

# Flax and the Prevention of Cardiovascular Disease

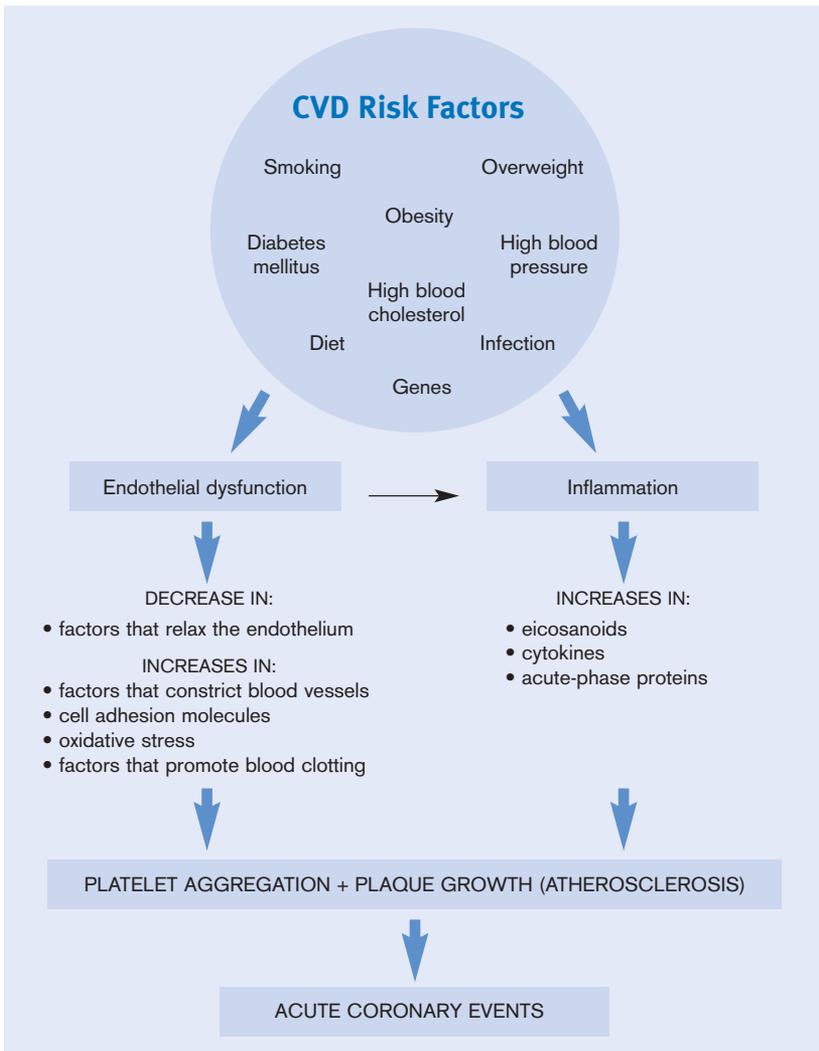
Cardiovascular disease (CVD) includes all diseases of the blood vessels and circulatory system such as coronary heart disease (CHD), ischemic heart disease (IHD), myocardial infarction (MI) and stroke (187). CVD is the leading cause of death in Canada and the United States (187,188). This chapter describes how acute coronary events like MI and stroke develop through atherosclerosis. It reviews the evidence that flax and its major nutritional components, alpha-linolenic acid (ALA) and lignans, protect against CVD, and it examines the mechanisms by which flax helps reduce CVD risk.

## How CVD Develops through Atherosclerosis

CVD is the result of atherosclerosis, an inflammatory disease that begins in childhood and involves changes in the lining of blood vessels or endothelium, as it is called (189). The endothelium maintains vascular **homeostasis** by controlling the balance between agents that dilate blood vessels and those that constrict them, while also preserving vascular **hemostasis** by balancing the actions of clotting and anti-clotting agents (190). A healthy endothelium keeps blood fluid and free-flowing, maintains an environment of low oxidative stress, reduces the activity of blood platelets and limits inflammatory reactions. Over the course of a lifetime, the health of the endothelium can be affected by smoking, diabetes and certain infections, as shown in the box labeled “CVD Risk Factors” in **Figure 5**. Diet affects endothelial health through its effects on blood cholesterol levels, blood pressure, gene expression (activation) and inflammation (190-193).

FIGURE 5

## Links among CVD risk factors, endothelial dysfunction and inflammation<sup>a,b</sup>



<sup>a</sup>Abbreviation = CVD, cardiovascular disease.

<sup>b</sup>Source: Adapted from Corti et al. (190) and Rosamond et al. (187).

Heart disease and stroke arise from changes in the health of the endothelium (the lining of blood vessels). Over time, exposure to cigarette smoke, high blood glucose (diabetes), high blood cholesterol, high blood pressure, diet and other factors damages the endothelium and increases inflammatory reactions. Eventually, the endothelium becomes dysfunctional and loses its ability to maintain normal vascular tone. The result is increased platelet aggregation and the growth of atherosclerotic plaques within the blood vessel wall. The presence or rupture of plaques can cause a heart attack, stroke or angina.

