**Dietary lignans: physiology and potential for cardiovascular disease risk reduction**

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**Abstract**

We reviewed lignan physiology and lignan intervention and epidemiological studies to determine if they decreased 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, which included these studies, also suggested 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 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.

**Keywords:**lignans, cardiovascular disease, review

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**Introduction**

The lignans are bioactive, non-nutrient, non-caloric phenolic plant compounds that are found in highest concentration 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R1) and other biochemical properties suggest potential for nutritional significance in the prevention of cardiovascular and other chronic diseases.[2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R2)-[4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R4) This article briefly describes the chemistry and biosynthesis of lignans in plants (including flaxseed and sesame), major food sources, their metabolism in humans, and recent studies of their associations with cardiovascular disease biomarkers, events and mortality in humans.

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**Chemistry and occurrence of lignans**

Monolignols ([Figure 1a](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F1/)), derived from hydroxycinnamic acids (*p*-coumaric, ferulic, and sinapic acids), are either dimerized to *lignans* ([Figure 1b](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F1/)) in the cell or polymerized into larger lignin structures in the cell wall ([Figure 1c](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F1/)). These structurally diverse compounds are involved in plant defense (as antioxidants, biocides, phytoalexins, etc.),[5](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R5) providing protection against diseases and pests, and possibly participating in plant growth control.[6](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R6),[7](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R7)



[Figure 1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F1/)

**Structures of monolignols, lignans, and lignins**

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 (C8-C8) ([Figure 1b](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F1/)).[8](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R8)

In the plant, *lignans* (monolignol dimers) usually occur free or bound to sugars.[6](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R6),[7](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R7)Diglucosides of pinoresinol, secoisolariciresinol, and syringaresinol are common.[9](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R9)-[12](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R12)Sesaminol triglucoside and sesaminol diglucoside occur in sesame seeds.[13](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R13)-[15](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R15) In flax, secoisolariciresinol is present as a diglucoside and is part of an ester-linked complex or oligomer ([Figure 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F2/)) containing 3-hydroxyl-3-methylglutaric acid, a number of cinnamic acid glycosides (usually ferulic or *p*-coumaric acid) and the flavonoid herbacetin.[16](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R16)-[21](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R21)



[Figure 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F2/)

**Sketch of flaxseed seocisolariciresinol lignan oligomer**

The plant *lignans* most commonly distributed in foods are lariciresinol, matairesinol, pinoresinol, and secoisolariciresinol ([Figure 3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F3/)). 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R12),[22](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R22) ([Figure 3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F3/)). Other lignans found in foods but not often quantified include arctigenin, cyclolariciresinol (isolariciresinol), 7′-hydroxymatairesinol, and 7-hydroxysecoisolariciresinol.[2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R2),[12](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R12) (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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R23)



[Figure 3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F3/)

**Structure and sources of individual lignans common in foods**

*Lignins* are large plant polymers built from the *p*-coumaryl, coniferyl, and sinapyl hydroxycinnamic alcohols (see [Figure 1c](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F1/)). They are racemic (non-stereospecific) polymers, with monolignol units binding at C8 and four other sites (C5-C5, C5-C8, C5-*O*-C4, C8-*O*-C4).[24](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R24) *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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R25)Nutritionally lignins are considered components of insoluble dietary fiber.[26](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R26) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R24)

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**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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R27) (335 mg/100g) and sesame seeds (373 mg/100g),[22](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R22),[28](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R28) which have a lignan content a hundred times higher than other dietary sources.

