Dietary lignans: physiology and potential for cardiovascular disease risk reduction

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The present review of the literature on lignan physiology and lignan intervention and epidemiological studies was conducted to determine if lignans decrease the risks of cardiovascular disease in Western populations. Five intervention studies using flaxseed lignan supplements indicated beneficial associations with C-reactive protein, and a meta-analysis that included these studies also suggested lignans have a lowering effect on plasma total and low-density lipoprotein cholesterol. Three intervention studies using sesamin supplements indicated possible lipid- and blood pressure-lowering associations. Eleven human observational epidemiological studies examined dietary intakes of lignans in relation to cardiovascular disease risk. Five showed decreased risk with either increasing dietary intakes of lignans or increased levels of serum enterolactone (an enterolignan used as a biomarker of lignan intake), five studies were of borderline significance, and one was null. The associations between lignans and decreased risk of cardiovascular disease are promising, but they are yet not well established, perhaps due to low lignan intakes in habitual Western diets. At the higher doses used in intervention studies, associations were more evident.

INTRODUCTION

Lignans are bioactive, non-nutrient, non-caloric, phenolic plant compounds that are found in the highest concentrations in flax and sesame seeds and in lower concentrations in grains, other seeds, fruits, and vegetables. The enterolignans (sometimes referred to as mammalian lignans) are metabolites of food lignans produced by human intestinal bacteria. They have been identified in human urine and plasma. Their weak estrogenic[1] and other biochemical properties suggest potential for nutritional significance in the prevention of cardiovascular and other chronic diseases.[2–4] The present review briefly describes the chemistry and biosynthesis of lignans in plants (including flaxseed and sesame), the major food sources of lignans, their metabolism in humans, and recent studies of their associations with cardiovascular disease biomarkers, events, and mortality in humans.

CHEMISTRY AND OCCURRENCE OF LIGNANS

Monolignols (Figure 1a), derived from hydroxycinnamic acids (*p*-coumaric, ferulic, and sinapic acids), are either

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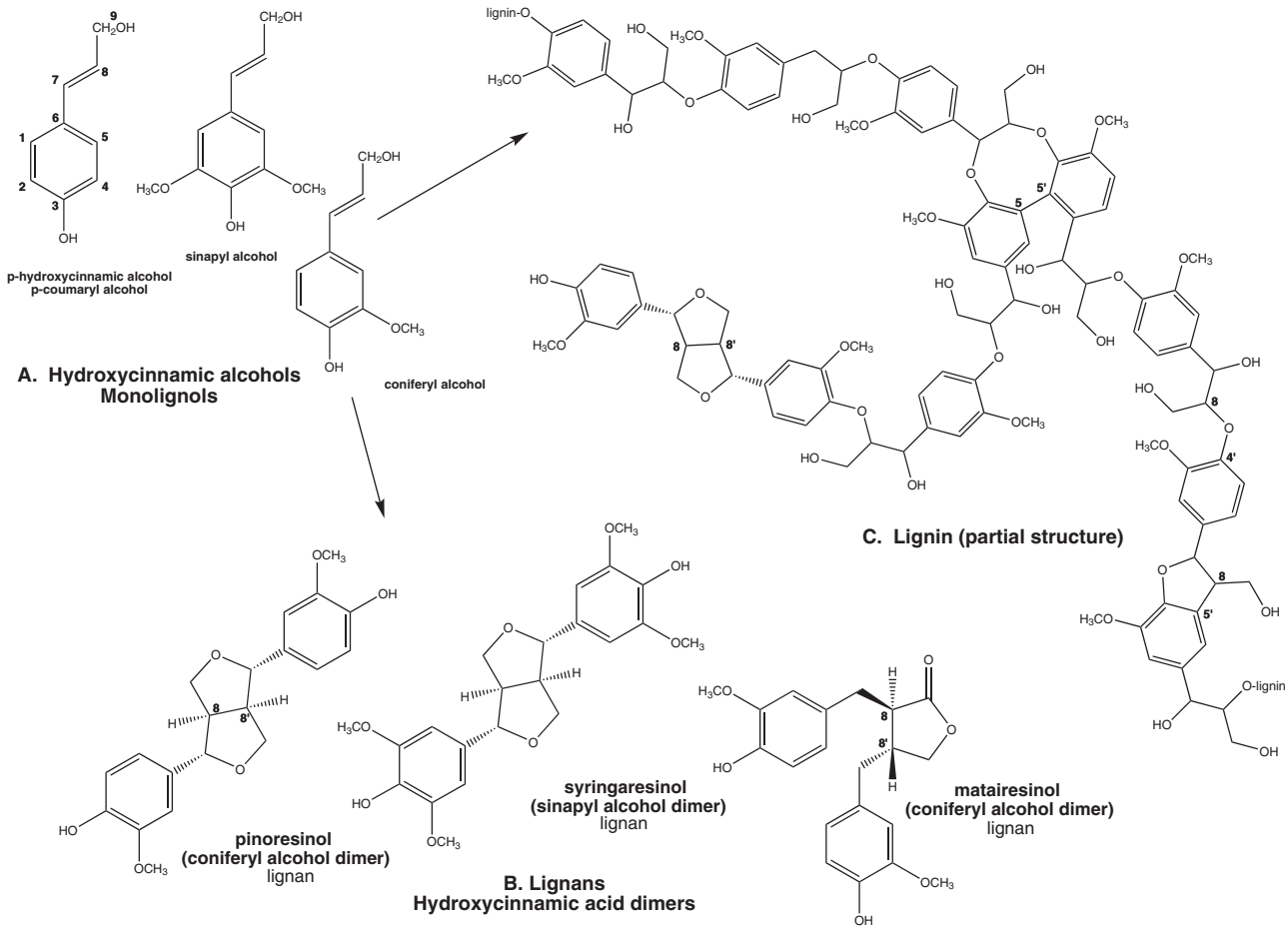


Figure 1 **Structures of monolignols, lignans, and lignins. (Coniferic acid is a synonym for ferulic acid.)**

dimerized to lignans (Figure 1b) in the cell or polymerized into larger lignin structures in the cell wall (Figure 1c). These structurally diverse compounds are involved in plant defense (as antioxidants, biocides, phytoalexins, etc.),[5] providing protection against diseases and pests, and possibly participating in plant growth control.[6,7]

Lignans and lignins are very different and should not be confused with each other. Lignans are stereospecific dimers of these cinnamic alcohols (monolignols) bonded at carbon 8 (C_8-C_8) (Figure 1b).[8]

In the plant, lignans (monolignol dimers) usually occur free or bound to sugars.[6,7] Diglucosides of pinoresinol, secoisolariciresinol, and syringaresinol are common.[9–12] Sesaminol triglucoside and sesaminol diglucoside occur in sesame seeds.[13–15] In flax, secoisolariciresinol is present as a diglucoside and is part of an ester-linked complex or oligomer (Figure 2) containing 3-hydroxyl-3-methyl-glutaric acid, a number of cinnamic acid glycosides (usually ferulic or *p*-coumaric acid), and the flavonoid herbacetin.[16–21]

The plant lignans most commonly distributed in foods are lariciresinol, matairesinol, pinoresinol, and secoisolariciresinol (Figure 3). Several other lignans are present in some foods, including medioresinol (in sesame seeds, rye, and lemons), syringaresinol (in grains), sesamin and the lignan precursor sesamolin (in sesame seeds)[12,22] (Figure 3). Other lignans found in foods but not often quantified include arctigenin, cyclolariciresinol (isolariciresinol), 7′-hydroxymatairesinol, and 7-hydroxysecoisolariciresinol.[2,12] (Some cyclolariciresinol occurs naturally and some is formed from lariciresinol during extraction and analysis under acidic conditions.) The nutritional significance of lignans is unknown. Although lignans are not classified as dietary fibers, they share some of the chemical characteristics of lignin, which is an insoluble fiber.[23]

Lignins are large plant polymers built from the *p*-coumaryl, coniferyl, and sinapyl hydroxycinnamic alcohols (see Figure 1c). They are racemic (non-stereospecific) polymers, with monolignol units binding at C_8 and four other sites (C_5-C_5, C_5-C_8, C_5-*O*-C_4, C_8-*O*-C_4).[24] Lignins are found in vessels and secondary tissues of all higher plants. They are present in a large variety of foods and are particularly abundant in cereal brans.[25] Nutritionally, lignins are considered components of

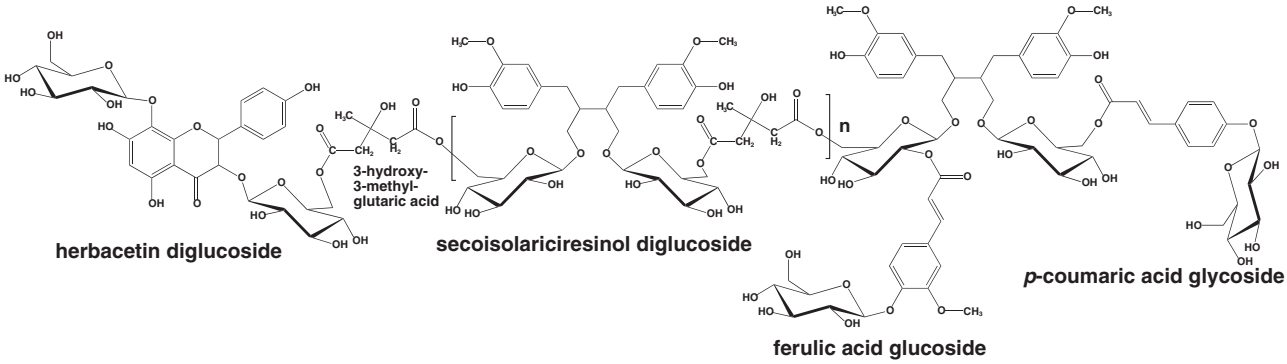


Figure 2 **Sketch of flaxseed seocisolariciresinol lignan oligomer.** The flavonoid herbacetin can be interchanged with secoisolariciresinol diglucoside. The number of units (*n*) are usually 1–7 with an average of 3. The terminal unit can have 3-hydroxy-3-methy-glutaric acid, ferulic acid glucoside, or *p*-coumaric acid glucoside. Both cinnamic acid glycosides (ferulic acid glucoside or *p*-coumaric acid glucoside) are shown here to demonstrate where each one is esterified to secoisolariciresinol diglucoside.
Based on work by Strandas et al. (2008),[18] Struijs et al. (2007),[19] Struijs et al. (2008),[20] and Struijs et al. (2009).[21]

insoluble dietary fiber.[26] Lignins are important in plants because they strengthen the plant cell walls, aid water transport, keep polysaccharides in the plant cell walls from degrading, help plants resist pathogens and other threats, and provide texture in edible plants.[24]

FOOD SOURCES OF LIGNANS

The lignan content of foods is generally low and usually does not exceed 2 mg/100 g. The exceptions are flaxseed[27] (335 mg/100 g) and sesame seeds (373 mg/100 g),[22,28] which have a lignan content a hundred times higher than other dietary sources.