When the endothelium becomes inflamed, cholesterol and other lipids begin to accumulate in blood vessel walls. This process is a complex series of events involving increased oxidative stress and the release of inflammatory compounds like cell adhesion molecules, eicosanoids, cytokines and acute-phase proteins (194). Eventually, platelets clump together (aggregate), plaques form in the blood vessel wall and the endothelium becomes dysfunctional – that is, it is less able to preserve homeostasis and hemostasis.

The development of plaques is a serious issue for two reasons. First, plaques can grow large enough to restrict blood flow to the heart and brain; secondly, plaques can become unstable and rupture, leading to the formation of a clot or thrombus. Both plaque formation and rupture involve inflammation (195). When a clot forms in the heart and blocks blood flow, it can cause an MI, sudden death or unstable angina pectoris (196). When a clot blocks blood flow in the brain, it causes a stroke. These occurrences are acute coronary events.

## Clinical Studies of Flax and CVD Risk Factors

The sections below describe the findings of clinical studies related to flax and its effects on CVD risk factors. Clinical studies build on work in rabbits, rats and hamsters showing that flax has antioxidant effects and decreases blood lipids, inflammation and plaque growth (197-203).

### Blood lipids

In the past few decades, interventions to reduce CVD risk have focused on decreasing blood total cholesterol, low-density lipoprotein (LDL) cholesterol and triacylglycerols (triglycerides) while preserving the level of high-density lipoprotein (HDL) cholesterol. The study of blood lipids has been a major area of flax research, as outlined below.

**MILLED FLAX.** Eating 3-6 tbsp (30-50 g) of milled flax daily for as little as 4 weeks reduced blood total and LDL-cholesterol significantly in clinical trials. Blood total cholesterol decreased 6-13% and LDL-cholesterol decreased 9-18% in studies of healthy young adults (79,204), men and women with moderately high levels of blood cholesterol (205), postmenopausal women (183,185), adults with systemic lupus erythematosus (206), and men with prostate cancer (207). These study volunteers ate milled flax for 4-12 weeks. HDL cholesterol and triacylglycerol levels were unchanged by diets containing milled flax.

One short-term study found no effect of flax on blood lipids among postmenopausal women who consumed 40 g (5 tbsp) of milled flax daily for 2 months (184). Two long-term interventions of one year's duration similarly reported no changes in blood lipids among postmenopausal women (208) or adults with lupus nephritis (209) who consumed between 3 3/4 tbsp and 5 tbsp (30-40 g) of milled flax daily. The lack of blood lipid effects in the long-term studies was likely due to problems of compliance with the high-flax intake among study volunteers.

Whereas most clinical studies used traditional milled flax, one study examined the effects of partially defatted flax on blood lipids (210). Partially defatted flax contains less than 10% fat by weight, whereas regular flax contains about 41% fat. In this study, 29 men and women with high blood cholesterol ate muffins made with wheat bran or muffins made with partially defatted flax for 3 weeks. The flax muffins provided 50 g (6 tbsp) of partially defatted flax altogether. The subjects' total cholesterol decreased about 5.5% and LDL-cholesterol decreased 9.7%, while triacylglycerols increased 10%, on the partially defatted flax diet.

In this same study, apolipoprotein B (apo B) decreased significantly by 6% when the volunteers consumed partially defatted flax in their diets (210). Apo B is the major protein in LDL and very-low-density lipoproteins (VLDL) and is associated with increased risk of atherosclerosis (211). Two other studies found significant reductions in apo B concentrations of 7.5% among postmenopausal women who ate 40 g (5 tbsp) of milled flax daily for 3 months (185) and 19% among men who consumed a mixture of vegetable oils including flax oil for 18 days (212).

Although the data set is small, most (8 of 11) clinical studies found that consuming traditional milled flax or partially defatted flax decreased total cholesterol, LDL-cholesterol and apo B levels without a significant decrease in HDL-cholesterol. One study (210) found a significant increase in triacylglycerols in volunteers who consumed partially defatted flax, whereas the remaining 10 studies reported either no change or a non-significant decrease in triacylglycerols.

**FLAX OIL.** Most clinical studies show no effect of flax oil consumption on blood total cholesterol and LDL-cholesterol levels (78, 213-223). One study reported a significant decrease in blood total cholesterol among men who consumed 2 tbsp of flax oil daily for 12 weeks (224).

HDL-cholesterol decreased significantly between 4% and 10% in four of the 13 studies (216,219,220,224). Triacylglycerols decreased significantly between 9% and 25% in three studies (221-223).

**LIGNAN COMPLEX ISOLATED FROM FLAX.** Hallund and coworkers (160) studied the effects of a lignan complex isolated from flax on CVD risk factors in 22 healthy postmenopausal women who consumed daily a low-fat muffin with or without the lignan complex for 6 weeks. The lignan complex provided 500 mg of secoisolariciresinol diglucoside (SDG) per day, a dose which corresponds to 38-82 g of whole flax seeds (~3 1/2-7 1/2 tbsps). (SDG is the main lignan in flax.) Plasma concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerols did not differ after the two intervention periods, indicating that the lignan complex had no effect on blood lipids.

Which component of flax is likely responsible for its blood cholesterol lowering effects? The findings of one clinical study in which volunteers ate partially defatted flax suggest that the dietary fibre in flax is mainly responsible for its lipid-lowering effects (210). Studies in rabbits (201) and rats (197,198) fed diets containing low-ALA or defatted flax appear to support this finding.