[Table 1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T1/) provides examples of the distribution of lignans in foods.[10](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R10),[12](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R12),[28](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R28)-[35](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R35) 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 also present in fruits and vegetables such as asparagus, grapes, kiwi fruit, lemons, oranges, pineapple, wine and even in coffee and tea.[12](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R12),[29](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R29)-[32](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R32)



[Table 1](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T1/)

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

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 intestinal bacterial metabolism in the animals' guts, but these are exceptions.[36](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R36)-[39](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R39) Little has been done to investigate the effects of storage and processing on lignans in most foods,[29](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R29)-[32](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R32),[40](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R40)-[45](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R45) although it is known that the lignan content is apparently not changed considerably with flaxseed[46](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R46)-[50](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R50) and sesame seed processing.[51](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R51)-[59](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R59)

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**Lignan intake**

The lignan content of most foods is low and consumption of lignan-rich flaxseed and sesame seed is also low. However, these populations do eat many plant foods that contain small amounts of lignans and they do so often enough to raise their exposure to lignans.[60](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R60) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R61)-[64](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R64) (secoisolariciresinol and matairesinol) to about 1600 μg/day[65](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R65) (secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, syringaresinol, medioresinol, enterolactone, enterodiol) ([Table 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T2/)).[61](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R61)-[76](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76) Intakes of the two most commonly measured lignans vary from 70 to 1000 μg/day for secoisolariciresinol[61](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R61),[66](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R66) and 2 to 74 μg/day for matairesinol.[66](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R66),[67](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R67) Methods are now available to quantify lariciresinol and pinoresinol in foods.[11](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R11),[28](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R28) Lariciresinol[68](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R68),[69](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R69) varies in the diet from 74 to 500 μg/day and pinoresinol[67](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R67),[69](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R69) varies from 73 to 423 μg/day. Syringaresinol and medioresinol may also be measured.[28](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R28)



[Table 2](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T2/)

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

Total lignan intakes vary from country to country because of different dietary sources, but they vary 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R60) Valsta et al's 2003 study[70](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R70) measuring only matairesinol and secoisolariciresinol found the mean total lignan intake of Finns to be 434 μg/day. Milder et al's 2005 study[71](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R71) of lariciresinol, matairesinol, pinoresinol, and secoisolariciresinol found median total lignan intake of the Dutch was 979 μg/day. Hedelin et al's 2008 study[65](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R65) including lariciresinol, matairesinol, medioresinol, pinoresinol, secoisolariciresinol and syringaresinol of Swedish women had a median total lignan intake of 1632 μg/day. These studies indicate that, 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R17) and Li et al[16](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R16) discuss these issues in greater depth using examples from their work on secoisolariciresinol in flaxseed, its diglucoside and its oligomer.

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**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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R12) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77),[78](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R78)

**Bacterial metabolism in the gut**

Lignan glycosides, such as the flax secoisolariciresinol diglucoside ester-linked complex[17](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R17),[79](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R79)and the sesame seed sesamolin triglucoside,[14](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R14),[22](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R22),[80](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R80) are hydrolyzed by some of the anaerobic microbes in the gut to lignan aglycones.[80](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R80)-[83](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R83) The free lignans are then converted into enterolignans through a series of metabolic reactions by various gut bacteria[77](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77),[84](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R84)-[86](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R86) ([Figure 4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F4/)). 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R87)-[90](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R90)



[Figure 4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/figure/F4/)

**Bioconversion of plant lignans to enterolignans in the human gut**

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 hours into the enterolignans enterolactone (46%) and enterodiol (54%) whereas other plant lignans were incompletely converted – 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R9) Other lignans that are metabolized to enterolactone include arctigenin, 7-hydroxymatairesinol, sesamin, and syringaresinol.[9](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R9),[22](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R22),[77](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77) Smeds et al[91](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R91) found cyclolariciresinol, lariciresinol and matairesinol but not secoisolariciresinol in serum samples from a Finnish population. Penalvo et al[22](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R22),[92](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R92)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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R6),[93](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R93) In contrast, *lignins* are thought to be largely inert and not absorbed in the human gut due to their polymeric nature.[94](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R94)-[97](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R97) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R25) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R98)

Enterolactone is the main circulating enterolignan and 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77),[84](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R84),[99](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R99)