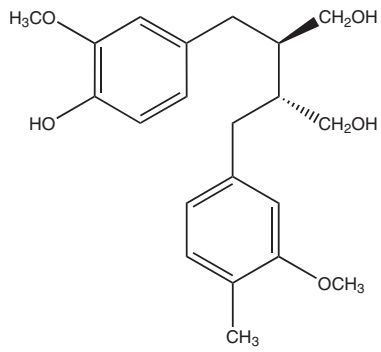
Table 1 provides examples of the distribution of lignans in foods.[10,12,28–35] They are present in many plant families, although the types and amounts vary from one family to another. Lignans are found in whole grains (especially in the bran layer) and seeds (in the seed coat). Barley, buckwheat, flax, millet, oats, rye, sesame seeds, and wheat contain fairly high levels of lignans. Nuts and legumes are also reasonably good sources. Although in lesser amounts than in grains, lignans are present in fruits and vegetables such as asparagus, grapes, kiwi fruit, lemons, oranges, pineapples, wine, and even in coffee and tea.[12,29–32]

In contrast to plants, there are virtually no lignans in animal foods. Minute amounts of the enterolignans enterodiol and enterolactone are sometimes found in animal foods (milk products) as a result of their production by bacterial metabolism in the animals' guts, but these are exceptions.[36–39] Little has been done to investigate the effects of storage and processing on lignans in most foods,[29–32,40–45] although it is known that the lignan content is apparently not changed considerably during the processing of flaxseed[46–50] and sesame seed.[51–59]

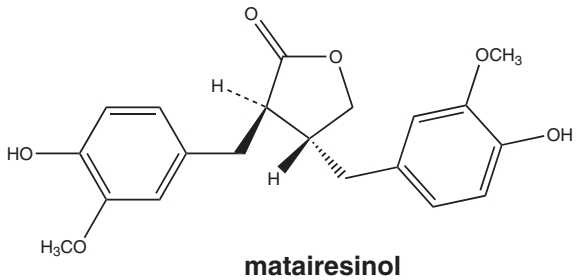
LIGNAN INTAKE

The lignan content of most foods is low and consumption of lignan-rich flaxseed and sesame seed is also low in many Western populations. However, populations that do not consume much flaxseed or sesame seed may eat many plant foods that contain small amounts of lignans, and these populations may do so often enough to raise their exposure to lignans.[60] Lignan intake does not usually exceed 1 mg per day in most Western populations. Estimates of lignan intakes vary from about 150 µg/day[61–64] (secoisolariciresinol and matairesinol) to about 1,600 µg/day[65] (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, syringaresinol, medioresinol, enterolactone, and enterodiol) (Table 2).[61–76] Intakes of the two most commonly measured lignans vary from 70 to 992 µg/day for secoisolariciresinol[61,66] and 2 to 74 µg/day for matairesinol.[66,67] Methods are now available to quantify lariciresinol and pinoresinol in foods.[11,28] Lariciresinol[68,69] in the diet varies from 74 to 500 µg/day and pinoresinol[67,69] varies from 73 to 423 µg/day. Syringaresinol and medioresinol may also be measured.[28]

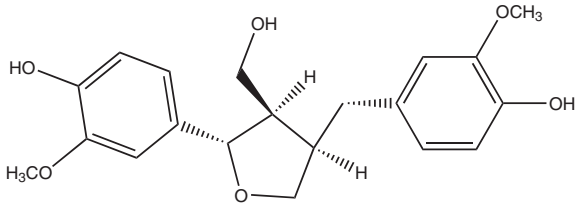
Total lignan intakes vary from country to country because of different dietary sources, but they differ even more depending on variations in the completeness of the food composition tables used, other methodological differences, and on how many individual lignans were analyzed and reported by investigators. More recent studies tend to have more complete analyses.[60] The 2003 study of Valsta et al.[70] measuring only matairesinol and secoisolariciresinol found the mean total lignan intake of Finns to



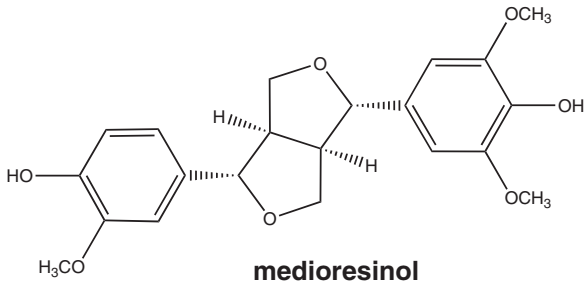
secoisolariciresinol
(cashews, chickpeas, coffee, cranberry, flax, peas, sunflower seeds, wine)



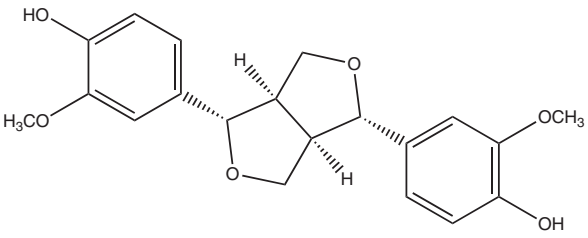
matairesinol
(flax, oats, pineapple, rye, wine)



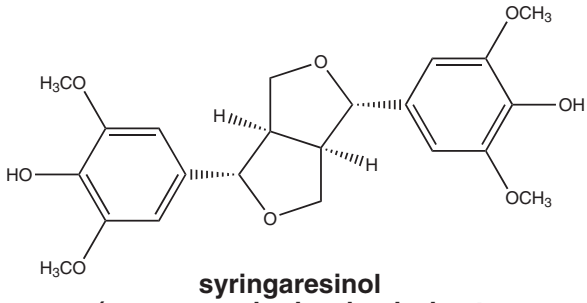
lariciresinol
(buckwheat, eggplant, oats, pineapple, rye)



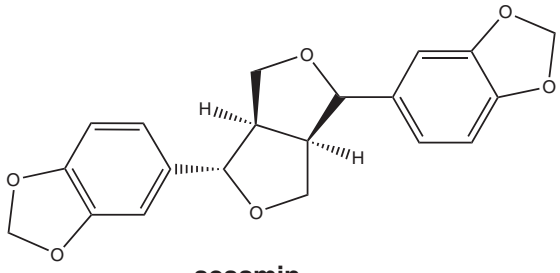
medioresinol
(lemon, rye, sesame seeds)



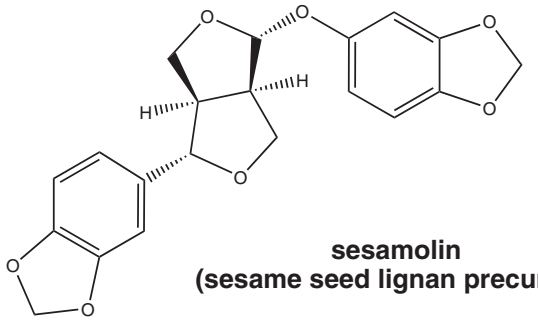
pinoresinol
(asparagus, flax, lemon, rye)



syringaresinol
(asparagus, barley, buckwheat, millet, oranges, rye, wheat)



sesamin
(sesame seeds)



sesamolin
(sesame seed lignan precursor)

Figure 3 **Structure and sources of individual lignans common in foods.**

be 434 μg/day. The 2005 study of Milder et al.,[71] which measured lariciresinol, matairesinol, pinoresinol, and secoisolariciresinol intakes in the Dutch population, found median total lignan intake to be 979 μg/day. A 2008 study of Hedelin et al.,[65] which measured lariciresinol, matairesinol, medioresinol, pinoresinol, secoisolariciresinol, and syringaresinol in Swedish women found a median total lignan intake of 1,632 μg/day. These studies indicate that,

Table 1 **Total µg per serving and 100 g (fresh weight) and distribution of lignans (as aglycones) in common foods and their botanical origin.**

Common food	Serving size	Total µg per serving	Total µg per 100 g	Seco	Mat	Lar	Pino	Med	Syr	Family	Genus and species
Beverages											
Coffee, arabica Nescafe®	1 tsp	7	694	694	†					Rubiaceae	*Coffea arabica*
Coffee, Maxwell House®	1 tsp	5	485	485						Rubiaceae	*Coffea arabica*
Tea, black china brewed	8 fl oz	8	3	3	0					Theaceae	*Camellia sinensis*
Tea, black Prince of Wales® brewed	8 fl oz	19	8	7	1					Theaceae	*Camellia sinensis*
Tea, green china brewed	8 fl oz	22	9	9	1					Theaceae	*Camellia sinensis*
Tea, green japanese sencha brewed	8 fl oz	15	7	6	1					Theaceae	*Camellia sinensis*
Wine, cabernet sauvignon, France, red	5 fl oz	1,117	760	686	74					Vitaceae	*Vitis vinifera*
Wine											
Chardonnay, France, white	5 fl oz	288	196	174	22					Vitaceae	*Vitis vinifera*
Chardonnay, Italy, white	5 fl oz	224	153	136	17					Vitaceae	*Vitis vinifera*
Chianti, reserve, Italy, red	5 fl oz	2,026	1,378	1,280	98					Vitaceae	*Vitis vinifera*
Cereals											
Barley, whole grain	1 c	681	370	30	3	85	72	11	169	Poaceae	*Hordeum vulgare*
Barley, whole meal	1 c	75	51	51	0					Poaceae	*Hordeum spp*
Buckwheat, whole grain	1 c	1,474	867	131	1	362	92	33	248	Polygonaceae	*Fagopyrum esculentum*
Corn, whole meal	1 c	9	7	7	0					Poaceae	*Zea mays*
Millet, common whole grain	1 c	490	245	67	3	20	85	8	62	Poaceae	*Panicum miliaceum*
Oat, whole grain	1 c	1,340	859	19	71	183	194	40	352	Poaceae	*Avena sativa*
Oat, whole meal	1 c	19	12	12	0					Poaceae	*Avena sativa*
Rice, brown	1 c	26	14	14	0					Poaceae	*Oryza sativa*
Rye, whole grain	1 c	3,196	1,891	38	27	324	381	148	973	Poaceae	*Secale cereale*
Rye, whole meal	1 c	128	100	42	58					Poaceae	*Secale cereale*
Wheat, whole grain	1 c	647	539	35	3	62	37	30	372	Poaceae	*Triticum aestivum*
Wheat, whole meal (emmer)	1 c	9	7	7	0					Poaceae	*Triticum turgidum dicoccoides*