However, ALA-rich diets obtained from either flax oil or perilla oil have been shown to decrease blood cholesterol and/or triacylglycerol levels in rats (225-227), hamsters (199,228-230) and guinea pigs (231) and in some (212,232), but not all (233,234), human populations. Animal models suggest that ALA-rich flax oil increases cholesterol secretion into bile, increases cholesterol synthesis and turnover and decreases atherogenic factors such as blood cholesterol (228). In humans, the effects of flax oil on cholesterol metabolism are not well understood, but some of the cardioprotective effects of flax oil may result from its ability to inhibit inflammatory reactions associated with atherosclerosis, as described in the section on systemic inflammation (see page 63).

Although a flax-derived SDG/lignan complex did not affect blood lipids in one clinical trial (160), studies in rabbits found a lipid-lowering effect of a flax SDG/lignan complex. Serum total cholesterol decreased by 20% and LDL-cholesterol decreased by 14%, whereas HDL-cholesterol increased by 30%, in hypercholesterolemic rabbits fed the flax SDG/lignan complex (203).

These findings suggest that dietary fibre, ALA and lignans may all contribute to the lipid-lowering effects of flax. It is not clear whether humans benefit more from consuming isolated components such as pure SDG or the SDG/lignan complex versus traditional milled flax.

## Blood pressure

Blood pressure is the force or pressure of blood against the walls of arteries. High blood pressure, or hypertension, is a risk factor for CVD (235).

Flax consumption had no effect on blood pressure in studies among healthy men (222) and among adults with lupus nephritis (206), mild to moderate hyperlipidemia (215,222) or mild hypertension (222). In one study among hyperlipidemic adults who ate muffins made with partially defatted milled flax (50 g/day), systolic and diastolic blood pressure decreased from baseline during the flax diet period but did not differ from the wheat bran comparison group by the end of the intervention (210). Consumption of a lignan complex derived from flax and baked into muffins likewise had no effect on blood pressure in 22 healthy postmenopausal women (160). The dietary interventions in these studies lasted 3-6 weeks.

However, flax lowered blood pressure in three clinical studies of longer duration. Supplementing the diet with flax oil (~1 tbsp providing 8 g ALA/day) for 12 weeks lowered systolic and diastolic blood pressure significantly in middle-aged men with high blood cholesterol levels compared with a group of men whose diet was supplemented with safflower oil for 12 weeks. The magnitude of the effect (~5 mmHg) was clinically relevant (236). Healthy menopausal women who consumed 40 g (5 tbsp) of milled flax daily for one year experienced significant reductions of 5% in systolic blood pressure and 4.1% in diastolic blood pressure at 12 months, although the changes were not different from the wheat germ placebo group (208). Another study reported a significant reduction in systolic blood pressure during a mental stress test among postmenopausal women who consumed 30 g/day (~3 3/4 tbsp/day) of one of 3 different flax cultivars for 3 months (237). The findings from these few studies suggest that interventions of at least 3 months are needed to show an effect of flax consumption on blood pressure.

## Endothelial dysfunction

Endothelial dysfunction is the earliest detectable stage in the development of atherosclerosis, and several methods of measuring it have been used in clinical studies (191). (Refer to **Figure 5.**)

Nestel and colleagues (216) used a measurement called systemic arterial compliance (SAC) to assess endothelial function and found that mean arterial pressure decreased and SAC increased significantly among 15 obese adults who ate daily a diet enriched with flax oil (providing 20 g of ALA) for 4 weeks. An increase in SAC denotes an improvement in endothelial function. The main study finding was impressive: The increase in SAC with flax oil was similar to that achieved through exercise training (238).

Using a slightly different approach, West and coworkers (239) measured endothelial function by the method of flow-mediated vasodilation (FMD) in 18 healthy adults with type 2 diabetes. FMD uses high-resolution ultrasound to measure the diameter of the brachial artery before and after a short period of ischemia induced by a blood pressure cuff. An increase in the artery's diameter during FMD indicates healthy vessels (240). In this study, FMD was measured before and 4 hours after 3 test meals, each providing 50 g of a different fat – monounsaturated fat (MUFA) obtained from high-oleic safflower and canola oils, the MUFA meal plus EPA and DHA from sardine oil, or the MUFA meal plus ALA from canola oil. In volunteers with type 2 diabetes and high fasting triacylglycerols, the meals containing omega-3 fatty acids increased FMD by 50-80%. Marine and plant omega-3 fats were equally effective in improving endothelial function as measured by FMD.

These findings suggest that flax oil, ALA-rich vegetable oils and omega-3 fats in general improve endothelial function (240-242). A walnut diet providing 3.7-6.0 g of ALA, for instance, increased vasodilation by 64% compared with an olive oil diet (243).

By comparison, FMD did not change in postmenopausal women who ate a low-fat muffin containing a flax lignan complex (500 mg of SDG) every day for 6 weeks (244). Because only this one study has been published, it is impossible to draw firm conclusions about the effects of an SDG/lignan complex on endothelial function.

