-0.02 [-0.05, 0.02]	
Brazil nut	4	307	0.04 [-0.54, 0.63]	
Cashew nut	3	432	-0.02 [-0.11, 0.07]	
Hazelnut	5	313	0.11 [-0.02, 0.25]	
Macadamia	5	342	-0.10 [-0.21, 0.00]	
Mixed nuts	11	888	-0.01 [-0.07, 0.06]	
Peanut	10	1021	-0.09 [-0.16, -0.02]	
Pecan	6	295	-0.11 [-0.24, 0.03]	
Pistachio	9	498	-0.12 [-0.21, -0.03]	
Walnut	35	3109	-0.09 [-0.12, -0.06]	

Table based on data from a meta-analysis by Houston et al (177). To convert mmol/L cholesterol to mg/dL multiply by 39 and to convert mmol/L triglycerides to mg/dL multiply by 88.

#### Whole Grains

Whole grains include barley, brown rice, buckwheat, bulgur (cracked wheat), millet, oatmeal, and wild rice. Whole grains contain ~80% more dietary fiber than refined grains, as the latter are milled, a process that removes bran and germ. Refined grains include white flour, white rice, white bread, and corn flower. Health benefits ascribed to whole grains are mainly due to the presence of fiber and bran. A meta-analysis of fifty-five trials with 3900 participants comparing various grains

found that oat bran was the most effective intervention strategy for lowering LDL-C (- 12.5mg/dL; 95% CI – 17.2 to – 7.4mg/dL) compared with control (179). Oats also reduced LDC (- 6.6mg/dL; 95% CI – 10.9 to 2.73mg/dL). Barley, brown rice, wheat and wheat bran were not effective in improving blood lipid levels compared with controls. Another meta-analysis also found that whole-grain oats decreased LDL-C levels (-16.7 mg/dL; P < 0.0001) (180).

#### Soy Protein

Soybeans and soy products as well as supplements contain soy proteins. In a meta-analysis of 43 randomized studies with 2,607 participants the decrease in LDL-C levels reductions for soy protein ranged between -4.2 and -6.7 mg/dL (P<0.006) (181). Numerous other meta-analyses have reported similar decreases in LDL-C (182-187). In addition, soy protein also decreases TG levels (~2-10mg/dL) and increases HDL-C levels (~1-2mg/dL). Soy protein does not affect Lp(a) levels (188). The amount of soy protein that is recommended for lipid lowering is 25–50 grams per day (189).

The decrease in LDL-C is due to the indirect effect of soy protein decreasing the intake of animal protein (SFA and cholesterol) and the intrinsic effects of bioactive compounds in soy protein (190). The intrinsic effect of soy protein might be mediated by phytoestrogens that could increase levels of HDL-C and TG and decrease levels of LDL-C (189).

## Garlic

Garlic supplements are available in several different forms, including garlic powder, allicin, aged garlic extract, and garlic oil. Several meta-analyses have shown that garlic lowers TC levels with variable effects on LDL-C, HDL-C, and TG (191-198). Some studies find a decrease in LDL-C and others a decrease in TG levels. The longer the duration of treatment and the higher the baseline TC the greater the effect. In one meta-analysis TC was reduced by 17 ± 6 mg/dL and low-density lipoprotein cholesterol by 9 ± 6 mg/dL in individuals with elevated TC levels (>200 mg/dL) if treated for longer than 2 months (191). In another meta-analysis garlic powder and aged garlic extract were more effective in reducing TC levels, while garlic oil was more effective in lowering serum TG levels (192). In a meta-analysis of garlic administration to patients with diabetes TC decreased 16.9mg/dL, LDL decreased 9.7mg/dL, TG decreased 12.4mg/dL, and HDL-C increased 3.19mg/dL (all p=0.001) (199). Lp(a)

levels are not altered by garlic (198).The mechanism by which garlic alters lipid levels is unknown.