Table 1 **Continued**

Common food	Serving size	Total µg per serving	Total µg per 100 g	Seco	Mat	Lar	Pino	Med	Syr	Family	Genus and species
Fruits											
Apples	1 med	0	0	0	0					Rosaceae	*Malus domestica*
Bananas	1 med	3	3	3	0					Musaceae	*Musa X paradisiaca*
Cantaloupe	1 med wedge	12	18	18	0					Cucurbitaceae	*Cucumis melo var cantalupensis*
Cranberry	1 c	136	136	136	0					Ericaceae	*Vaccinium macrocarpon*
Currant, black	1 c	80	72	70	2					Grossulariaceae	*Ribes nigrum*
Currant, red	1 c	30	27	27	0					Grossulariaceae	*Ribes rubrum*
Grapes	10 grapes	62	126	32	0	37	28	8	21	Vitaceae	*Vitis vinifera*
Guava	1 fruit	74	134	134	0					Myrtaceae	*Psidium guajava*
Kiwi	1 med fruit	112	147	116	0	10	8	5	8	Actinidiaceae	*Actinidia deliciosa*
Lemon	1 slice	23	335	4	0	25	185	64	57	Rutaceae	*Citrus limon*
Lychee	1 fruit	1	10	10	0					Sapindaceae	*Litchi chinensis*
Oranges	1 fruit	160	122	11	0	19	9	6	77	Rutaceae	*Citrus sinensis*
Papaya	1 c cubes	1	1	1	0					Caricaceae	*Carica papaya*
Pineapple	1 c chunks	284	172	7	10	67	4	3	81	Bromeliaceae	*Ananas comosus*
Plum	1 fruit	0	1	1	0					Rosaceae	*Prunus domestica*
Raspberry, red	10 raspberries	4	20	20	0					Rosaceae	*Rubus idaeus*
Strawberries	1 c whole	206	143	136	7					Rosaceae	*Fragaria X ananassa*
Nuts, seeds, and spices											
Cashews	1 oz (18 kernels)	70	247	244	4					Anacardiaceae	*Anacardium occidentale*
Hazelnut, European hazel	1 oz (21kernels)	33	116	113	4					Betulaceae	*Corylus avellana*
Walnuts	1 oz (14 halves)	45	160	156	5					Juglandaceae	*Juglans nigra*
Caraway seed	1 tsp	4	204	199	5					Apiaceae	*Carum carvi*
Cumin	1 tsp whole	4	208	203	5					Apiaceae	*Cuminum cymicum*
Flax seed	1 tbsp	34,505	335,002	323,670	5,202	3,670	2,460	0	0	Linaceae	*Linum usitatissimum*
Sesame seed‡	1 tbsp	11,905	132,275	240	1,137	14,835	47,136	4,153	2,050	Pedaliaceae	*Sesamum indicum*
Sunflower seed	1 oz	165	581	581	0					Asteraceae	*Helianthus annuus*

Vegetables and legumes											
Alfalfa	1 tbsp	0	2	2	0					Fabaceae	*Medicago* spp.
Asparagus	1 c	461	344	183	2	47	49	5	58	Asparagaceae	*Asparagus officinalis*
Avocado	1 avocado	50	25	21	4					Lauraceae	*Persea americana*
Broccoli	0. 5 c chopped	21	47	44	2					Brassicaceae	*Brassica oleracea* var *italica*
Cabbage	1 c chopped	2	3	3	0					Brassicaceae	*Brassica oleracea*
Carrot	1 medium	14	23	22	0					Apiaceae	*Daucus carota* subsp *sativus*
Cauliflower	1 c	8	8	8	0					Brassicaceae	*Brassica oleracea* var *botrytis*
Celery	1 c chopped	5	5	5	0					Apiaceae	*Apium graveolens*
Chickpeas	1 tbsp	4,383	35,067	35,067	0					Fabaceae	*Cicer arietinum*
Chives	1 tbsp	4	117	117	0					Liliaceae	*Allium schoenoprasum*
Cucumber	0. 5 c slices	2	4	2	0	1	1	0	0	Cucurbitaceae	*Cucumis sativus*
Eggplant	1 c cubes	88	107	5	0	68	28	4	2	Solanaceae	*Solanum melongena*
Garlic	1 clove	5	158	157	1					Alliaceae	*Allium sativum*
Kidney beans	1 c	170	92	92	0					Fabaceae	*Phaseolus vulgaris*
Lentils	1 tbsp	0	3	3	0					Fabaceae	*Lens culinaris*
Onion	1 medium	11	10	9	1					Alliaceae	*Allium cepa*
Peas	1 c	12,114	8,355	83,55	0					Fabaceae	*Pisum sativum*
Peanuts	1 c halves	401	279	279	0					Fabaceae	*Arachis hypogaea*
Pepper	10 strips	2	8	7	0					Solanaceae	*Capsicum* spp
Potato, sweet	1 c cubes	5	4	2	1					Convolvulaceae	*Ipomea batatas*
Radish	0. 5 c slices	12	21	1	1	14	2	1	2	Brassicaceae	*Raphanus sativus*
Soybeans	1 c	243	131	131	0					Fabaceae	*Glycine max*
Tomato	1 med	26	21	1	0	11	5	2	2	Solanaceae	*Lycopersicon esculentum*

† Blanks indicate no data available at this time for these compounds on this item.

‡ Includes 62,724 µg sesamin per 100 g sesame seed in total and per serving calculations.

Data from Adlercreutz and Mazur (1997),[33] Kunle et al. (2009),[29]Mazur et al. (1996),[34] Mazur (1998),[35] Mazur et al. (1998),[10] Milder et al. (2005),[30] Penalvo et al. (2005),[28] Penalvo et al. (2008),[31] Smeds et al. (2007),[12] and Thompson et al. (2006).[32]

Abbreviations: Seco, secoisolariciresinol; Mat, matairesinol; Lar, lariciresinol; Pino, pinoresinol; Med, medioresinol; Syr, syringaresinol; all as aglycones.

Table 2 **Individual lignan intakes (μg/day) in Western countries.**

Location	Total	Seco	Mat	Lar	Pino	Syr	Med	Enl	End	No. of subjects	Year
USA	106	70	34							545	2002[61]
	579	534	25	†						939	2002[72]
	137	110	23							195	2006[62]
	140	115	25							846[§]	2006[63]
Canada	857	533	7	74	107					3,471	2008[68]
Mexico	463[‡]	123	2	237	102					50	2007[67]
	372[‡]	123	2	174	73					50	2007[67]
Finland	434[‡]	396	38							2,862[§,††]	2003[70]
France	1,112	178	11	500	423					58,049	2007[69]
Germany	563	529	29							666	2004[73]
	183	167	15							7	2005[74]
	570	549	21							47	2005[74]
Italy	666	335	21	176	97					242**	2009[75]
The Netherlands	1,081	992	74							16,165	2005[66]
	977	152	11	476	334					570[‖]	2006[76]
	979	191	9	488	362					637[§]	2007[71]
Sweden	1,632	115	24	179	149	831	322	9	0	45,448	2008[65]
UK	110	101	8							108[††]	2005[64]
	149	142	9							108	2005[64]

† Blanks indicate no data.
‡ Means; all others are medians.
§ Both men and women all others are women only, except ‖.
‖ Men.
** 3-day weighed record; all others are FFQs except ††.
†† 24-h recall.
NB: Studies that provided only combined values for matairesinol and secoisolariciresinol were not included.
Abbreviations: Seco, secoisolariciresinol; Mat, matairesinol; Lar, lariciresinol; Pino, pinoresinol; Syr, syringaresinol; Med, medioresinol; Enl, enterolactone; End, enterodiol.

as expected, when more lignans are measured and quantified in foods, total lignan intakes increase. This challenges the interpretation of studies, particularly of meta-analyses, on lignans and health because it is difficult to compare the intakes that were reported. Muir et al.[17] and Li et al.[16] discuss these issues in greater depth using examples from their work on secoisolariciresinol in flaxseed, its diglucoside, and its oligomer.

LIGNAN METABOLISM

Absorption of plant lignans and bioconversion of plant lignans to enterolignans and their subsequent absorption varies greatly from person to person. Lignans are present in plants both as aglycones (without sugars) and as glycosides (with sugars).[12] At present, only in flaxseed has secoisolariciresinol been found as a lignan oligomer. Lignan glycosides are absorbed in the gastrointestinal tract after metabolism by intestinal bacteria to lignan aglycones and the enterolignans (enterolactone and enterodiol), which are formed from them. The extent of hydrolysis to release the lignans from the sugars (and in flax from the oligomer), the formation of enterolignans, and the bioavailability of these compounds vary quite significantly from person to person. Due to these differences in metabolism in the gastrointestinal tract, lignan intake is an imperfect measure of tissue exposure.[77,78]

Bacterial metabolism in the gut

Lignan glycosides, such as the flax secoisolariciresinol diglucoside ester-linked complex[17,79] and the sesame seed sesamolin triglucoside,[14,22,80] are hydrolyzed by some of the anaerobic microbes in the gut to lignan aglycones.[80–83] The free lignans are then converted into enterolignans through a series of metabolic reactions by various gut bacteria[77,84–86] (Figure 4). The efficiency of conversion depends on many factors and differs considerably from one individual to another. The metabolism of the lignans in the tissues is influenced by genetic factors, but as yet these are not well understood.[87–90]

The predominant plant lignan compound in foods, secoisolariciresinol diglucoside, is metabolized in the gut to secoisolariciresinol, then to the enterolignan enterodiol, and finally to enterolactone, but the conversion is never 100%. The plant lignan matairesinol is metabolized directly in the gut to the enterolignan enterolactone. In an in vitro fecal microflora metabolism system, lariciresinol was completely converted in 24 h into the enterolignans enterolactone (46%) and enterodiol (54%), whereas other plant lignans were