Another outcome of endothelial dysfunction is a tendency for white blood cells (leukocytes) to stick to the endothelium in a process controlled by cell adhesion molecules. Cell adhesion molecules include

E-selectin, vascular cell adhesion molecule type 1 (VCAM-1) and intercellular adhesion molecule type 1 (ICAM-1) (245). High blood levels of these adhesion molecules occur in several inflammatory disorders such as rheumatoid arthritis (246), in people with angina, and in patients who have had a heart attack (247).

In a study among 23 adults with high blood cholesterol, eating a diet rich in ALA obtained from walnuts, walnut oil and flax oil produced a significant decrease in VCAM-1, ICAM-1 and E-selectin compared with eating an average American diet (98). In a study of Greek men with abnormal blood lipids, consuming 1 tbsp of flax oil daily for 12 weeks reduced VCAM-1 levels by 18.7% (220). These findings suggest that eating an ALA-rich diet containing flax oil has a beneficial effect on the endothelium.

## **Oxidative stress**

Reactive oxygen species or free radicals are produced during normal metabolism, and their production is balanced by the presence of antioxidants like vitamin E and  $\beta$ -carotene. In pathological conditions such as atherosclerosis, the balance between pro-oxidants and antioxidants shifts toward increased oxidation and oxidative stress (248). Oxidative stress is estimated by various methods. The oxidation of lipids and LDL particles can be determined by measuring the production of conjugated dienes and malondialdehyde (MDA). MDA can be estimated by the thiobarbituric acid-reactive substances (TBARS) method. The concentration of antioxidants can also be measured.

Studies among healthy adults found no effect of consuming regular milled flax on oxidation status measured by blood TBARS, urinary TBARS, and blood levels of fatty acid peroxides, retinol and vitamin E. The amount of milled flax consumed in two studies ranged from 2 tbsp daily for 3 months (205) to ~6 1/4 tbsp daily for 4 weeks (204). Consuming experimental margarines made with canola oil and flax oil (providing 4.5 g or 9.5 g of ALA/day) for 6 months had no effect on LDL lag time (which measures the time until oxidation can be detected) or the ferric-reducing ability of plasma in a study of adults with moderate hyperlipidemia (249). Likewise, a lignan complex derived from flax, which provided 500 mg SDG/day, had no effect on serum lipoprotein oxidation lag time and antioxidant capacity among healthy post-menopausal women (160).

One study measured the protein thiol and carbonyl groups in serum as indicators of long-term oxidative stress (210). In this study, the mean protein thiol concentration was significantly lower in serum from volunteers who ate 50 g of partially defatted flax (~6 1/4 tbsp) daily for 3 weeks compared with volunteers who ate wheat bran daily for 3 weeks. Although a decrease in protein thiol concentrations suggests an increase in oxidative stress, the serum carbonyl content did not change in either group over the course of the 3-week period. The researchers could not explain these conflicting findings and commented that although the protein thiol results might be considered undesirable, some pro-oxidant activity is beneficial in cancer prevention.

Overall, most clinical studies show that flax consumption does not contribute to oxidative stress in humans. In a mouse model of acute lung injury, lipid oxidation in lung tissue decreased in mice fed a milled flax diet, due possibly to the antioxidant activities of SDG and its metabolites, enterodiol and enterolactone (250).

## Hemostasis (blood clotting)

Blood clotting or hemostasis is a complex balance between the actions of factors that promote clotting to prevent bleeding and those that decrease the rate of clotting to keep the blood from becoming too thick or viscous. Blood clotting requires the actions of platelets, immune cells and proteins such as fibrinogen, tissue factor, factor VIIc, factor VIII, thrombin and plasminogen activator inhibitor 1 (PAI-1) (251). Fibrinogen and PAI-1 both promote thrombosis, partly through platelet aggregation (252,253), and high levels of fibrinogen and factor VIIc are associated with increased risk of fatal IHD (254,255).

Flax oil consumption did not affect clotting factors such as fibrinogen, PAI-1 activity, factors VIIc or VIII (224,256,257) or antithrombin III activity or bleeding time (257,258) in clinical studies. One study reported a 40% increase in the activated protein C (APC) ratio in men who consumed a flax oil diet for 6 weeks, suggesting a role for flax oil in preventing thrombosis (256). APC is a potent anticoagulant (259).

Consuming milled flax (30-40 g or 3-4 tbsp daily) for 2 months decreased fibrinogen levels by 5% and PAI-1 activity, factor VIII and thrombin antithrombin III activity by about 12-15% in one study (184). Because statistical analyses of the decreases in clotting factors from baseline were not reported, it is not possible to know whether the changes were meaningful.

Three studies assessed the effect of flax on platelet aggregation. One study reported no effect of flax oil on platelet aggregation (257), while another suggested a role for milled flax in reducing platelet aggregation, based on a 25% decrease in platelet aggregation after thrombin stimulation (205). In a study of 9 patients diagnosed with systemic lupus erythematosus who ate 15 g, 30 g or 45 g of milled flax daily for 4 weeks, platelet aggregation in response to platelet-activating factor (PAF) was inhibited significantly (206). PAF is a major participant in inflammatory reactions, contributes to tissue damage and is elevated in lupus nephritis, an inflammation of the kidney (101).