### Теа

Green tea contains catechins many (e.q., epigallocatechin-3-gallate) that influence lipid metabolism in animal models and have been shown to upregulate LDL receptors in liver and suppress PCSK9 production (200,201). Epigallocatechin gallate may also interfere with the intestinal absorption of lipids (202). Most but not all meta-analyses have shown that drinking green tea or black tea decreases TC and LDL-C levels with no significant effect on HDL-C or TG levels (203-214). The reduction in LDL-C is approximately 5-10mg/dL.

#### Coffee

Coffee contains cholesterol-increasing compounds; diterpenes such as cafestol and kahweol (215,216). The amount of these cholesterol increasing compounds in coffee depends on how the coffee is prepared (215,216). Boiling coffee beans extracts diterpenes due to the prolonged contact with hot water resulting in high concentrations in the coffee whereas brewed filtered coffee because of the short contact with hot water and retention of diterpenes by the filter paper has lower concentrations of diterpenes. Instant coffee has very low levels of diterpenes (216). The concentration of the cholesterol-raising compound cafestol is negligible in drip-filtered, instant, and percolator coffee but high in unfiltered coffee such as French press, Turkish, or Scandinavian boiled coffee. Levels of cafestol are intermediate in espresso and coffee made in a Moka pot.

A meta-analysis of 18 trials found that the consumption of unfiltered, boiled coffee dosedependently increased TC and LDL-C concentrations (23 mg/dL and 14 mg/dL, respectively), while consumption of filtered coffee resulted in only small changes (TC increased by 3 mg/dL and no effect on LDL-C concentration) (217). Additionally, decaffeinated coffee had a smaller effect and the increase in cholesterol levels was greatest in individuals with hypercholesterolemia. Thus coffee, depending upon how it is prepared, can increase TC and LDL-C levels.

#### **Chocolate and Cocoa**

Cocoa is the non-fat component of finely ground cocoa beans that is used to produce chocolate. Cocoa is rich in flavanols which are low-molecular-weight monomeric compounds, such as epicatechin or complex higher-molecular-weight oligomeric and polymeric compounds (218). The flavanol content in cocoa products can vary greatly and is dependent on the crop type, post-harvest handling practices, and manufacturer processing techniques. The flavanol content of milk and white chocolate is low or even absent (218).

In a meta-analysis of 21 studies with 986 participants very small effects on LDL-C and HDL-C levels were observed (LDL-C 2.7mg/dL decrease; HDL-C 1.2mg/dL increase) with no change in TG levels with chocolate and/or cocoa intake (219). In another metaanalysis there was a decrease in TG levels (-8.8mg/dL), an increase in HDL-C (2.3mg/dL), and a non-significant decrease in LDL-C (-10.1mg/dL) (220). In studies where the epicatechin dose was greater than 100mg per day the decrease in LDL-C levels was greater (5.5mg/dL) (219). Another meta-analysis of 19 studies found that LDL decreased by 3.3mg/dL and HDL-C increased by 1.8mg/dL with cocoa intake (221). A meta-analysis of 10 clinical trials with 320 participants that focused on dark chocolate found a 6.23mg/dl decrease in LDL-C with no significant HDL-C and ΤG changes in (222). Thus chocolate/cocoa causes a small decrease in LDL-C levels.

## Alcohol

It is recommended that females consume no more than 1 drink per day of alcohol (equivalent to 15 grams per day) and that males consume no more than 2 drinks per day (equivalent to 30 grams per day). Alcohol has a relatively high caloric level (7 calories/gram).

## EFFECT OF ALCOHOL ON LIPID LEVELS

In a meta-analysis of 25 studies with an average consumption of 40.9 grams of alcohol per day HDL-C concentrations increased by 5.1 mg/dL (223). HDL-C levels increased by 0.122- 0.133 mg/dL per gram of alcohol per day. Consuming 30 grams of alcohol a day would therefore increase HDL-C concentrations by approximately 3.99 mg/dL compared with an individual who abstains (an 8.3% increase from pretreatment values). The increase in HDL-C was observed regardless of sex, duration of study, median age, or beverage type but the increase was greater in individuals with baseline HDL-C < 40mg/dL and who were sedentary. As expected apo A1 levels also increased. In a meta-analysis of 35 studies TG concentrations increased by 0.19 mg/dL per gram of alcohol consumed a day (P=0.001) and 5.69 mg/dL per 30 g consumed per day (5.9% increase over baseline) (223). The increase in TG levels was seen regardless of beverage type and appeared to be greater in males than females.