**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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R100) and most are conjugated to glucuronides in the tissues. They are usually detectable in the blood 8 to 10 hours after dietary intake.[77](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77),[78](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R78) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R22) The mechanisms responsible for the uptake of plant lignans in the small intestine are still unknown.[77](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77),[85](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R85) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R100)-[102](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R102) Some free lignans and aliphatic or aromatic hydroxylated metabolites from hepatic metabolism may also be excreted.[77](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R77),[85](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R85),[102](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R102)-[104](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R104) 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 two days.[78](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R78)

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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R100)Glucuronides and sulfates of secoisolariciresinol, enterolactone and enterodiol may undergo enterohepatic recirculation or simply be eliminated in the bile or urine.[86](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R86),[105](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R105)-[108](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R108)

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 Horn-Ross et al's lignan food frequency questionnaire validation study[62](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R62) using only matairesinol and secoisolariciresinol, the correlations with urinary total enterodiol and enterolactone were only 0.16. In Bhakta et al's food frequency questionnaire validation study[64](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R64) 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.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**Animal and cell lignan studies in cardiovascular areas**

There are some animal[109](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R109)-[119](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R119) and a few in vitro cell[120](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R120)-[122](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R122) studies on food lignans in the area of cardiovascular disease. For purposes of this review, we have limited the focus to humans and only to food lignans, but the area is worth investigating further. However, caution is indicated since rodent, particularly rat, diets contain other phytoestrogens that may influence results. Several non-food lignans,[123](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R123),[124](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R124) such as honokiol[125](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R125),[126](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R126) and magnolol,[127](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R127)-[130](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R130) have shown cardiovascular associations in animal and in vitro cell studies.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**Lignans and cardiovascular disease risk factors**

**Randomized controlled trials**

Most of the controlled trials 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 interventional studies with higher levels of lignan intakes, that usual intakes are below the threshold necessary to produce cardiovascular effects. Interventional 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R131) of the associations of flaxseed interventions, which included 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 of healthy volunteers, which may show few associations with risk factors, while others were of individuals at risk.

**Blood pressure studies**

As shown in [Table 3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T3/),[122](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R122),[132](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R132)-[134](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R134) in a randomized double blind placebo-controlled trial of lignan supplementation in ninety-two healthy older individuals with a walking program, a daily dose of 543 mg secoisolariciresinol diglucoside (187 mg secoisolariciresinol) plus exercise for six months significantly reduced diastolic blood pressure (-2 mm Hg) in middle-aged hypertensive Canadian men (n=42) but did not in women (n=50), and had no association with systolic blood pressure.[132](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R132) In a Chinese study of seventy-three type 2 diabetics of the same age range who were fed 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for twelve weeks no significant associations with systolic or diastolic blood pressure were observed at this dose.[133](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R133)



[Table 3](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T3/)

**Randomized controlled trials of lignans and blood pressure**

However, in a Japanese double blind crossover placebo controlled study, 60 mg sesamin (in 180 mg wheat germ oil) per day for four 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R134) But among thirty-three overweight Australian men and women with one or more risk factors for metabolic syndrome, fed ∼50 mg per day of sesame lignans in a five week randomized controlled crossover study to determine if the sesame supplement reduced 20-hydroxyeicosatetraenoic acid (20-HETE) (a metabolite of arachidonic acid and a proposed prohypertensive agent in humans), neither systolic nor diastolic blood pressure were lowered. However, the sesame lignan supplementation decreased both plasma and urine 20-HETE significantly, suggesting that lignans may have other cardiovascular disease risk modulating activity.[122](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R122)

**Lipoprotein studies**

As shown in [Table 4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T4/),[131](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R131)-[133](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R133),[135](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R135)-[139](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R139) in the Chinese study of seventy-three diabetics who were fed 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for twelve weeks, no associations with lipid profiles, fasting glucose levels or vascular sensitivity were evident although glycemic control was improved.[133](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R133) When twenty-two healthy Danish postmenopausal women were fed 500 mg secoisolariciresinol diglucoside (172 mg of secoisolariciresinol) per day for six weeks, secoisolariciresinol did not have any significant association with total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) or triglycerides.[135](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R135)