In these few studies, flax oil did not affect clotting factors, but it increased the APC ratio substantially. Milled flax reduced platelet aggregation. These actions suggest a role for flax in preventing thrombosis.

## Inflammatory compounds

Eicosanoids and cytokines contribute to the inflammation associated with atherosclerosis (194). Pro-inflammatory eicosanoids such as thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>) are derived from arachidonic acid, an omega-6 fatty acid. TXA<sub>2</sub> is one of the most potent promoters of platelet aggregation known (85,189). LTB<sub>4</sub> increases the release of reactive oxygen species and cytokines like tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), IL-6 and IL-8 (84).

In a clinical study of healthy men who consumed 1 3/4 tbsp of flax oil daily for 4 weeks, the TXB<sub>2</sub> concentration in immune cells decreased 30% (100). (TXB<sub>2</sub> is an inactive metabolite of TXA<sub>2</sub>.) A study of 64 patients with chronic obstructive pulmonary disease (COPD) found that serum LTB<sub>4</sub> levels decreased 32% and sputum LTB<sub>4</sub> levels decreased 41% in patients who received an ALA-rich nutritional support (1.4% ALA) daily for 24 months compared with those who received a low-ALA nutritional support (0.18% ALA) during the same period (260).

The cytokines TNF-α, IL-1β, IL-6 and IL-8 are at the center of the body's response to inflammatory stress (84). Serum levels of IL-6 decreased 25% in men who consumed 1 tbsp of flax oil daily for 12 weeks (219), whereas the concentrations of TNF-α and IL-1β in immune cells decreased 26% and 28%, respectively, when healthy men consumed flax oil for 4 weeks (100). The serum level of TNF-α decreased by 43% and the production by immune cells of TNF-α and two other

cytokines, IL-6 and IL-1 $\beta$ , decreased between 18% and 22% when adults with hypercholesterolemia consumed a diet rich in ALA compared with the average American diet (99). The ALA in the latter study was obtained from a combination of walnuts, walnut oil and flax oil. In the COPD study mentioned previously, sputum TNF- $\alpha$  and IL-8 concentrations decreased 48% and 55%, respectively, in the patients who received the high-ALA nutritional support, whereas the sputum cytokine concentrations did not change in the patients who received the low-ALA nutritional support for 2 years (260). A reduction of 18-55% in the concentrations of these pro-inflammatory compounds is a significant clinical outcome.

## Systemic inflammation

During inflammation the liver releases acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA) in response to acute injury, infection, malignancy, hypersensitivity reactions and trauma (261,262). CRP and SAA are markers of systemic (whole body) inflammation, and they are present in the lesions of atherosclerosis. CRP is an independent risk factor for CVD (261).

Consuming flax oil reduced CRP and SAA levels in a study of 50 Greek men with high blood cholesterol levels who consumed 1 tbsp of flax oil daily for 12 weeks. Serum CRP decreased 48% and serum SAA decreased 32% after 12 weeks (219). In a U.S. study of 23 adults with high blood cholesterol levels, consuming a high-ALA diet based on walnuts, walnut oil and flax oil resulted in a ~75% decrease in CRP levels after 6 weeks (98).

Support for an anti-inflammatory effect of ALA comes from a community-based study in two small towns in Tuscany, Italy (263). The researchers examined the relationship between the concentration of fatty acids in plasma and the level of inflammatory markers in 1123 persons aged 20-98 years. A low plasma ALA concentration was associated with higher levels of CRP and interleukin 1 receptor antagonist (IL-1ra). IL-1ra is considered an acute-phase protein and a reliable measure of the pro-inflammatory state. Thus, ALA-rich diets containing flax oil have substantial effects on systemic markers of inflammation.

## Epidemiologic Studies of ALA, Lignans and CVD Risk

Despite its long culinary use in ancient Egypt, India and China dating back at least 5000 years (264), there are no epidemiologic studies of flax intake and CVD risk because there are no present day populations that both consume flax within a traditional diet and have good nutritional surveillance programs. Fortunately, several large-scale population studies have examined the relationship of ALA and lignans to CVD risk, which allows us to consider the role flax can play in reducing CVD risk by increasing the dietary intakes of ALA and lignans. The sections below describe the findings of epidemiologic studies related to these two components of flax.

Epidemiologic studies are concerned with determining how many people in the community have a certain disease and identifying the risk factors associated with its development. Measurements are made on hundreds, sometimes thousands, of individuals, and then the data are examined for trends and links between diet or lifestyle and the presence of disease. Some epidemiologic studies compare people with a condition like nonfatal myocardial infarction (the cases) with people who do not have the condition (the controls). Other studies follow a group of people – a cohort – for several years and note who develops the condition and who does not.

### ALA and CVD risk

Four case-control studies (265-269), one cross-sectional study (270), three prevention trials (271-274) and three cohort studies (275-282) found a benefit of ALA-rich diets in lowering the risk of CHD, IHD, nonfatal MI and stroke. One prevention trial found no change in the estimated 10-year IHD risk but reported a significant decrease in fibrinogen and CRP levels on ALA-rich diets (283,284). The number of participants in the studies ranged from 233 to 76,283, as shown in Table 14.