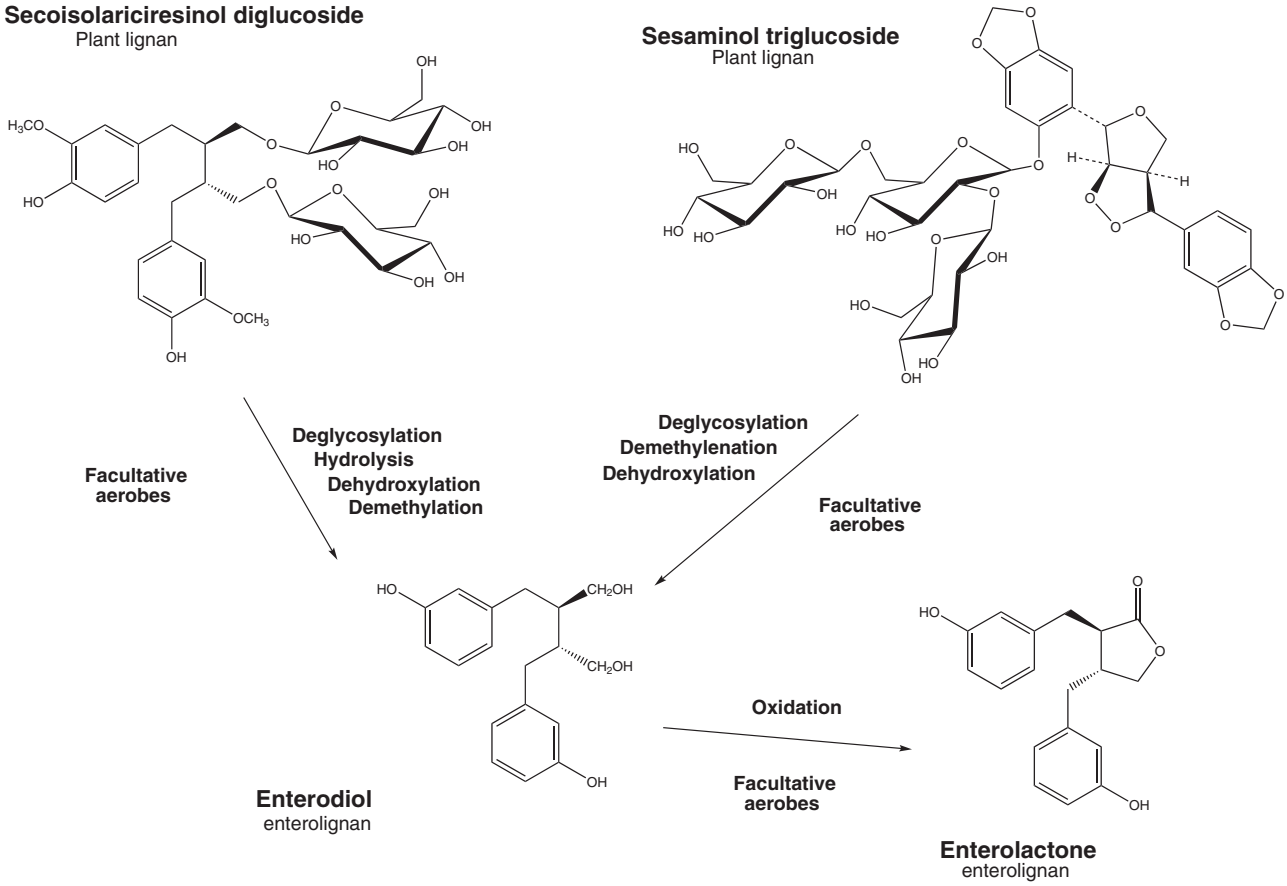


Figure 4 **Bioconversion of plant lignans to enterolignans in the human gut.**
Simplified from and based on work by Clavel et al. (2006),[84] Kuijsten et al. (2005),[78] and Lampe et al. (2006)[85] for secoisolariciresinol diglucoside and Jan et al. (2009)[80] and Liu et al. (2006)[86] for sesaminol triglucoside.

incompletely converted, i.e., matairesinol (62%), secoisolariciresinol diglucoside (72%), and pinoresinol diglucoside (55%). All four were metabolized to enterolactone, in part, but secoisolariciresinol and pinoresinol diglucosides were converted to enterodiol (50% of the secoisolariciresinol and 32% of the pinoresinol total doses) and then in small amounts to enterolactone (21% of the secoisolariciresinol and 19% of the pinoresinol total doses).[9] Other lignans that are metabolized to enterolactone include arctigenin, 7-hydroxymatairesinol, sesamin, and syringaresinol.[9,22,77] Smeds et al.[91] found cyclolariciresinol, lariciresinol, and matairesinol but not secoisolariciresinol in serum samples from a Finnish population. Penalvo et al.[22,92] determined the presence of cyclolariciresinol, lariciresinol, matairesinol, pinoresinol, as well as anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, secoisolariciresinol, and sesamin in plasma of Finns after the ingestion of sesame seeds (50 g).

The enterolignans enterodiol and enterolactone have been detected in the blood and urine of both humans and animals, but only small amounts of the plant lignans cyclolariciresinol, lariciresinol, matairesinol, pinoresinol, secoisolariciresinol, and syringaresinol have been found in human urine.[6,93] In contrast, lignins are thought to be largely inert and not absorbed in the human gut due to their polymeric nature.[94–97] It is possible that they are dietary precursors of enterolignans, but the ability of gut bacteria to transform and metabolize lignins into enterolignans has yet to be demonstrated in human studies.[25] This possibility is worth pursuing since conversion of food lignins to lignans might explain the relatively high concentrations of enterolignans in biofluids compared to lignan intakes.[98]

Enterolactone is the main circulating enterolignan; therefore, serum enterolactone levels and urinary enterolactone excretion are used as biomarkers for plant lignan intakes. However, these are imperfect surrogates. Differences between lignan intakes and enterolactone production may arise because of variations in the composition of the gut microflora, conversion of some lignans into other compounds, intestinal transit time, the metabolic half-life of enterolactone, the redox state of the colon, the types of lignans present in the diet, and the use of antibiotics.[77,84,99]

Systemic metabolism

Once they are formed from the parent plant lignans by gut microbiota, the enterolignans enterodiol and enterolactone are absorbed through the colonic barrier,[100] and most are conjugated to glucuronides in the tissues. They are usually detectable in the blood 8–10 h after dietary intake.[77,78] In a recent study, some plant lignans (anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, cyclolariciresinol, lariciresinol, matairesinol, pinoresinol, secoisolariciresinol, and sesamin) were rapidly absorbed in the small intestine and appeared in the systemic circulation within an hour after the ingestion of sesame seeds.[22] The mechanisms responsible for the uptake of plant lignans in the small intestine are still unknown.[77,85] The pharmacokinetic characterization of lignans is an under-researched area that must be pursued if further insights are to be gained about the actual lignan compounds providing putative health benefits.

The enterolignans either enter enterohepatic circulation or are excreted in the urine, usually as glucuronides and sulfate esters.[100–102] Some free lignans and aliphatic or aromatic hydroxylated metabolites from hepatic metabolism may also be excreted.[77,85,102–104] One study found that the total amount of enterolactone and enterodiol detected in the urine was up to 40% of the ingested dose (0.9 mg/kg body wt, average 60–66 mg) of secoisolariciresinol diglucoside, and the majority of it was excreted within 2 days.[78]

The enterohepatic recirculation of secoisolariciresinol, sesame lignans, and enterolignans is significant. In general, lignans permeating the gastrointestinal mucosa are likely to undergo extensive first pass metabolism by phase II enzymes, resulting in glucuronidation or sulfation, either in the mucosa and/or in the liver prior to their appearance in the systemic circulation.[100] Glucuronides and sulfates of secoisolariciresinol, enterolactone, and enterodiol may undergo enterohepatic recirculation or simply be eliminated in the bile or urine.[86,105–108]

Lignan intakes, as evaluated with available food composition data and dietary records or even with biomarkers, are such imperfect estimates of exposure that they may obscure diet-disease relationships. In the lignan food frequency questionnaire validation study, conducted by Horn-Ross et al.[62] using only matairesinol and secoisolariciresinol, the correlations with urinary total enterodiol and enterolactone were only 0.16. In the food frequency questionnaire validation study of Bhakta et al.[64] the correlation of matairesinol and secoisolariciresinol "true intake" with plasma enterolactone was only 0.11. Since several other lignans are present in the diet and can be converted to enterolactone or enterodiol at varying rates, and some lignans are absorbed without conversion, such low correlations are not surprising. However, these problems do point to the need to improve dietary assessment methodology for these compounds.

ANIMAL AND CELL LIGNAN STUDIES IN CARDIOVASCULAR AREAS

There are some animal[109–120] and a few in vitro cell[121,122] studies on food lignans in the area of cardiovascular disease. For the purpose of this review, we have limited the focus to humans and only to food lignans, but the area is worth investigating further. Caution is indicated, however, since rodent, particularly rat, diets contain other phytoestrogens that may influence results. Several non-food lignans,[123,124] such as honokiol[125,126] and magnolol,[126–130] have shown cardiovascular associations in animal and in vitro cell studies.

LIGNANS AND CARDIOVASCULAR DISEASE RISK FACTORS

Randomized controlled trials

Most of the controlled trials reported to date have not used standardized, well-characterized products in which the lignans and other bioactive constituents are quantified. Dose-response data are often incomplete; so the appropriate lignan dose to obtain beneficial health effects is unknown. Another limitation of the epidemiological studies is that, in Western diets, usual lignan intakes are extremely low. It is possible, given the positive results in some intervention studies with higher levels of lignan intakes, that usual intakes are below the threshold necessary to produce cardiovascular effects. Intervention studies with higher doses may provide more insight into the associations of lignans with cardiovascular disease. In addition, other components, such as unsaturated fatty acids present in intact flaxseed and sesame seed, could influence cardiovascular disease risk factors.

There are currently eight randomized controlled trials of lignan supplementation and blood pressure or other intermediate markers of cardiovascular disease risk in the literature; five using secoisolariciresinol diglucoside from flaxseed and three using sesamin from sesame seed. In addition, there is a recently published comprehensive meta-analysis[131] of the associations of flaxseed interventions, which includes the five studies of flaxseed lignans on cardiovascular disease risk.

The population assessed may have a significant bearing on the outcomes of the lignan intervention. It is important to note that some studies were conducted with healthy volunteers, which may show few associations with risk factors, while others evaluated individuals at risk.

Blood pressure studies

As shown in Table 3,[122,132–134] in a randomized, double-blind, placebo-controlled trial of lignan supplementation in 92 healthy older individuals with a walking program, a daily dose of 543 mg secoisolariciresinol diglucoside (187 mg secoisolariciresinol) plus exercise for 6 months significantly reduced diastolic blood pressure (−2 mm Hg) in middle-aged hypertensive Canadian men ($n = 42$); however, it had no such effect in women ($n = 50$) and there was no association with systolic blood pressure.[132] In a Chinese study, 73 type 2 diabetics in the same age range were fed 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for 12 weeks but no significant associations with systolic or diastolic blood pressure were observed at this dose.[133]

In a Japanese, double-blind, crossover, placebo-controlled study, however, 60 mg sesamin (in 180 mg wheat germ oil) per day for 4 weeks significantly reduced both diastolic (−1.9 mm Hg) and systolic (−3.9 mm Hg) blood pressure in mildly hypertensive middle-aged men ($n = 23$) and women ($n = 2$).[134] In contrast, neither systolic nor diastolic blood pressure were lowered in a study of 33 overweight Australian men and women (age 55.1 ± 8.7) with one or more risk factors for metabolic syndrome who were fed approximately 50 mg per day of sesame lignans in a 5-week, randomized, controlled, crossover study. The goal of this study was to determine if the sesame supplement reduced 20-hydroxyeicosatetraenoic acid (20-HETE) (a metabolite of arachidonic acid and a proposed prohypertensive agent in humans); significant decreases were found in both plasma and urine 20-HETE, suggesting that lignans may have other cardiovascular disease risk-modulating activity.[122]