In a more recent meta-analysis of 33 studies with 796 participants HDL-C levels were increased by 3.67mg/dL by alcohol intake (224). Apo A1 levels were also increased but there were no significant differences in TC, LDL-C, TG, or Lp(a) with alcohol intake. The greater the consumption of alcohol the greater the increase in HDL-C levels. When the consumption of alcohol was greater than 60 grams per day (4 drinks) TG levels were also increased (24.4mg/dL).

In a meta-analysis of 14 studies, comparing 548 beer drinkers and 532 controls TC levels were significantly higher in the beer drinkers compared to controls (difference 3.52 mg/dL; p<0.001) (225). In a meta-analysis of 18 studies, comparing 626 beer drinkers

and 635 controls HDL-C levels were higher in the beer drinkers compared to controls (difference 3.63 mg/dL: p<0.001) (225). This increase in HDL-C levels in beer drinkers were seen in both males and females. LDL-C and TG levels were not significantly different between beer drinkers and controls (LDL-C difference -2.85 mg/dL; p = 0.070; TG difference 0.40 mg/dL; p = 0.089) (225).

Genetic factors play a role in the HDL response to alcohol (226). Individuals with an apoE2 allele have greater HDL-C increase and those with an apoE4 allele have a blunted increase in HDL-C with alcohol intake (226).In addition to an increase in HDL-C levels studies have suggested that the ability of HDL to facilitate the efflux of cholesterol from cells is enhanced by alcohol intake (226,227).

One should note in the meta-analyses described above alcohol doesn't appear to have a major impact on TG levels. However, it must be recognized that the amount of alcohol consumed is a key variable (228,229). At low to moderate amounts alcohol has either no effect or might even decrease TG levels (228). However, at high amounts of alcohol intake increases in TG levels are observed (228,229). As noted above one meta-analysis noted that the consumption of 60 grams per day of alcohol increased TG levels (224). Moreover, alcohol consumed with a meal increases and prolongs the postprandial increase in TG levels (228,229). Additionally, genetic factors and the presence of other abnormalities play a role in the TG response to alcohol intake (229). For example, the increase in TG levels after red wine was -4%, 17%, and 33% in individuals with a BMI 19.60-24.45, 24.46- 26.29, and 26.30-30.44, respectively (P

= .001) demonstrating that the increase in TG was strongly influenced by BMI (230). Finally, in patients with pre-existing hypertriglyceridemia moderate alcohol intake increased TG levels ( $338 \pm 71 \text{ mg/dL}$  to  $498 \pm 117 \text{ mg/dL}$ ; P < 0.05) (231).

## MECHANISM FOR THE EFFECT OF ALCOHOL ON HDL

The mechanism for the increase in HDL-C levels is likely due to an increased production of apo A1 and A2 (232). Additionally, alcohol inhibits cholesteryl ester transfer protein (CETP) activity, which will also increase HDL-C levels (229).

## MECHANISM FOR THE EFFECT OF ALCOHOL ON TRIGLYCERIDES

Alcohol increases VLDL secretion by the liver (229). The increased production and secretion of VLDL is due to a number of factors including a) alcohol increases lipolysis in adipose tissue and increases the delivery of fatty acids to the liver b) alcohol increases hepatic fatty acid transporters increasing the uptake of circulating fatty acids c) alcohol increases hepatic de novo fatty acid synthesis d) alcohol decreases the beta oxidation of fatty acids in the liver (229,233,234). Together these effects lead to an increased supply of fatty acids in the liver facilitating TG synthesis and the formation and secretion of VLDL.

While moderate alcohol intake increases lipoprotein lipase (LPL) activity acute alcohol intake inhibits LPL activity, which could explain the observation that alcohol consumed with a meal increases postprandial TG levels ((228,229).