Probably the most famous of the prevention trials is the Lyon Diet Heart Study, which was a secondary prevention trial designed to reduce the risk of CVD deaths in survivors of a heart attack (272). The key finding was that the 302 men and women who ate a Mediterranean-type diet rich in ALA had a 70% reduction in their risk of heart attack compared with the 303 men and women in the control group who ate a prudent diet that resembled the American Heart Association diet.

This result was achieved without a reduction in blood cholesterol. In a follow-up at 46 months, ALA continued to be the key fatty acid whose presence in the diet was associated with a good prognosis for preventing a second, fatal heart attack. Dietary intakes of the long-chain omega-3 fatty acids (EPA and DHA) found mainly in fatty fish like salmon and mackerel were not as important as ALA in this study (273).

The Health Professionals Follow-up Study, which began in 1986 with a group of more than 51,000 middle-aged and elderly men, found a specific preventive effect of ALA. Those men with the highest ALA intakes had the lowest risk of heart attack and fatal heart disease. The effect of ALA was independent of other dietary and non-dietary risk factors. Intake of marine omega-3 fatty acids (EPA and DHA) was not associated with heart attack risk in this study population, suggesting that the cardiovascular effects of ALA are different from those of EPA and DHA (279). Other large-scale population studies such as the Family Heart Study (275) and the Nurses' Health Study (281) found the risk of having a fatal heart attack and CHD decreased as the intake of ALA increased.

One study did not find a beneficial effect of ALA on CVD risk. The Zutphen Elderly Study of 667 men aged 64-84 years found a small, non-significant association between ALA intake and CVD risk, due mainly to the fact that the men's ALA intake was obtained chiefly from foods like margarine, meat and bread that contain *trans* fatty acids (285). ALA intake from foods without *trans* fatty acids was not associated with CVD risk. The increased risk of CVD seen with high ALA intakes in this study may be due to *trans* fatty acids or other nutrients in the diet (286).

## ALA and stroke risk

Two population studies found a benefit of ALA in reducing stroke risk. In the Edinburgh Artery Study, significantly lower levels of ALA were found in the red blood cell phospholipids of men and women who had had a stroke compared with participants who had no evidence of disease (287). In the Multiple Risk Factor Intervention Trial (MRFIT), 96 men who had had a stroke were compared with 96 men without stroke who were matched for age. In the multivariate model, each increase of 0.13% in the serum ALA level was associated with a 37% decrease in risk of stroke (288). After controlling for risk factors of stroke like smoking and blood pressure, ALA emerged as an independent predictor of stroke risk – that is, men with higher levels of ALA in their serum phospholipids had a lower stroke risk.

TABLE 14

## Epidemiologic studies of ALA intake or tissue levels and CVD risk<sup>a</sup>

Studies showing a benefit of ALA on CVD risk	Number of study participants	Average intake of ALA g/day	Main findings
<b>Case-control and cross-sectional studies</b>			
Cardiovascular Health Study (265)	179 cases, 54 controls	NR	A higher intake of ALA was associated with a lower risk of fatal IHD.
Costa Rica study (266,267)	482 cases, 482 controls	NR	A higher concentration of ALA in adipose tissue was associated with a lower risk of nonfatal acute MI. The greatest protection against MI was seen in those with high levels of ALA and low levels of <i>trans</i> fatty acids in adipose tissue.
EURAMIC study (268)	639 cases, 700 controls in eight European countries and Israel	NR	A higher concentration of ALA in adipose tissue was associated with a lower risk of MI.
India study (269)	340 cases, 700 controls	NR	Consumption of mustard oil, which is rich in ALA, was associated with a lower risk of IHD.
National University of Singapore Heart Study (270)	145 Asian Indian men and 147 Chinese men	NR	In this cross-sectional study, Asian Indian men had significantly lower plasma concentrations of ALA, DHA and total omega-3 fatty acids compared with Chinese men.
<b>Prevention trials</b>			
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (271)	21,930 men who smoked cigarettes	0.9-2.5 (median = 1.5)	A higher ALA intake was associated with a lower relative risk of coronary death.
Lyon Diet Heart Study (272,273)	605 men and women who had survived a heart attack	1.74 – 1.8	An ALA-rich diet was associated with a 70% reduction in heart attacks and cardiac deaths.
MARGARIN Study (283,284)	282 men and women	6.3	Although the ALA-rich diet did not reduce the estimated 10-year risk of IHD, it significantly decreased two factors associated with increased risk: <ul style="list-style-type: none"> <li>• fibrinogen levels (283)</li> <li>• C-reactive protein (284)</li> </ul>