Lipoprotein studies

As shown in Table 4,[131–133,135–139] in the Chinese study of 73 diabetics who were fed 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for 12 weeks, no associations with lipid profiles, fasting glucose levels, or vascular sensitivity were evident although glycemic control was improved.[133] When 22 healthy Danish postmenopausal women were fed 500 mg secoisolariciresinol diglucoside (172 mg of secoisolariciresinol) per day for 6 weeks, secoisolariciresinol did not have any significant association with total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), or triglycerides.[135]

In the Canadian study of secoisolariciresinol supplementation (approximately 187 mg secoisolariciresinol as 543 mg secoisolariciresinol diglucoside per day) and a walking program conducted with 92 healthy middle-aged adults for 26 weeks, HDL, LDL, total cholesterol, triglycerides, and the metabolic syndrome composite score were not significantly affected by lignan supplementation.[132] However, the administration of secoisolariciresinol diglucoside at 600 mg per day (approximately 206 mg secoisolariciresinol) in a Chinese, randomized, double-blind, placebo-controlled trial[136] of 55 hypercholesterolemic adults significantly reduced total and LDL cholesterol over 8 weeks. Triglycerides were reduced, but not significantly, and HDL was not affected. When 11 perimenopausal women in the United States with mild hyperlipidemia took 200 mg secoisolariciresinol diglucoside per day (approximately 69 mg secoisolariciresinol) for 14 weeks, LDL, total cholesterol, and lipoprotein (a) were reduced.[137] When all these data[132,133,135–137] were pooled in a meta-analysis,[131] total and LDL cholesterol were significantly reduced, although the type of intervention as well as the gender, and initial lipid values of the subjects affected the observed associations. The authors of the meta-analysis concluded that the effectiveness of flaxseed or lignan interventions on blood lipids in hypercholesterolemic men or premenopausal women still remains unclear and needs to be evaluated in the future.[131]

Other cardiovascular risk factors

As shown in Table 5[132,137,139–141] (and in Table 4), in a randomized placebo-controlled Japanese trial,[138] 65 mg per day of sesamin significantly reduced total and LDL cholesterol as well as apolipoprotein B in 12 hypercholesterolemic adults over 8 weeks, while HDL and triglycerides were not affected. However, in the Australian study of Wu et al.,[139] in which 33 overweight adults used approximately 50 mg per day sesamin (39.5 mg sesamin and 12.2 mg sesamolin in 26.2 g sesame seeds) for 5 weeks, no association was found with any reductions in lipids or C-reactive protein levels, but levels of F_2-isoprostanes were lowered. It is possible that the doses were too low, the study duration was too short, or the other compounds in the sesame seeds, such as fatty acids, obscured potential positive associations.

In a study of 22 Danish women, 500 mg secoisolariciresinol diglucoside (172 mg secoisolariciresinol) per day for 6 weeks blunted a rise in C-reactive protein, which was evident in controls.[140] Pan et al.[141] found that 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for 12 weeks significantly decreased C-reactive protein in 64 type 2 diabetic patients, particularly women ($n = 39$). Marblestone[137] found that 69 mg secoisolariciresinol per day for 14 weeks reduced C-reactive protein in 11 perimenopausal women with mild hyperlipidemia.

Overall, it appears that, in sufficient doses, secoisolariciresinol and sesamin may reduce risk factors for cardiovascular disease. However, the studies to date have

Table 3 **Randomized controlled trials of lignans and blood pressure.**

Outcome	Reference	Adult population	Vehicle	Lignan dosage per day	Study duration (weeks)	N	Response
Systolic	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.9 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−0.4 mmHg, $P = 0.268$
	Cornish et al. (2009)[132]	M, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	42	No effect
	Cornish et al. (2009)[132]	F, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	50	No effect
	Wu et al. (2009)[122]	M, F, Australia, age 55.1 ± 8.7 y, overweight adults (BMI 25–35), ≥risk factor metabolic syndrome[†] or LDL >3.4 mmoL/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	−0.7 mmHg, $P = 0.835$
	Miyawaki et al. (2009)[134]	M, F, Japan, middle-aged, mild hypertensives	Capsule 180 g wheat germ oil	Sesamin 60 mg	4	25	−3.5 mmHg, $P = 0.044$
Diastolic	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−1.5 mmHg, $P = 0.751$
	Cornish et al. (2009)[132]	M, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	42	−2 mmHg, $P = 0.046$
	Cornish et al. (2009)[132]	F, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	50	No effect
	Wu et al. (2009)[122]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmoL/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	0.3 mmHg, $P = 0.223$
	Miyawaki et al. (2009)[134]	M, F, Japan, middle-aged, mild hypertensives	Capsule 180 g wheat germ oil	Sesamin 60 mg	4	25	−1.9 mmHg, $P = 0.045$
20-HETE, plasma	Wu et al. (2009)[122]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	−236 pmol/mmol, $P = 0.001$
20-HETE, urine/ creatinine	Wu et al. (2009)[122]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	−47 pmol/L, $P = 0.001$

[†] Metabolic syndrome composite score based on fasting glucose, HDL, triglycerides, abdominal adiposity, blood pressure, and inflammatory cytokines.

Abbreviations: M, males; F, females; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein cholesterol; Seco, secoisolariciresinol, SDG, secoisolariciresinol diglucoside.

Table 4 **Randomized controlled trials of lignans and lipoproteins.**

Outcome	Reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	No. of subjects	Response
HDL	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmoL/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	−3.86 mg/dl, $P < 0.001$ from baseline
	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−0.77 mg/dl, $P = 0.243$
	Hallund et al. (2006)[135]	F, Denmark, postmenopausal age 61 ± 7 y, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	−1.54 mg/dl, $P = 0.531$
	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	−5.4 mg/dl, $P = 0.167$
	Wu et al. (2009b)[139]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome† or LDL >3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	0.00 mg/dl, $P = 0.764$
	Hirata et al. (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	No effect
LDL	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmoL/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	−28.6 mg/dl, $P < 0.001$ from baseline
	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−4.25 mg/dl, $P = 0.404$
	Hallund et al. (2006)[135]	F, Denmark, postmenopausal age 61 ± 7 y, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	−7.72 mg/dl, $P = 0.184$
	Cornish et al. (2009)[132]	M, F Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	92	No effect
	Marblestone (2008)[137]	F, USA, perimenopausal, age 36–48 y	Flaxseed source by Brevail	Seco 69 mg (200 mg SDG)	14	11	Reduced
	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmoL/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	−38.6 mg/dl, $P = 0.003$

Table 4 **Continued**

Outcome	Reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	No. of subjects	Response
	Pan et al. (2009)[131]	Meta-analysis, 7 comparisons (5 articles)		Flaxseed lignan supplements			−6.18 mg/dl, $P = 0.03$
	Wu et al. (2009b)[139]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmoL/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	2.70 mg/dl, $P = 0.292$
	Hirata et al. (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	−30.7 mg/dl, $P < 0.05$
Total cholesterol	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmol/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	−39.8 mg/dl, $P < 0.001$ from baseline
	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmol/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−6.56 mg/dl, $P = 0.367$
	Hallund et al. (2006)[135]	F, Denmark, postmenopausal age 61 ± 7 y, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	−8.88 mg/dl, $P = 0.262$
	Cornish et al. (2009)[132]	M, F, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	92	No effect
	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmoL/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	−68.3 mg/dl, $P < 0.001$
	Pan et al. (2009)[131]	Meta-analysis, 7 comparisons (5 articles)		Flaxseed lignan supplements			−10.81 mg/dl, $P = 0.04$
	Wu et al. (2009b)[139]	M, F, Australia, age 55 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmoL/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	0.77 mg/dl, $P = 0.227$
	Hirata et al. (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	−23.7 mg/dl, $P < 0.05$

Triglycerides	Zhang et al. (2008)[136]	M, F, China, age 53–58 y, LDL ≥3.62 mmoL/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 103 mg (300 mg SDG)	8	18	−46.0 mg/dl, not significant from baseline
	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan complex	Seco 124 mg (360 mg SDG)	12	73	−17.70 mg/dl, $P = 0.720$
	Hallund et al. (2006)[135]	F, Denmark, postmenopausal age 61 ± 7 y, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	3.5 mg/dl, $P = 0.595$
	Cornish et al. (2009)[132]	M, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	49	Group effect (controls increased $P = 0.017$)
	Cornish et al. (2009)[132]	F, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	52	No effect
	Zhang et al. (2008)[136]	M, W, China, age 53–58 y, LDL ≥3.62 mmoL/L hypercholesterolemic	Tablets flaxseed lignan complex	Seco 206 mg (600 mg SDG)	8	55	−76.1 mg/dl, $P = 0.068$
	Wu et al. (2009b)[139]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmoL/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	−10.6 mg/dl, $P = 0.254$
	Hirata et al. (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 32.4 mg 4 weeks then 64.8 mg 4 weeks	8	12	No effect
Apo A1	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−2.5 mg/dl, $P = 0.751$
Apo B	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	73	−1.6 mg/dl, $P = 0.528$
	Hirata et al. (1996)[138]	M, Japan, hypercholesterolemic	Capsule 180 g wheat germ oil	Sesamin 64.8 mg	8	12	−20.3 mg/dl, $P < 0.05$
Lp(a)	Marblestone (2008)[137]	F, USA, perimenopausal, age 36–48 y	Flaxseed source by Brevail	Seco 69 mg (200 mg SDG)	14	11	Reduced
	Pan et al. (2007)[133]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	62	−2.52 mg/dl, $P = 0.339$

[†] Metabolic syndrome composite score based on fasting glucose, HDL, triglycerides, abdominal adiposity, blood pressure, and inflammatory cytokines.

Abbreviations: Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Lp(a), lipoprotein (a); M, males; F, females; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; Seco, secoisolariciresinol; SDG, secoisolariciresinol diglucoside.

Table 5 **Randomized controlled trials of lignans and other cardiovascular risk factors.**

Outcome	Reference	Adult population	Vehicle	Lignan dosage per day	Study duration weeks	No. of subjects	Response
C-reactive protein	Marblestone (2008)[137]	F, USA, perimenopausal, age 36–48 y	Flaxseed source by Brevail	Seco 69 mg (200 mg SDG)	14	11	reduced
	Pan et al. (2009)[141]	M, F, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	64	–0.45 mg/l, $P = 0.021$
	Pan et al. (2009)[141]	F, China, type 2 diabetics, age 50–70 y, postmenopausal, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	39	–0.67 mg/l, $P = 0.016$
	Pan et al. (2009)[141]	M, China, type 2 diabetics, age 50–70 y, LDL ≥2.90 mmoL/L	Capsule flaxseed lignan extract	Seco 124 mg (360 mg SDG)	12	25	–0.20 mg/l, $P = 0.49$
	Hallund et al. (2008)[140]	F, Denmark, postmenopausal age 61 ± 7 y, healthy, BP<160/90	Muffin with flaxseed lignan complex	Seco 172 mg (500 mg SDG)	6	22	–0.18 mg/l, $P = 0.028$
	Wu et al. (2009b)[139]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome† or LDL >3.4 mmol/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	–0.11 mg/l, $P = 0.845$
F_2-isoprostanes	Wu et al. (2009b)[139]	M, F, Australia, age 55.1 ± 8.7 y, overweight (BMI 25–35), ≥1 risk factor metabolic syndrome or LDL >3.4 mmoL/L	Bars with 26.2 g sesame seeds	Sesamin 39.5 mg, sesamolin 12.2 mg	5	33	–35 pmol/l, $P = 0.047$
Metabolic syndrome composite score†	Cornish et al. (2009)[132]	M, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	39	0.34 (controls 0.81, $P = 0.058$)
	Cornish et al. (2009)[132]	F, Canada, age ≥50 y, healthy, with walking intervention	Tablet flaxseed lignan complex	Seco 187 mg (543 mg SDG)	26	53	No effect

† Metabolic syndrome composite score based on fasting glucose, HDL, triglycerides, abdominal adiposity, blood pressure, and inflammatory cytokines.