[Table 4](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T4/)

**Randomized controlled trials of lignans and lipoproteins**

In the Canadian study of secoisolariciresinol supplementation (approximately 187 secoisolariciresinol as 543 mg secoisolariciresinol diglucoside per day) and a walking program of ninety-two healthy middle aged adults for twenty-six weeks, HDL, LDL, total cholesterol, triglycerides and the metabolic syndrome composite score were not significantly affected by lignan supplementation.[132](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R132) However, the administration of secoisolariciresinol diglucoside 600 mg per day (approximately 206 mg secoisolariciresinol) in a Chinese randomized double blind placebo controlled trial[136](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R136) of fifty-five hypercholesterolemic adults significantly reduced total and LDL over eight weeks. Triglycerides were reduced but not significantly and HDL was not affected. When eleven perimenopausal United States (US) women with mild hyperlipidemia took 200 mg secoisolariciresinol diglucoside per day (approximately 69 mg secoisolariciresinol) for fourteen weeks, LDL, total cholesterol and lipoprotein (a) were reduced.[137](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R137) When all these data[132](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R132),[133](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R133),[135](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R135)-[137](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R137) were pooled in a meta-analysis,[131](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R131) total and LDL were significantly reduced, although type of intervention, sex and initial lipid values affected the observed associations. The authors concluded that the association of flaxseed or lignan interventions on blood lipids subjects was suggestive but remained unclear and required further evaluation.[131](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R131)

**Other cardiovascular risk factors**

As shown in [Table 5](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T5/),[132](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R132),[137](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R137),[139](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R139)-[141](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R141) In a randomized placebo controlled Japanese trial,[138](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R138) 65 mg per day of sesamin significantly reduced total and LDL and apolipoprotein B in twelve hypercholesterolemic adults over eight weeks although HDL and triglycerides were not affected. However, Wu et al's Australian study[139](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R139)of thirty-three overweight adults using ∼50 mg per day sesamin (39.5 mg sesamin and 12.2 mg sesamolin in 26.2 g sesame seeds) for five weeks had no association with any lipids or C-reactive protein but did lower F2-isoprostanes. It is possible that 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.



[Table 5](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T5/)

**Randomized controlled trials of lignans and other cardiovascular risk factors**

Five hundred mg secoisolariciresinol diglucoside (172 mg secoisolariciresinol) per day for six weeks blunted a rise in C-reactive protein in twenty-two Danish women, which was evident in controls.[140](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R140) Pan et al[141](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R141) found that 360 mg secoisolariciresinol diglucoside (124 mg secoisolariciresinol) per day for twelve weeks significantly decreased C-reactive protein in sixty-four type 2 diabetic patients, particularly women (n=39). Marblestone[137](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R137) found 69 mg secoisolariciresinol per day for fourteen weeks reduced C-reactive protein in eleven perimenopausal women with mild hyperlipidemia.

Overall it appears that, in sufficient doses, secoisolariciresinol and sesamin may reduce risk factors of cardiovascular disease. However, the studies to date have 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 high enough in lignan content and have trial durations that are long enough to be expected to demonstrate beneficial associations.

**Observational studies: Lignan intake**

There are significant challenges in measuring lignan intakes, including the incompleteness of food tables, the failure to measure all 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T6/) shows that the evidence for a cardiovascular benefit from dietary lignan intake in existing epidemiological studies is mixed.[66](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R66),[72](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R72),[75](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R75),[76](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76),[142](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R142)-[145](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R145) We found 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76) assessed lignan intakes in Dutch elderly men and followed them for cardiovascular disease mortality over 15 years. The rate ratios [and 95% confidence interval (CI)] per 1-SD (standard deviation) difference in matairesinol intake (which is metabolized directly to enterolactone) were 0.72 (0.53, 0.98) for coronary heart disease mortality and 0.83 (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.