Studies showing a benefit of ALA on CVD risk	Number of study participants	Average intake of ALA g/day	Main findings
<b>Prevention trials cont.</b>			
MRFIT (274)	6250 men in the usual care group	1.69	A higher intake of ALA was associated with a lower risk of CHD and all-cause mortality.
<b>Population-based studies</b>			
Family Heart Study (275-278)	1575 – 4584 men and women	Men = 0.81 Women = 0.68	In both men and women, a higher ALA intake was associated with: <ul style="list-style-type: none"> <li>• a lower risk of CHD (275).</li> <li>• lower blood levels of triglycerides (276).</li> <li>• a lower prevalence of carotid artery plaques (277).</li> <li>• a lower prevalence of calcified atherosclerotic plaque (278).<sup>b</sup> The reduction in CHD risk appeared to be independent of fish consumption (275).</li> </ul>
Health Professionals Follow-up Study (279,280)	43,757 men (279), 45,722 men (280)	0.8–1.5	A higher ALA intake was associated with a lower risk of nonfatal heart attack and total CHD.
Nurses' Health Study (281,282)	76,283 women	1.1 g <sup>c</sup> (median range = 0.66–1.39 g)	A higher ALA intake was associated with a lower risk of fatal IHD (281) and sudden cardiac death (282).
<b>Study showing no benefit of ALA on CVD risk</b>			
Zutphen Elderly Study (285)	667 men	1.32 <sup>d</sup>	ALA intake showed a modest link with risk of CHD, due mainly to its being found in foods containing <i>trans</i> fatty acids; ALA intake from foods without <i>trans</i> fatty acids was not associated with CHD risk. <sup>e</sup>

<sup>a</sup> Abbreviations = ALA, alpha-linolenic acid; CHD, coronary heart disease; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction (heart attack); NR, not reported.

<sup>b</sup> Calcified plaques occur when calcium is deposited in the walls of arteries, forming a lesion; the presence of calcified plaques can be used to predict heart attacks and coronary death.

<sup>c</sup> Mean ALA intake in 1984 when a 116-item food questionnaire was completed by the cohort of women assessed for risk of IHD.

<sup>d</sup> Mean intake.

<sup>e</sup> The association between ALA intake and CHD risk in this study was not statistically significant ( $p = .17$ ) after adjusting for age, body mass index, smoking, intakes of alcohol, energy, fibre, *trans* fatty acids and other factors.

## **ALA and cardiac rhythm (arrhythmia)**

The rhythmic pumping action of the heart is controlled by the heart's electrical system. Arrhythmias are abnormal rhythms of the heart muscle. Growing evidence suggests that ALA and other omega-3 fats help prevent sudden death from arrhythmias in rabbits (289) and in heart cells taken from rats (290) and dogs (291).

In humans, the ALA content of adipose tissue was inversely related to risk of MI in one case-control study conducted in Europe and Israel (268) and with nonfatal acute MI in another study carried out in Costa Rica (266). In the Nurses' Health Study, a prospective cohort study involving 76,763 women, the dietary intake of ALA was inversely associated with the risk of sudden cardiac death, but not with other fatal CHD or nonfatal MI (282).

The mechanism by which ALA helps lower the risk of fatal or nonfatal MI appears to involve its effect on cardiac rhythm. In the Family Heart Study, Djoussé and colleagues (292) found that the higher the dietary ALA intake, the lower the risk of abnormally prolonged repolarization of the heart muscle – an indicator of cardiac arrhythmia. In a clinical study among women referred for elective coronary angiography (293), the ALA content of adipose tissue was positively correlated with 24-hour heart rate variability. That is, women with a higher content of ALA in their adipose tissue had better heart rate variability scores which made them less likely to develop ventricular arrhythmias. Taken together, these findings suggest that ALA helps maintain the heart's normal rhythm, thus partly explaining how ALA helps reduce CVD risk.

## **Lignans and CVD risk**

The study of lignans and CVD risk factors is in its infancy, which may explain why there is considerable variability in the study findings. For example, an analysis of lignan intake and CVD risk factors among 468 men participating in the Health Professionals Follow-up Study found that blood levels of LDL-cholesterol and apo B tended to increase with increasing lignan intake, suggesting that lignan intake may be associated with increased CVD risk in men (294). However, an analysis of lignan intake among 570 men participating in the Zutphen Elderly Study found that total lignan intake was not associated with all-cause mortality (295). Indeed, a higher intake of one lignan, matairesinol, was associated with a lower mortality due to CVD, CHD, cancer and all causes. Admittedly, these two prospective cohort studies had different end points and study

populations (one based in the United States, the other based in The Netherlands), but whereas one (294) suggested an increased CVD risk from higher lignan intakes, the other (295) suggested that at least one lignan had a cardioprotective effect.

Likewise, two Finnish studies were equally equivocal. One case-control study reported that men without CHD (the control group) had higher serum enterolactone concentrations than men with CHD (the cases) (167). (Serum enterolactone is a mammalian lignan derived from the metabolism of plant lignans consumed in the diet.) Indeed, men with the highest serum enterolactone levels had a 65% lower risk of CHD than men with the lowest levels. Another Finnish study found that CHD risk was similar for male smokers, regardless of their serum enterolactone levels (296).

Reconciling these disparate findings is difficult, especially considering that diets rich in fruits, vegetables and whole grains and cereals – all sources of lignans – are associated with reduced CVD risk (123). More researches will provide insights into the relationship of lignans to CVD risk.

## **Cardioprotective Mechanisms of Flax**

**Figure 6** summarizes the data from flax dietary studies in animals and humans and shows the mechanisms by which flax, ALA and lignans protect against CVD. The figure follows the same general outline as the topics presented in **Figure 5** and cites some papers not described in this chapter (297-307).