Abbreviations: M, males; F, females; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein cholesterol; Seco, secoisolariciresinol; SDG, secoisolariciresinol diglucoside.

been mostly small and in populations with varying susceptibility. Clinical trials with flaxseed and sesame seed products have resulted in ambiguous results because little attention was paid to providing an adequate description of the test material. Without knowledge of the actual lignan content in the tested material, it is difficult to ascribe outcomes to lignan administration. A major issue with many of the clinical trials (until more recently) is product quality and lack of a detailed description for the tested material. Future controlled trials should focus on target groups at high risk of cardiovascular disease. Interventions should include doses of well-characterized supplement products with sufficiently high lignan content and have trial durations that are long enough to allow beneficial associations to be demonstrated.

Observational studies: Lignan intake

There are significant challenges in measuring lignan intakes, including the incompleteness of food tables, the failure to measure all of the lignans present, the inability to account for individual differences in production of enterolignans in the gut, and the failure to use validated biomarkers of intake. Table 6 shows that the evidence in existing epidemiological studies is mixed for cardiovascular benefit from dietary lignan intake.[66,72,75,76,142–145] The literature search for this review revealed only two studies on dietary intake of lignans and their associations with cardiovascular disease or coronary heart disease events or mortality and five studies with heart disease risk factor endpoints.

Milder et al.[76] assessed lignan intakes in Dutch elderly men and followed them for cardiovascular disease mortality over 15 years. The rate ratio and 95% confidence interval (CI) per 1-SD (standard deviation) difference in matairesinol intake (which is metabolized directly to enterolactone) were 0.72 and 0.53–0.98 for coronary heart disease mortality and 0.83 and 0.69–1.00 for cardiovascular disease mortality. Neither total lignans nor the other lignans consumed (lariciresinol, pinoresinol, secoisolariciresinol) were related to coronary heart disease or cardiovascular disease mortality. There was also no association between lignan intakes and diastolic blood pressure, systolic blood pressure, HDL, and total cholesterol.

In the Dutch EPIC cohort study[66] of women who were followed for a median of 6.25 years, lignan intakes (matairesinol and secoisolariciresinol) of approximately 1,100 μg/day were not associated with CVD disease risk. While increasing lignan intake was associated with lower CHD risk, this was only among smokers. Relationships with individual lignans were not reported in this study.[66]

Supporting the findings of Milder et al.[76] are the findings of Pellegrini et al.,[75] which showed that greater matairesinol intakes were significantly associated with increased flow-mediated dilatation in older Italian men and women but that no significant associations were observed with secoisolariciresinol, pinoresinol, or lariciresinol or total lignans. These findings are intriguing because, compared to the other lignans, matairesinol is found in much lower amounts (e.g., only a tenth) than other lignans in the diet.

Three observational studies examining blood pressure outcomes found negligible associations with greater lignan intake.[72,76,142] In a cross-sectional study of postmenopausal women in the United States, lignan intake was associated with a borderline, non-statistically significant association with lower diastolic or systolic blood pressure.[72] In a Dutch cross-sectional study of women, although there was a trend toward lower systolic and diastolic blood pressure and a lesser prevalence of hypertension with higher intake (above 1,140 μg) of two lignans (matairesinol and secoisolariciresinol), these findings were not significant.[142]

Observational studies of the relationship between lignan intake and total cholesterol and its subfractions are mixed. Two observational studies[72,143] of Dutch and US women found no significant association with LDL, HDL or total cholesterol, but a third observational study[144] of US men found that lignan intake was associated significantly with increased LDL and apolipoprotein B and non-significantly with increased total cholesterol. This same study found that lignan intake was significantly associated with lower C-peptide.[144] In the cross-sectional study performed in Framingham, Massachusetts (USA), postmenopausal women with greater intakes of lignans had lower fasting triglyceride concentrations.[72]

In regard to markers of vascular function, in addition to the aforementioned study of flow-mediated dilatation,[75] a Dutch study[145] found lignan intake to be non-significantly associated with reduced aortic stiffness in all postmenopausal women but significantly associated with reduced aortic stiffness in the subset of women who were 20 to 30 years beyond menopause. Kreijkamp-Kasper et al.[142] also examined these markers in Dutch postmenopausal women but found no significant association with endothelial function, flow-mediated dilatation, and ankle brachial index.

In the Milder et al.[76] prospective cohort study and the Pellegrini et al.[75] cross-sectional vascular study, which measured specific lignan dietary intakes, matairesinol appeared to be the lignan most commonly associated with decreased cardiovascular disease risk. However, this may have been simply because matairesinol is more commonly measured in foods compared to the other lignans. Matairesinol is present particularly in wine, oats, and rye. Among populations consuming wine, the amount of matairesinol provided from this source could be high enough (e.g., 17–22 mg/100 g white wine or 74–98 mg/

Table 6 **Associations between matairesinol and secoisolariciresinol lignan intakes and cardiovascular disease risk and risk factors.**

Outcome	Reference	Study	Population characteristics	Cases (N)	$P \leq 0.05$	$P > 0.05$–0.15	$P > 0.15$
Cardiovascular disease mortality ‡	Milder et al. (2006)[76]	Prospective cohort, Zutphen, The Netherlands	570 M, elderly, 15 y follow up	84	Mat only†RR 0.83, CI 0.69–1.00, $P = 0.05$ [7 μg per SD unit]‖		Seco only RR 0.88, CI 0.71–1.08, $P = 0.23$ [51 μg per SD unit]‖
Coronary heart disease mortality ‡	Milder et al. (2006)[76]	Prospective cohort, Zutphen, The Netherlands	M, elderly, 15 y follow up	570	Mat only 0.72 RR (0.53, 0.98) CI $P = 0.03$ [7 μg per SD unit]‖		Seco only RR 0.84, CI 0.61–1.17, $P = 0.31$ [51 μg per SD unit]‖
Cardiovascular disease incidence	Van der Schouw et al. (2005)[66]	Prospective, EPIC, The Netherlands	16,165 F, age 49–70 y, healthy, 6.25 y follow up	518			HR 0.89, CI 0.66–1.19, NS [1.39 versus 0.74 mg/d]**,††
Coronary heart disease Incidence	Van der Schouw et al. (2005)[66]	Prospective, EPIC, The Netherlands	16,165 F, age 49–70 y healthy, 6.25 y follow up	371			HR 0.92, CI 0.65–1.29, NS [1.39 versus 0.74 mg/d]**,††
	Van der Schouw et al. (2005)[66]	Prospective, EPIC, The Netherlands	16,165 F, age 49–70 y, healthy, 6.25 y follow up sub analysis by smoking status	n/a	HR 0.63, CI 0.41–0.98, *P* for interaction = 0.01 [1.39 versus 0.74 mg/d]**,†† smokers		No association for non-smokers
Cerebrovascular disease incidence	Van der Schouw et al. (2005)[66]	Prospective, EPIC, The Netherlands	16,165 F, age 49–70 y, healthy, 6.25 y follow up	147			HR 0.80, CI 0.45–1.42, NS [1.39 versus 0.74 mg/d]**,††
Hypertension	Kreijkamp-Kaspers et al. (2004)[142]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301		OR 0.49, CI 0.18–1.29, $P = 0.15$ [2.01 versus 1.14 mg/d]‖,††	
Blood pressure, diastolic	Kreijkamp-Kaspers et al. (2004)[142]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301		−5.19 mm Hg, CI −11.41–1.03, $P = 0.07$ [2.01 versus 1.14 mg/d]‖,††	
	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			−1.1 mg Hg, CI −3.2–1.0, *P* for trend = 0.24 [0.79 versus 0.41 mg/d]**,††
‡	Milder et al. (2006)[76]	Prospective cohort, Zutphen, The Netherlands	M, elderly, 15 y follow up	570			No difference across tertiles of consumption $P = 0.77$

Blood pressure, systolic	Kreijkamp-Kaspers et al. (2004)[142]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301		OR −7.92, CI −17.91–2.07, $P = 0.12$ [2.01 versus 1.14 mg/d][‖,††]	
	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			−2.0 mmHg, CI −5.8–1.9, P for trend = 0.59 [0.79 versus 0.41 mg/d]**,††
‡	Milder et al. (2006)[76]	Prospective cohort, Zutphen, The Netherlands	M, elderly, 15 y follow up	570			No difference across tertiles of consumption $P = 0.47$
Cholesterol, HDL	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939		−2.7 mg/dl, CI −0.39–5.02), $P = 0.15$ [0.79 versus 0.41 mg/d]**,††	
	Kreijkamp-Kaspers et al. (2005)[143]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			0.39 mg/dl, CI −8.8–6.6), P for trend = 0.76 [2.01 versus 1.14 mg/d][‖,††]
‡	Milder et al. (2006)[76]	Prospective cohort, Zutphen, The Netherlands	M, elderly, 15 y follow up	570			No difference across tertiles of consumption $P = 0.26$
Cholesterol, LDL	Van der Schouw et al. (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47–83 y	301	12.9 mg/dl, CI 1.7–24.1, P for trend = 0.01 [1.15 versus 0.39 mg/d medians]**,††		
	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			−0.37 mg/dl, CI −7.3–6.6, P for trend = 0.84 [0.79 versus 0.41 mg/d]**,††
	Kreijkamp-Kaspers et al. (2005)[143]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			−8.11 mg/dl, CI −25.1–8.9, P for trend = 0.35 [2.01 versus 1.14 mg/d][‖,††]
Cholesterol, total	Van der Schouw et al. (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47–83 y	468		11.1 mg/dl, CI −2.4–24.5, P for trend = 0.08 [1.15 versus 0.39 mg/d medians]**,††	
	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939			−2.32 mg/dl, CI −9.6–5.0, P for trend = 0.47 [0.79 versus 0.41 mg/d]**,††
	Kreijkamp-Kaspers et al. (2005)[143]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			−8.11 mg/dl, CI −26.6–10.4, P for trend = 0.40 [2.01 versus 1.14 mg/d][‖,††]