[Table 6](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T6/)

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

In the Dutch EPIC cohort study[66](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R66) of women who were followed for a median of 6.25 years, lignan intakes (matairesinol and secoisolariciresinol) of approximately 1100 μg/day were not associated with CVD disease risk. However, increasing lignan intake was associated with lower CHD risk but only among smokers. Relationships with individual lignans were not reported in that study.[66](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R66)

Supporting Milder et al's findings,[76](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76) Pellegrini et al[75](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R75) also found greater matairesinol intakes were significantly associated with increased flow mediated dilatation in older Italian men and women but 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R72),[76](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76),[142](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R142) In a cross-sectional study of postmenopausal women in the US, lignan intake was associated with a borderline, non-statistically significant association with lower diastolic or systolic blood pressure.[72](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R72) 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 (albeit levels of 750 μg) of two lignans (matairesinol and secoisolariciresinol), these findings were not significant.[142](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R142)

Observational studies of the relationship between lignan intake and total cholesterol and its subfractions are mixed. Two observational studies[72](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R72),[143](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R143) of Dutch and US women had no significant association with LDL, HDL or total cholesterol, but a third observational study[144](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R144)of US men found that lignan intake was associated significantly with increased LDL and apolipoprotein B and nonsignificantly with increased total cholesterol. This same study found that lignan intake was significantly associated with lower C-peptide.[144](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R144) In the cross-sectional study in Framingham, Massachusetts (USA), postmenopausal women with greater intake of lignans had a lower fasting triglyceride concentration.[72](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R72)

In regard to markers of vascular function, in addition to the aforementioned study of flow mediated dilatation,[75](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R75) a Dutch study[145](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R145) found lignan intake non-significantly associated with reduced aortic stiffness in all postmenopausal women but significantly associated with reduced aortic stiffness in the subset of women 20 to 30 years beyond menopause. Kreijkamp-Kasper et al's study[142](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R142) 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 prospective cohort[76](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76) and the Pellegrini et al cross-sectional vascular[75](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R75)studies, 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 occurs 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/100g white wine or 74-98 mg/100g 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R146) 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 caution in interpreting studies of a single measure of either biomarker in relation to disease outcome.[60](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R60),[78](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R78) It may be useful to keep in mind that it has been suggested that levels of enterolactone above 30 nmol/l or higher are protective, and levels below 15 nmol/l are too low to confer protections. Upper levels of enterolactone from diet appear to be 90-100 nmol/l, however variations in levels are high.[147](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R147),[148](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R148) [Table 7](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T7/) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R149)-[153](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R153) In most of the studies in [Table 7](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T7/), the highest quartiles and quintiles approached or were in the putative protective range.



[Table 7](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/table/T7/)

**Serum and plasma enterolactone (and enterodiol) and cardiovascular disease risk**

In a cohort study of 1889 Finnish men who were followed for an average of 12.2 years, Vanharanta et al[149](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R149) found 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R149)

In a nested case-control study of healthy Finnish men where 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 lowest quartile (<7.21 nmol/L).[150](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R150) In another Finnish study among men, where 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 vs 18.1 nmol/L) when adjusted for classic risk factors.[151](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R151) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R152)

Two Finnish nested case-control studies[149](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R149),[150](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R150) of blood pressure noted significant inverse associations with plasma enterolactone, where as in a third Finnish study[151](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R151) and a Dutch study[152](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R152) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R152) In a cross-sectional Finnish study, high enterolactone levels were associated with reduced F2-isoprostanes, a marker of lipid peroxidation.[153](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R153) The weak correlations between serum enterolactone and cardiovascular disease outcomes make it difficult to draw conclusions from those studies.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**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 the lignan intake were of women, whereas all but one of the enterolactone studies were of men. Because associations with lignans may vary by sex, 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.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R154) and a recent review[155](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R155) found that lignin did not lower lipids. However, several observational studies examining lignin and cancer risk found reduced risk of colorectal[156](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R156),[157](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R157) oral, pharyngeal and esophageal[158](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R158) cancers but not with breast,[159](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R159) ovarian,[160](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R160) and renal[161](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R161) cancers.