Flax influences CVD risk through its favourable effects on several factors associated with CVD risk, including blood lipids, blood pressure and blood glucose levels (187). Flax improves endothelial health by decreasing lipid oxidation, an effect achieved through the actions of its main lignan SDG, while also reducing the activation of immune cells and the release of cell adhesion molecules. Flax inhibits the production of pro-inflammatory agents such as eicosanoids, cytokines, and acute-phase proteins, thus reducing inflammatory reactions; and it decreases platelet activation and aggregation, thus reducing the risk of thrombus (clot) formation. These actions help the endothelium maintain normal homeostasis and hemostasis. Flax decreases the size of aortic atherosclerotic plaques in animals. In short, flax and its nutritional components have beneficial effects on CVD risk factors and on cellular and tissue processes associated with atherosclerosis.

FIGURE 6

## Mechanisms by which animal and clinical studies support a role for flax in preventing cardiovascular disease<sup>a</sup>

Flax cardioprotective mechanisms		CVD Risk Factors and Processes Affected by Flax or One of Its Components
ANIMAL STUDIES	HUMAN STUDIES	
<ul style="list-style-type: none"> <li>• Decreased blood total and LDL-cholesterol (197-199, 201,202,225,227-231,297)</li> <li>• Decreased blood triacylglycerols in some studies (197,198,229)</li> <li>• Decreased blood glucose and insulin levels and insulin resistance (228)</li> </ul>	<ul style="list-style-type: none"> <li>• Decreased blood total and LDL-cholesterol (79,183,185,204-207, 224)</li> <li>• Decreased blood pressure in long-term studies of 3+ months (208,236,237)</li> <li>• Improved blood glucose (184,307)</li> </ul>	→ <b>CVD Risk Factors</b>
<ul style="list-style-type: none"> <li>• Decreased lipid oxidation (202,203,250)</li> <li>• Decreased oxidative species (200,250)</li> <li>• Decreased activation of immune cells (200)</li> <li>• Increased oxidative reserve (202)</li> </ul>	<ul style="list-style-type: none"> <li>• Improved endothelial function due to high-ALA oil (flax or canola) (216,239)</li> <li>• Did not contribute to oxidative stress (204,205,249)</li> <li>• Decreased cell adhesion molecules (98,220)</li> <li>• Increased APC (an anticoagulant) (256)</li> </ul>	→ <b>Endothelial function</b>
<ul style="list-style-type: none"> <li>• Decreased inflammatory eicosanoids (298-304)</li> <li>• Decreased cytokines (305)</li> </ul>	<ul style="list-style-type: none"> <li>• Decreased inflammatory eicosanoids (100,260)</li> <li>• Decreased cytokines (99,100,219,260)</li> <li>• Decreased inflammatory acute-phase proteins (98,219,263)</li> </ul>	→ <b>Inflammation</b>
<ul style="list-style-type: none"> <li>• Inhibition of platelet aggregation induced by platelet-activating factor (101,306)</li> </ul>	<ul style="list-style-type: none"> <li>• Decreased platelet aggregation in two of three studies (205,206)</li> </ul>	→ <b>Platelet aggregation</b>
<ul style="list-style-type: none"> <li>• Decreased fatty streak area and aortic atherosclerosis in hamsters (199) and rabbits (200-203)</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced risk of MI, IHD and stroke, which are consequences of atherosclerosis, based on epidemiologic studies of ALA-rich diets and CVD risk as shown in Table 14</li> </ul>	→ <b>Plaque growth (atherosclerosis)</b>

<sup>a</sup> Abbreviations = ALA, alpha-linolenic acid; APC, activated protein C; CVD, cardiovascular disease; IHD, ischemic heart disease; LDL-cholesterol, low-density lipoprotein cholesterol; MI, myocardial infarction.

## Flax in the CVD Prevention Diet

Flax helps protect against CVD by altering the omega-3 fat content of cell membranes (308), by improving blood lipids and endothelial function and by exerting antioxidant, anti-inflammatory, anti-thrombotic effects (309). The beneficial effects of flax in the clinical studies cited previously were achieved with intakes of 2-6 tbsp of milled flax or between 1 tsp and 2 1/2 tbsp of flax oil daily. These flax intakes provide 3.6-10.8 g of ALA if consumed as milled flax or ~3-20 g of ALA if consumed as flax oil. In epidemiologic studies, ALA intakes associated with reduced CVD risk averaged about 2 g/day (range = 0.7-6.3 g). A meta-analysis of prospective studies suggested that increasing the intake of ALA by 1.2 g/day – which is equivalent to about 2 tsp of milled flax daily – decreases the risk of fatal CHD by at least 20% (310).

The 2-6 tbsp of milled flax used in clinical studies provided 60-180 mg of total lignans, based on data reported by Thompson and coworkers (144). (Refer to **Table 12** in Chapter 4.) There are too few population studies of lignan intake to draw conclusions about the potential role of lignans in preventing CVD, although this situation may change now that a comprehensive database of the lignan content of commonly eaten foods is available (144).

New research suggests an effect of omega-3 fatty acid on gene expression (311). Thus, genetic background may modify an individual's risk of CVD (267,312). More studies are needed to clarify the role of flax in reducing CVD risk. In particular, there is an urgent need for randomized, controlled clinical trials with good study designs, clearly defined outcomes, appropriate control groups, realistic dietary interventions and thorough statistical analyses (313).