Table 16. Major Effects of Specific Foods on Lipid Levels			
Nuts and Seeds	Decrease TC and LDL-C		
Whole Grains	Decrease LDL-C		
Garlic	Decrease TC, LDL-C, TG		
Green and Black Tea	Decrease TC and LDL-C		
Coffee (depends on method of preparation)	Increase TC, LDL-C, TG		
Cocoa and Chocolate	Decrease LDL-C		

#### Summary of the Effect of Specific Foods on Lipid Levels

#### SPECIFIC DIETS

The effect of several dietary strategies on lipid levels is discussed below. Randomized controlled trials on the effect of specific diets on cardiovascular outcomes were discussed in earlier sections (saturated fatty acids section and monounsaturated fatty acids section).

#### Mediterranean Diet

Mediterranean diets have an abundance of plant foods, including vegetables, legumes, nuts, fruits, and grains, fish, and low to moderate red wine consumption. Low consumption of meat and meat products and moderate consumption of milk and dairy products is encouraged. In the PREDIMED trial the Mediterranean diet resulted in a small but significant increase in HDL-C levels and a small decrease in both LDL-C and TG levels (76). In the Lyon Diet Heart Study lipid levels were similar in the Mediterranean and usual diet groups (77). The cardiovascular outcome benefits of both of these randomized outcome trials are discussed in the effect of MUFA on CVD section. In a meta-analysis of the effect of a Mediterranean diet on lipid levels little or no change in LDL-C, HDL-C, and TGs was observed (235). Another meta-analysis reported a 4.6mg/dL decrease in LDL-C and a 0.61mg/dL increase in HDL-C (236).

## Dietary Approach to Stop Hypertension (DASH) Diet

The DASH diet promotes the consumption of fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts and a decrease in the intake of red meat, sweets, sugar-containing beverages, total fat, saturated fat, and cholesterol. In the initial DASH trial total fat and SFA intake was reduced in the DASH diet group (total fat 27% vs. 39% of calories; SFA 6.2% vs. 15% of calories). MUFA and PUFA intake were similar but cholesterol intake was decreased (194mg/day vs 324mg/day). As expected, CHO and fiber intake were increase (CHO 59% vs. 49% of calories; fiber 35grams/day vs. 17grams/day). The DASH diet lowered TC (15.6 to 19.5mg/dL), LDL-C (11.7 to 15.5mg/dL), and HDL-C (3.12 to 3.90mg/dL) (237). TG levels were not significantly affected. In a meta-analysis of twenty studies of the DASH diet reporting data for 1917 participants TC was decreased (7.8mg/dL; P=0.001) and LDL was decreased (3.9mg/dL; p<0.03) (238). HDL-C and TG levels were not significantly altered (238). Similar results were seen in other meta-analyses (239,240).

#### **Portfolio Diet**

The portfolio dietary pattern is a plant-based dietary pattern that includes four cholesterol-lowering foods; a) tree nuts or peanuts, b) plant protein from soy products, beans, peas, chickpeas, or lentils, c) viscous soluble fiber from oats, barley, psyllium, eggplant, okra, apples, oranges, or berries, and d) plant sterols initially provided in a plant sterol-enriched margarine. In a meta-analysis of 5 studies with 439 participants LDL-C was lowered by 17% (28.5mg/dL; p< 0.001) and TGs by 16% (24.6mg/dL; p< 0.001) with no change in HDL-C or weight (241).

## Nordic Diet

The Nordic diet is based on the consumption of different healthy foods such as whole grains, fruits (such as berries, apples, and pears), vegetables, legumes (such as oats, barley, and almonds), rapeseed oil, fatty fish (such as salmon, herring and mackerel), shellfish, seaweed, low-fat choices of meat (such as poultry and game), low-fat dairy, and decreased intake of salt and sugar-sweetened products. In a meta-analysis of 5 studies LDL-C was decreased by 11.7mg/dL (p= 0.013) with no changes in TG or HDL-C levels (242). In another meta-analysis of 6 studies LDL-C was decreased by 10.1mg/dL with no changes in TG or HDL-C levels (243).