Dietary fiber may be responsible in part for associations observed with lignan intake. Dietary fiber,[162](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R162)-[166](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R166) particularly soluble fiber,[164](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R164),[167](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R167)-[169](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R169) reduces risk of cardiovascular disease. Dietary fiber lowers blood pressure,[170](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R170),[171](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R171) decreases C-reactive protein levels,[172](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R172)-[176](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R176)decreases metabolic syndrome[177](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R177)-[179](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R179) and decreases insulin resistance.[180](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R180) Although some studies indicate dietary fiber has weak lipid lowering associations,[181](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R181),[182](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R182) soluble fiber is more highly associated with lower serum lipids,[183](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R183)-[188](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R188) lower blood pressure[189](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R189) and fewer symptoms of metabolic syndrome.[190](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R190),[191](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R191)

Cereal fiber consists more of insoluble fibers (lignins) than soluble fibers. Cereal fiber is associated with decreased insulin resistance,[192](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R192) lower serum lipids,[193](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R193) lower blood pressure,[194](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R194),[195](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R195) less progression of coronary atherosclerosis in postmenopausal women with established coronary artery disease,[196](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R196) reduced risk not only of coronary heart disease,[165](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R165),[197](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R197),[198](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R198) but also of cardiovascular disease[199](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R199) and stroke[200](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R200) in many[201](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R201) but not all studies.[164](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R164),[202](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R202),[203](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R203) Insoluble fiber is associated with lower blood pressure,[189](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R189) lower C-reactive protein levels,[176](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R176) lower insulin resistance,[180](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R180) and lower risk of both cardiovascular disease[168](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R168) and myocardial infarction.[164](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R164),[168](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R168)

The studies on lignan intakes and cardiovascular disease risk, which were reviewed earlier in the article,[66](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R66),[72](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R72),[75](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R75),[76](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R76),[142](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R142)-[145](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R145) were adjusted for fiber intakes, but not separately for insoluble and soluble fiber. Thus, the associations with lignan intake described here were over and above those of fiber. In the four epidemiological studies using enterolactone as the marker of lignan intakes, results were mixed.[149](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R149)-[152](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R152) Serum enterolactone was positively correlated with fiber intake in one study[150](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R150) but fiber intake had no consistent association with the risk of acute coronary events. In a second study by the same investigator[149](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R149) energy adjusted fiber intake was associated with enterolactone and explained 6% of its variation. However, in a third study, another group of investigators[151](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R151) found that adjusting for fiber and other dietary factors had little association with results. The fourth study also found fiber intake significantly associated with plasma enterolactone and enterodiol.[152](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/#R152) 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 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 in 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.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**Acknowledgments**

*Funding and support.* This work was supported in part with resources from the United States Department of Agriculture (USDA), Cooperative State Research, Education, and Extension Service grant #2006-35200-17259, the USDA, Agricultural Research Service, under agreement No. 58-1950-7-707, and NIH National Heart, Lung and Blood Institute grant R21HL087217. Any opinions, findings, conclusions or recommendations expressed here are those of the authors and do not necessarily reflect the view of the USDA.

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**Abbreviations**

BMI

body mass index

BP

blood pressure

CI

confidence interval

HDL

high density lipoprotein cholesterol

HR

hazard rate ratio

LDL

low density lipoprotein cholesterol

OR

odds ratio

RR

rate ratio

SD

standard deviation

US or USA

United States of America

USDA

United States Department of Agriculture

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

**Footnotes**

**Conflict of Interest:** None

[Go to:](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951311/)

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