Table 6 **Continued**

Outcome	Reference	Study	Population characteristics	Cases (N)	$P \leq 0.05$	$P > 0.05$–0.15	$P > 0.15$
‡	Milder et al. (2006)[76]	Prospective cohort, Zutphen, The Netherlands	M, elderly, 15 y follow up	570			No difference across tertiles of consumption $P = 0.52$
Triglycerides	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939	−20.4 mg/dl, CI −32.7 – −7.96, $P = 0.001$ [0.79 versus 0.41 mg/d]**,††		
	Kreijkamp-Kaspers et al. (2005)[143]	Cross-sectional, EPIC, Netherlands	F, postmenopausal, age 60–75 y, healthy	301			−2.65 mg/dl, CI −12.4–11.5, *P* for trend = 0.78 [2.01 versus 1.14 mg/d]‖,††
Apolipoprotein B	Van der Schouw et al. (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47–83 y	468	10.0 mg/dl, CI 1.6–18.4, *P* for trend = 0.02 [1.15 versus 0.39 mg/d medians]**,††		
Lipoprotein (a)	Kreijkamp-Kaspers et al. (2005)[143]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			OR 0.47, CI 0.17–1.31, *P* for trend = 0.18 [2.01 versus 1.14 mg/d]‖,††
C-peptide	Van der Schouw et al. (2005)[144]	Cross-sectional, Health Professionals, USA	M, age 47–83 y	468	−0.55 ng/dl, CI −0.97 – −0.13), *P* for trend = 0.01 [1.15 versus 0.39 mg/d medians]**,††		
Ankle brachial index	Kreijkamp-Kaspers et al. (2004)[142]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			0.01, CI −0.04–0.07, *P* for trend = 0.60 [2.01 versus 1.14 mg/d]‖,††
Endothelial function (pimax)	Kreijkamp-Kaspers et al. (2004)[142]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			−0.01 pimax, CI −0.08–0.06, *P* for trend = 0.80 [2.01 versus 1.14 mg/d]‖,††

Flow-mediated dilatation[§]	Pellegrini et al. (2010)[75]	Cross-sectional, longitudinal follow-up, Italy	242 M, F, healthy, postmenopausal	101	Mat only 4.1% to 8.1% change, *P* for trend = 0.016 [0.039 versus 0.009 mg/d means]**	Seco only 4.6% to 6.8% change, *P* for trend = 0.099 [0.625 versus 0.158 mg/d means]**	
	Kreijkamp-Kaspers et al. (2004)[142]	Cross-sectional, EPIC, The Netherlands	F, postmenopausal, age 60–75 y, healthy	301			–0.09%, CI –1.93–2.12, *P* for trend = 0.92 [2.01 versus 1.14 mg/d][‖,††]
Reduced aortic stiffness	Van der Schouw et al. (2002)[145]	Cross-sectional, EPIC, The Netherlands	F, healthy, postmenopausal	403		–0.41, CI –0.93–0.11, *P* for trend = 0.06 [0.87 versus 0.33 mg/d]**,††	
	Van der Schouw et al. (2002)[145]	Cross-sectional, EPIC, The Netherlands	F, healthy, long (20–30 y) postmenopausal time span	180	–0.80, CI –1.54 – –0.05, *P* for trend = 0.03 [0.87 versus 0.33 mg/d]**,††		
	Van der Schouw et al. (2002)[145]	Cross-sectional, EPIC, The Netherlands	F, healthy, short (8–12 y) postmenopausal time span	199			–0.19, CI –0.95–0.57, *P* for trend = 0.40 [0.87 versus 0.33 mg/d]**,††
Metabolic syndrome score	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939	–0.55, –0.82 – –0.28, *P* = 0.0001 [0.79 versus 0.41 mg/d]**,††		
Waist hip ratio	De Kleijn et al. (2002)[72]	Cross-sectional, Framingham, USA	F, postmenopausal	939	–0.017, CI –0.030 – –0.0016, *P* = 0.03 [0.79 versus 0.41 mg/d]**,††		

[†] All intakes "Mat & Seco" unless marked "Mat only" or "Seco only".
[‡] Not significant for lariciresinol, pinoresinol, and total lignans (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol) in Milder et al. (2006).[76]
[§] Flow-mediated dilatation was not significant for lariciresinol and pinoresinol, but approached significance for total lignans (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol) 4.7% to 7.5%, *P* for trend = 0.066, 666 μg/d median intake in Pellegrini et al. (2009).[75]
[‖] Highest versus lowest tertile of intake.
** Highest versus lowest quartile of intake.
[††] Intake from FFQ but food items scored for Mat and Seco, analytical values were not used.
Underlying causes of death coded according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10). Cardiovascular disease deaths defined as ICD-9 codes 390-459 and ICD-10 codes I20-I99, coronary heart disease deaths as ICD-9 codes 410-414 (ischemic heart disease) and 492.2 (atherosclerotic heart disease) and ICD-10 codes I20-I25, and stroke as ICD-9 codes 430-438 (ischemic and hemorrhagic cerebrovascular disease) and ICD-10 codes I60-I69 (cerebrovascular diseases).
Abbreviations: M, males; F, females; CI, 95% confidence interval; HR, hazard rate ratio; OR, odds ratio; RR, rate ratio; [ ], definition of comparison groups or per SD unit; Seco, secoisolariciresinol; Mat, matairesinol.

100 g red wine) to provide additional protection beyond the alcohol content alone, although confounding by other components of wine cannot be ruled out. Many epidemiologic studies[146] show that whole grain intake is cardioprotective. Matairesinol may be one of the important components responsible for this association. The soluble fiber content of oats is known to be cardioprotective, and the considerable matairesinol content of whole grain oats may contribute to these protective associations.

Observational studies: Serum enterolactone

Serum levels of enterolactone are somewhat better measures of systemic lignan exposure in tissues than are lignan intakes alone, although the short half-life of both metabolites requires that caution be taken when interpreting studies that used single measures of either biomarker in relation to disease outcome.[60,78] It may be useful to keep in mind prior suggestions that enterolactone levels of 30 nmoL/L or higher are protective and levels below 15 nmoL/L are too low to confer protection. Upper levels of enterolactone from diet appear to be 90–100 nmoL/L; however, variations in levels are high.[147,148] Table 7 illustrates findings from four epidemiological studies that examined plasma enterolactone in relation to risk of coronary heart disease mortality, cardiovascular disease mortality and events, and other related risk factors (blood pressure, HDL, and LDL).[149–153] In most of the studies in Table 7, the highest quartiles and quintiles either approached or were in the putative protective range.

In a cohort study of 1,889 Finnish men who were followed for an average of 12.2 years, Vanharanta et al.[149] found a lower risk of fatal coronary heart disease (rate ratio [RR] = 0.44, $P = 0.03$) and fatal cardiovascular disease (RR 0.55, $P = 0.04$) with greater concentrations of serum enterolactone. In contrast, associations with all-cause mortality were weaker and not significant (data not shown).[149]

In a nested case-control study of healthy Finnish men, in which blood levels of enterolactone was measured up to 7.7 years prior to diagnosis, those with mean serum concentrations of enterolactone in the highest quartile (>30.1 nmoL/L) had a 65.3% lower risk of acute coronary events than men in the lowest quartile (<7.21 nmoL/L).[150] In another Finnish study of men, in which blood was measured up to 11 years before diagnosis, the association between mean serum enterolactone concentration and coronary heart disease risk (acute and fatal) was not significant in cases compared to healthy controls (17.8 nmoL/L versus 18.1 nmoL/L) when adjustments were made for classic risk factors.[151] In a Dutch nested case-control study of men and women, no significant differences were found between serum enterolactone levels in coronary heart disease acute events.[152]

Two Finnish nested case-control studies[149,150] of blood pressure noted significant inverse associations with plasma enterolactone, whereas in a third Finnish study[151] and a Dutch study[152] associations were not statistically significant. All of the nested case-control studies of cardiovascular disease and coronary heart disease outcomes found no association between enterolactone levels and blood lipids (HDL, LDL, total cholesterol, apolipoprotein B), apart from a borderline positive association in one Dutch study.[152] In a cross-sectional Finnish study, high enterolactone levels were associated with reduced F_2-isoprostanes, a marker of lipid peroxidation.[153] The weak correlations between serum enterolactone and cardiovascular disease outcomes make it difficult to draw conclusions from those studies.

LIMITATIONS OF EXISTING STUDIES

Although many of the studies reviewed suggest possible associations with dietary or biomarker measures of lignan exposure, several limitations are worth noting. More research on the food content of lignans, and on food sources in relation to health outcomes in epidemiologic studies is needed. It may be that a certain threshold of intake is required and many Western populations either do not reach those levels, or the appropriate foods are not assessed on research questionnaires. If possible, repeated measures of these biomarkers would benefit studies of the association between enterolactone and chronic disease outcomes. Finally, it is of interest that most studies of lignan intake were of women, whereas all but one of the enterolactone studies were of men. Because associations with lignans may vary by gender, more research including both men and women is needed. Future studies should employ both complete dietary intakes of lignans and serum (or plasma) enterolignan markers in high-risk groups.

ARE LIGNANS THE COMPONENTS THAT PROVIDE CARDIOVASCULAR BENEFITS?

Can the cardioprotective benefits of foods rich in lignans be ascribed to lignans, lignins, dietary fiber, alkylresorcinols or other components? Both lignins and lignans are synthesized from similar subunits, and both, as well as other components of dietary fiber, are commonly found in cereals and grains.