## **Ketogenic Diet**

Low CHO diets can contain variable amounts of CHO. When the CHO levels are very low, they stimulate the formation of ketones. In a typical ketogenic diet CHO contribute <10% of calories (< 50 grams/day), protein approximately 30% of calories, and fat approximately 60% of calories with no restrictions on the type of fat or cholesterol levels. These diets can be high in beef, poultry, fish, oils, various nuts/seeds, and peanut butter, with moderate amounts of vegetables, salads with low-carbohydrate dressing, cheese, and eggs. Fruits and fruit juices, most dairy products with the exception of hard cheeses and heavy cream, breads, cereals, beans, rice, desserts/sweets, or any other foods containing substantial amounts of CHO are avoided.

It is well recognized that a ketogenic diet results in an increase in LDL-C levels, which varies depending upon the type of fat ingested, the degree of carbohydrate restriction, the presence of other

medical conditions, weight loss on the diet, and genetic background (244). This increase in LDL-C levels is best illustrated in children treated with a ketogenic diet for epilepsy and in healthy individuals on a ketogenic diet (245-250). In some studies HDL-C is also increased (246-249). A meta-analysis of randomized studies in normal-weight adults found that a ketogenic diet increased LDL-C by 42mg/dL and HDL-C by 13.7mg/dL with no significant changes in TG levels (251). It should be noted that the increase in LDL-C is often not observed or is modest in patients with obesity or the metabolic syndrome (252,253).

While the typical increases in LDL-C levels observed with a ketogenic diet are relatively modest, recently a series of reports have described marked elevations in LDL-C levels in some patients on a ketogenic diet (253-255). For example, Goldberg et al reported 5 patients with marked increases in LDL-C levels on a ketogenic diet (256). Three patients had LDL-C levels greater than 500mg/dL. Similarly, Schaffer et al described 3 patients in which a very low carbohydrate diet induced LDL-C levels greater then 400mg/dL (257). Finally, Schmidt et al reported 17 patients with LDL-C levels greater than 200mg/dL on a ketogenic diet (258). In these patients there was an average increase in their LDL-C level of 187 mg/dL (258). The elevations in LDL-C levels decrease towards normal with cessation of the ketogenic diet (256-258). It should be noted that most of the patients with marked elevations in LDL-C in response to a ketogenic diet had normal LDL-C levels prior to the dietary change (255).

Many of the individuals who develop marked increases in LDL-C on a very low carbohydrate ketogenic diet have low TG levels, elevated HDL-C levels, and are thin (253,255). This phenotype has been called the lean mass hyper-responder (LMHR) phenotype (253,255). LMHR individuals have been defined as having TG <70mg/dL, HDL-C > 80mg/dL, and LDL-C > 200mg/dL (253,255). The mechanism for the marked increase in LDL-C levels is unknown. It may be due to a genetic predisposition in certain

individuals (Apo E2/E2 genotype or high polygenic risk score for hypercholesterolemia) (256). Therefore, it is important for clinicians to monitor lipid levels in patients electing to follow a very low CHO/high fat diet.

## Comparison of Low Fat vs. Low Carbohydrate Weight Loss Diets

Numerous randomized studies have compared the effect of low fat vs. low CHO weight loss diets on lipid levels. In a study by Foster et al 154 obese individuals were randomized to a low-fat diet and 153 obese individuals to a low CHO diet (259). In the low CHO diet during the first 12 weeks of treatment participants were instructed to limit CHO intake to 20 grams/day in the form of low–glycemic index vegetables after which the diet was gradually liberalized. In the low-fat diet participants were instructed to limit energy intake with approximately 55% of calories from CHO, 30% from

fat, and 15% from protein. Participants were instructed to limit calorie intake, with a focus on decreasing fat intake. After 6 months weight loss was similar in both diet groups. The effect on lipid levels at 6 months is shown in table 17. As one would expect the low CHO was very effective at lowering TG levels and increasing HDL-C levels while the low-fat diet was very effective at lowering LDL-C levels. The large weight loss in this trial may have contributed to the large reduction in lipid levels. A review of a large number of meta-analyses comparing a low CHO diet vs. low fat weight loss diet similarly described that the low CHO diet lowered TG levels and increased HDL-C and LDL-C levels compared to the low-fat diet (244). Note the increase in LDL-C with the low-CHO diet was blunted in patients with diabetes or pre-diabetes (244). Also, the increase in LDL-C levels is likely to be greater in low CHO diets that are enriched in SFA (244).

Table 17. Comparison of Low Fat vs. Low Carbohydrate Weight Loss Diet on Lipid Levels			
	Low Fat Diet	Low Carbohydrate Diet	
Weight	-11.3kg	-12.2kg	NS
TGs	-24mg/dL	-49mg/dL	P<0.001
LDL-C	-9.5mg/dL	0.5mg/dL	P<0.001
HDL-C	1.0mg/dL	6.2mg/dL	P<0.001

## Comparison of Vegetarian and Omnivore Diet on Lipid Levels

Vegetarian diets exclude all animal flesh. A metaanalysis of 19 studies comparing a vegetarian vs. omnivore diet found that consumption of vegetarian diets resulted in a 12.2mg/dL decrease in LDL-C (p < 0.001) and 3.4mg/dL decrease in HDL-C (p < 0.001) and a nonsignificant increase in TG levels (5.8 mg/dL; P = 0.090) compared with consumption of an omnivorous diet (260). Vegan diets, which exclude all animal products, were associated with larger LDL-C reductions than lacto-ovo vegetarian diets. A metaanalysis of 11 clinical trials comparing a vegetarian vs. omnivore diet observed similar results (LDL-C decreased 13.3mg/dL ; P<0.001; HDL decreased 3.9mg/dL; P<0.001) (261). It is likely that a decrease in dietary SFA and cholesterol and an increase in dietary fiber and phytosterols account for the differences in a vegetarian and omnivore diets.

## **Comparison of 14 Different Diets on Lipid Levels**

In a network meta-analysis of 121 eligible trials with 21,942 overweight or obese patients Ge and colleagues compared the effect of 14 different diets on LDL-C and HDL-C levels (236). The diets could be grouped into low CHO diets (Atkins, South Beach, Zone), moderate macronutrients diets (Biggest Loser, DASH, Jenny Craig, Mediterranean, Portfolio, Slimming World, Volumetrics, Weight Watchers), and low-fat diets (Ornish, Rosemary Conley). The effect of

these different diets on LDL-C and HDL-C levels are shown in table 18. It should be noted that despite considerable weight loss the effect of these diets on LDL-C and HDL-C levels was very modest except for the LDL-C lowering seen with the Portfolio diet. Unfortunately, a comparison of the effect of these diets on TG levels was not reported.

Table 18. Effect of Different Diets in Comparison with Usual Diet			
Diet vs. Usual Diet	Decrease in Weight	Change in LDL-C	Change in HDL-C
	(Kg)	(mg/dL)	(mg/dL)
Atkins	5.46	+2.75	-3.41
Zone	4.07	+2.89	+0.33
Dash	3.63	-3.93	+1.90
Mediterranean	2.87	-4.59	+0.61
Paleolithic	5.31	-7.27	+2.52
Low Fat	4.87	-1.92	+2.13
Jenny Craig	7.77	-0.21	+2.85
Volumetrics	5.95	-7.13	+0.13
Weight Watchers	3.90	-7.13	+0.88
Rosemary Conley	3.76	-7.15	+2.04
Ornish	3.64	-4.71	+4.87
Portfolio	3.64	-21.29	+3.26
Biggest Loser	2.88	-3.90	+0.01
Slimming World	2.15	N/A	N/A
South Beach	9.86	+0.64	-3.60
Dietary Advice	0.31	+2.01	+1.71

Summary of results of popular named diets network meta-analysis for outcomes at six months

In a study carried out in a single center the Atkins, Zone, Weight Watchers, and Ornish diets were compared and the effect on TG levels was also reported (262). Table 19 shows the results of this study at 2 months, a period at which dietary compliance was still high. The magnitude of weight loss was similar but the decrease in LDL-C that occurs with weight loss was blunted with a diet that was high in fat (Atkins diet). In contrast HDL-C levels increased with a high fat diet, particularly SFA (Atkins diet) and decreased with a very low-fat diet (Ornish diet). The weight loss induced decrease in TG levels was blunted by a high CHO intake (Ornish diet). These observations confirm and extend the results described above.