Of the few studies on lignins, the various types of lignins in foods were not examined independently. One study of fiber components[154] and a recent review[155] found that lignin intake did not lower lipid levels. However,

Table 7 **Serum and plasma enterolactone (and enterodiol) and cardiovascular disease risk.**

Outcome	Reference	Study	Population characteristics	Cases (N)	$P \leq 0.05$	$P > 0.05$–0.15	$P > 0.15$
Cardiovascular disease mortality	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	1889 M, age 42, 48, 54, or 60 y, 12.2 y follow up	103	RR 0.55, CI 0.29–1.01, $P = 0.04$ [23.9 versus 6.9 nmoL/L][†]		
Coronary heart disease mortality	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 12.2 y follow up	70	RR 0.44, CI 0.20–0.96, $P = 0.03$ [23.9 versus 6.9 nmoL/L][†]		
	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	340 cases (205 MI, 135 deaths) 420 controls			RR 0.57, CI 0.26–1.25, P for trend = 0.18 [28.25 versus 5.02 nmoL/L][‡]
Coronary heart disease risk (acute events & mortality)	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	340 cases (205 MI, 135 deaths) 420 controls		RR 0.63, CI 0.33–1.11, P for trend=0.07 [28.25 versus 5.02 nmoL/L][‡]	
Coronary heart disease risk (acute events)	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	340 cases (205 MI, 135 deaths) 420 controls		RR 0.67, CI 0.37–1.23), P for trend=0.10 [28.25 versus 5.02 nmoL/L][‡]	
[§]	Kuijsten et al. (2009)[152]	Prospective nested case control, The Netherlands	M, F, age 20–59 y, 11 y follow up	236 cases, 283 controls		OR 1.51, CI 0.87–2.61), P for trend = 0.12 [17.5 versus 3.8 nmoL/L][†]	
[§]	Kuijsten et al. (2009)[152]	Prospective nested case control, The Netherlands	F, premenopausal, age 20–59 y, 11 y follow up	34 cases	OR 0.16, CI 0.02–1.03, P for trend = 0.05 [per 13.7 nmoL/L, 17.5 versus 3.8 nmoL/L][†]		

Table 7 **Continued**

Outcome	Reference	Study	Population characteristics	Cases (N)	$P \leq 0.05$	$P > 0.05$–0.15	$P > 0.15$
[§]	Kuijsten et al. (2009)[152]	Prospective nested case control, The Netherlands	F, postmenopausal, age 20–59 y, 11 y follow up	30 cases	OR END 1.17, CI 1.00–1.36, *P* for trend = 0.05 [per 1.3 nmoL/L, 1.7 versus 0.4 nmoL/L][†]		OR 2.27, CI 0.57–8.95), *P* for trend = 0.24 [per 13.7 nmoL/L, 17.5 versus 3.8 nmoL/L][†]
	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls	OR 0.35, CI 0.14–0.88, *P* = 0.03 [30.1 versus 7.2 nmoL/L][†]		
Hypertension	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 12.2 y follow up	1,889 at baseline	−12%, *P* for heterogeneity <001 [23.9 versus 6.9 nmoL/L][†]		
Blood pressure, diastolic[§]	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls at baseline	−3 mm Hg, *P* for heterogeneity = 0.017 [30.1 versus 7.2 nmoL/L][†]		
	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 12.2 y follow up	1,889 at baseline	−3 mm Hg, *P* for heterogeneity <001 [23.9 versus 6.9 nmoL/L][†]		
	Kuijsten et al. (2009)[152]	Prospective nested case control, The Netherlands	M, F, age 20–59 y, 11 y follow up	283 controls at baseline		−3 mm Hg, *P* for trend = 0.08 [17.5 versus 3.8 nmoL/L][†]	
	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	420 controls at baseline			−6 mm Hg, *P* for heterogeneity = 0.21 [28.25 versus 5.02 nmoL/L][‡]

Blood pressure, systolic[§]	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 12.2 y follow up	1,889 at baseline	−5 mm Hg, *P* for heterogeneity <001 [23.9 versus 6.9 nmoL/L][†]		
	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls at baseline	−5 mm Hg, *P* for heterogeneity = 0.026 [30.1 versus 7.2 nmoL/L][†]		
	Kuijsten et al. (2009)[152]	Prospective nested case control, The Netherlands	M, F, age 20–59 y, 11 y follow up	283 controls at baseline		−4 mm Hg, *P* for trend = 0.09 [17.5 versus 3.8 nmoL/L][†]	
	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	420 controls at baseline			−6 mm Hg, *P* for heterogeneity = 0.84 [28.25 versus 5.02 nmoL/L][‡]
Cholesterol, HDL	Kuijsten[§] et al. (2009)[152]	Prospective nested case control, The Netherlands	M, F, age 20–59 y, 11 y follow up	283 controls at baseline		3.86 mg/dl, *P* for trend = 0.07 [17.5 versus 3.8 nmol/l][†]	
	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls at baseline			1.54 mg/dl, *P* for heterogeneity = 0.74 [30.1 versus 7.2 nmoL/L][†]
	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 12.2 y follow up	1,889 at baseline			1 mg/dl, *P* for heterogeneity = 0.66 [23.9 versus 6.9 nmoL/L][†]
	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	420 controls at baseline			1.16 mg/dl, *P* for heterogeneity = 0.47 [28.25 versus 5.02 nmoL/L][‡]

Table 7 **Continued**

Outcome	Reference	Study	Population characteristics	Cases (N)	$P \leq 0.05$	$P > 0.05$–0.15	$P > 0.15$
Cholesterol, LDL	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls at baseline			–2.32 mg/dl, *P* for heterogeneity = 0.52 [30.1 versus 7.2 nmoL/L][†]
	Vanharanta et al. (2003)[149]	Prospective, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 12.2 y follow up	1,889 at baseline			0.0 mg/dl, *P* for heterogeneity = 0.91 [23.9 versus 6.9 nmoL/L][†]
Cholesterol, total	Kuijsten[§] et al. (2009)[152]	Prospective nested case control, The Netherlands	M, F, age 20–59 y, 11 y follow up	283 controls at baseline			5.80 mg/dl, *P* for trend = 0.22 [17.5 versus 3.8 nmoL/L][†]
	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls at baseline			3.47 mg/dl, *P* for heterogeneity = 0.82 [30.1 versus 7.2 nmoL/L][†]
	Kilkkinen et al. (2006)[151]	Prospective case-cohort, ATBC, Finland	M, smokers, 11.1 y follow up	420 controls at baseline			3.86 mg/dl, *P* for heterogeneity = 0.22 [28.25 versus 5.02 nmoL/L][‡]
Apolipoprotein B	Vanharanta et al. (1999)[150]	Prospective nested case control, Kuopio, Finland	M, age 42, 48, 54, or 60 y, 7.7 y follow up	167 cases, 167 controls at baseline			41 mg/l, *P* for heterogeneity = 0.22 [30.1 versus 7.2 nmoL/L][†]
Reduced F2-isoprostanes	Vanharanta et al. (2002)[153]	Cross-sectional, ASAP, Finland	M, age 58.± 6.5	100	–37.4%, *P* for trend = 0.008 [25.6 versus 3.9 nmoL/L][‡]		

[†] Highest versus lowest quartile of serum (or plasma) enterolactone (or enterodiol).
[‡] Highest versus lowest quintile of serum (or plasma) enterolactone.
[§] In Kuijsten et al. (2009)[152] (the only study using plasma), diastolic and systolic blood pressure, HDL, total cholesterol and coronary heart disease risk (acute events) were not significant for enterodiol.
Underlying causes of death coded according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10). Cardiovascular disease deaths defined as ICD-9 codes 390-459 and ICD-10 codes I20-I99, coronary heart disease deaths as ICD-9 codes 410-414 (ischemic heart disease) and 492.2 (atherosclerotic heart disease) and ICD-10 codes I20-I25, and stroke as ICD-9 codes 430-438 (ischemic and hemorrhagic cerebrovascular disease) and ICD-10 codes I60-I69 (cerebrovascular diseases).
Abbreviations: M, males; F, females; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CI, 95% confidence interval; OR, odds ratio; RR, rate ratio; [ ], definition of comparison groups or per SD (standard deviation) unit; END, enterodiol; MI, myocardial infarction.

several observational studies examining lignin intake and cancer risk found reduced risk of colorectal,[156,157] oral, pharyngeal, and esophageal[158] cancers but not of breast,[159] ovarian,[160] and renal[161] cancers.

Dietary fiber may be responsible, in part, for the associations observed with lignan intake. Dietary fiber,[162–166] particularly soluble fiber,[164,167–169] reduces risk of cardiovascular disease. Dietary fiber lowers blood pressure,[170,171] decreases C-reactive protein levels,[172–176] decreases metabolic syndrome,[177–179] and decreases insulin resistance.[180] Although some studies indicate dietary fiber has weak lipid-lowering associations,[181,182] soluble fiber is more highly associated with lower serum lipids,[183–188] lower blood pressure[189] and fewer symptoms of metabolic syndrome.[190,191]

Cereal fiber consists more of insoluble fibers (lignins) than soluble fibers. Cereal fiber is associated with decreased insulin resistance,[192] lower serum lipids,[193] lower blood pressure,[194,195] less progression of coronary atherosclerosis in postmenopausal women with established coronary artery disease,[196] and reduced risk of coronary heart disease,[165,197,198] cardiovascular disease,[199] and stroke[200] in many[201] but not all studies.[164,202,203] Insoluble fiber is associated with lower blood pressure,[189] lower C-reactive protein levels,[176] lower insulin resistance,[180] and lower risk of both cardiovascular disease[168] and myocardial infarction.[164,168]

The studies on lignan intakes and cardiovascular disease risk, which were reviewed earlier in this article,[66,72,75,76,142–145] were adjusted for fiber intakes, but not adjusted separately for insoluble and soluble fiber. Thus, the associations with lignan intake described here were beyond those of fiber. In the four epidemiological studies using enterolactone as the marker of lignan intakes, results were mixed.[149–152] Serum enterolactone was positively correlated with fiber intake in one study,[150] but fiber intake had no consistent association with the risk of acute coronary events. In a second study by the same investigator[149] energy-adjusted fiber intake was associated with enterolactone and explained 6% of its variation. However, in a third study, another group of investigators[151] found that adjusting for fiber and other dietary factors had little association with results. The fourth study also found fiber intake to be significantly associated with plasma enterolactone and enterodiol.[152] It is possible that enterolactone is a biomarker for a heart-healthy diet, and that such a diet exerts its effects through many different constituents (alkylresorcinols, flavonoids, glucosinolates, lignans, lignins, phenolic acids, stilbenes, terpenes, etc.).

In cereals, the fiber fraction contains alkylresorcinols, folic acid, polyphenols, vitamin E, and other factors in addition to lignans, which may also be involved in cardioprotection. However, in some cohort studies the associations between lignan intake and cardiovascular disease mortality remain even after adjusting for dietary fiber intakes. Whether the associations observed with coronary heart disease and cardiovascular disease risk and lignan exposure might be explained by intakes of cereal fiber or alcohol rather than by lignan intakes themselves remains to be determined. Nevertheless, in several controlled trials that used higher lignan doses than those usually found in diets, such as a secoisolariciresinol diglucoside-enriched source (500 mg/day secoisolariciresinol diglucoside), there were positive associations. Since secoisolariciresinol diglucoside-enriched products are available today and some cardiovascular risk-reducing associations were noted with their use, there is some support for a role of lignans in cardiovascular disease risk reduction. Now that high-quality products with well-characterized lignan contents are available, studies done with these well-characterized products may shed light on whether lignans do in fact have cardioprotective properties. Studies in experimental animals will also be helpful, particularly for exploring possible mechanisms of action.

CONCLUSION

There is intriguing but not yet compelling evidence from epidemiological studies that lignans present in the very small quantities typical of usual Western diets decrease coronary heart disease and cardiovascular disease mortality. More research is needed to confirm or refute these associations. Intervention studies using higher doses have found positive associations with some cardiovascular risk factors. In addition, it is important to elucidate whether doses found in foods or only the larger doses that might be delivered in dietary supplements offer protection.

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