Table 19. Effect of Different Diets on Lipid Levels				
	Weight (kg)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Atkins	-3.6	1.3	3.2	-32
Zone	-3.8	-9.7	1.8	-54
Weight Watchers	-3.5	-12.1	-0.2	-9.2
Ornish	-3.6	-16.5	-3.6	-0.4



#### Summary

While diets can significantly affect lipid levels it should be recognized that the effect is typically relatively modest compared to drug therapy. Whether these modest effects on lipid levels can reduce the risk of CVD has not been tested in randomized controlled trials and given the difficulty of carrying out such longterm diet studies is likely not to be attempted. However, diet therapy can be initiated early in life and has the potential to result in long-term decreases in lipid levels. Given that studies have shown that longterm modest reductions in LDL-C levels can have major effects on the risk of CVD (a 10mg/dL life-long decrease in LDL-C due to polymorphisms in ATP citrate lyase, HMGCoA reductase, LDL receptor, PCSK9, and NPC1L1 resulted in a 16%-18% decrease in cardiovascular events (263)) it is likely that a similar long-term decrease induced by dietary changes would also be effective in decreasing CVD. A life-long 70mg/dL decrease in TG levels due to polymorphisms in the lipoprotein lipase gene resulted in a 23% decrease in coronary heart disease suggesting that long-term decreases in TG levels due to dietary changes would also be beneficial (264). Thus, long-term reductions in lipid levels induced by diet therapy may reduce the lifetime risk of developing CVD.

#### **CURRENT DIETARY GUIDELINES**

Most dietary guidelines recommended to the general population to prevent disease are very similar so I will only present the recommendations of two organizations. A brief summary of the Guidelines for Americans 2020-2025 is shown in table 20 and the guidelines from the American College of Cardiology/American Heart Association are shown in table 21.

Table 20. Guidelines for Americans 2020-2025	
Recommend	Limit
Vegetables of all types—dark green; red and	Added sugars—Less than 10 percent of calories
orange; beans, peas, and lentils; starchy; and other	per day
vegetables	
Fruits, especially whole fruit	Saturated fat—Less than 10 percent of calories
	per day
Grains, at least half of which are whole grain	Sodium—Less than 2,300 milligrams per day
Dairy, including fat-free or low-fat milk, yogurt,	Alcoholic beverages—Adults can
and cheese, and/or lactose-free versions and	choose not to drink or to drink in moderation by
fortified soy beverages and yogurt as alternatives	limiting intake to 2 drinks or less in a day for men
	and 1 drink or less in a day for women
Protein foods, including lean meats, poultry, and	
eggs; seafood; beans, peas, and lentils; and nuts,	
seeds, and soy products	
Oils, including vegetable oils and oils in food,	
such as seafood and nuts	

Full guideline is available at DietaryGuidelines.gov

 Table 21. ACC/AHA Dietary Recommendations to Reduce Risk of ASCVD (265)

1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended

2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial

3. A diet containing reduced amounts of cholesterol and sodium can be beneficial

4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages

5. As a part of a healthy diet, the intake of trans fats should be avoided

ASCVD- Atherosclerotic CVD

## DIETARY RECOMMENDATIONS FOR PATIENTS WITH LIPID DISORDERS

#### **Elevated LDL-C**

The dietary approach to reduce LDL-C levels is to avoid TFA and decrease SFA and cholesterol intake while increasing intake of fiber and phytosterols (266). Additionally, weight loss if appropriate can be helpful in lowering LDL-C levels (266). Certain foods are effective in lowering LDL-C levels such as tree nuts or peanuts, plant protein from soy products, beans, peas, chickpeas, or lentils, and viscous soluble fiber from oats, barley, psyllium, eggplant, okra, apples, oranges, or berries and if possible, can be added to the individual's diet (236,241). If one combines multiple nutritional changes one can have significant reductions in LDL-C levels (table 22).

Table 22. Effect of Multiple LDL-C Lowering Changes on LDL-C Levels			
Nutritional Intervention	Estimated LDL-C Decrease		
Replace 5% of energy from SFA with MUFA or PUFA	5% to 10%		
7.5 grams/day viscous fiber	6% to 9%		
2 grams/day plant sterols/stanols	5% to 8%		
Replace 30 grams animal protein or CHO with plant protein	3% to 5%		
Loss 5% body weight if excess adiposity	3% to 5%		
Total Effect	22% to 37%		

Table adapted from (267).

While diet alone usually does not reduce LDL-C sufficiently it adds to the beneficial effect of cholesterol lowering drugs. In a comparison of LDL-C lowering a low-fat diet alone lowered LDL-C by 5%, a statin alone by 27%, and the combination of low-fat diet plus statin by 32% demonstrating an independent and additive effect of combining diet and lipid lowering medications (268).

#### **Modestly Elevated Triglycerides**

The dietary approach to reduce TG levels is to reduce CHO intake particularly simple and refined sugars and to avoid or minimize alcohol intake (266). Weight loss if appropriate can be very helpful in lowering TG levels (25,266).

#### Markedly Elevated Triglycerides

In patients with marked elevations in TGs due to the Familial Chylomicronemia Syndrome a diet very low in fat is often necessary to prevent episodes of pancreatitis (<10% of calories from fat) (269). In patients with this disorder medium chain TGs may be helpful. In patients with the Multifactorial Chylomicronemia Syndrome who present with markedly elevated TGs (>1000mg/dL) initial dietary treatment should be a very low-fat diet until the TGs decrease. Once the TGs decrease one can initiate the diet described above for individuals with modestly elevated TGs.

#### **Elevated Lipoprotein (a)**

There is no evidence that healthy dietary changes significantly lower Lp(a) levels (62,270). In fact, it should be noted that reducing SFA intake while decreasing LDL-C levels increases Lp(a) levels (271). In certain patients with high Lp(a) levels one may need to balance the benefits of decreasing LDL-C levels with the risks of increasing Lp(a) levels (271).

## Effect of Dietary Advice on Lipid and Lipoprotein Levels

In a meta-analysis of 44 randomized studies with 18,175 healthy adult participants comparing dietary advise vs. no or minimal advice found that dietary advice reduced total serum cholesterol by 5.9mg/dL (95% CI 2.3 to 9.0) and LDL-C by 6.2mg/dL (95% CI 3.1 to 9.4) with no change in HDL-C and TG levels (272). In a meta-analysis of 7 studies with 1081 participants that compared consultation with a

#### ACKNOWLEDGEMENTS

dietician vs. usual care there was no difference in the absolute change in TC, LDL-C, or HDL-C levels but TG levels were decreased by 19.4mg/dL (95%CI -37.8 to -1.8; p=0.03) (273). Similarly, in a meta-analysis of 5 randomized trials in 912 patients with type 2 diabetes found that dietary advice from a dietician vs. usual care resulted in a small decrease in LDL-C (6.6mg/dL) in the group receiving advice from the dietician (274). Finally, as discussed earlier the Women's Health Initiative trial randomized 19,541 postmenopausal women 50-79 years of age to the diet intervention group and 29,294 women to usual dietary advice (52). The goal in the diet intervention group was to reduce total fat intake to 20% of calories and increase intake of vegetables/fruits to 5 servings/day and grains to at least 6 servings/day. Fat intake decreased by 8.2% of energy intake in the intervention vs the comparison group, with small decreases in SFA (2.9%), MUFA (3.3%), and PUFA (1.5%) with increased consumption of vegetables, fruits, and grains. LDL-C levels were reduced by 3.55 mg/dL in the intervention group while levels of HDL-C and TGs were not significantly different in the intervention vs comparison groups. Taken together these studies illustrate that diet therapy under many circumstances has only modest effects on lipid and lipoprotein levels. Of course, there are studies and individual patients where major reductions in lipid levels occur. For example, in a life style modification study including a vegetarian diet by Ornish and colleagues a marked decrease in LDL-C was observed (153mg/dL decreasing to 96mg/dL) (58). One is most likely to see dramatic effects the greater the change in diet (for example going from a typical Western diet to a vegetarian low-fat diet) and the higher the baseline lipid levels. Patient ability to follow the dietary advise is crucial for success.

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