Dietary phytoestrogens and vascular function in postmenopausal women: a cross-sectional study

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Objective **To investigate the effects of low levels of intake of phytoestrogens in Western habitual diet on vascular function.**

Design **A cross-sectional study.**

Setting **A population-based study.**

Participants **A total of 301 postmenopausal women aged 60–75 years living in The Netherlands.**

Determinant **Dietary phytoestrogen intake as assessed using a food frequency questionnaire covering the year prior to enrolment.**

Main outcome measures **Blood pressure, hypertension, endothelial function and ankle brachial index.**

Results **The median isoflavone intake was 0.2 mg in the lowest tertile and 11.4 mg in the highest tertile. Median lignan intake was 0.8 and 2.2 mg, respectively. No associations were found for higher intake of isoflavones, systolic and diastolic blood pressures, ankle–arm blood pressure index, endothelial function or hypertension. For lignans no association was found for ankle–arm blood pressure index or endothelial function, but we did observe lower systolic and diastolic blood pressures and a lower prevalence of hypertension (systolic blood pressure difference T3–T1, −11.2 mmHg, 95% confidence interval = −17.8 to −4.5, *P* for trend = 0.001; diastolic blood pressure difference T3–T1, −3.6 mmHg, 95% confidence interval = −7.8 to 0.6, *P* for trend = 0,08; and prevalence of hypertension, odds ratio T3 versus T1 = 0.41, 95% confidence interval = 0.22–0.76, *P* for trend over tertiles = 0.004).**

Conclusion **The results of this study suggest a protective effect of dietary lignan intake on blood pressure and hypertension, even at low levels. *J Hypertens* 22: 1381–1388 © 2004 Lippincott Williams & Wilkins.**

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Keywords: diet, phytoestrogens, lignans, isoflavones, blood pressure, endothelial function

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Introduction

Phytoestrogens are estrogen-like compounds naturally occurring in plants such as soy, beans and peas, fruits, vegetables, nuts and grains. Phytoestrogens bind to the estrogen receptor and can act both as an agonist and an antagonist. Because phytoestrogens have highest affinity for the estrogen receptor β and less for estrogen receptor α [1,2] phytoestrogens have little influence on endometrial and mammary tissue [3], and research has suggested a protective role on breast cancer while hormone supplementation therapy increases the risk of breast cancer [4,5]. The two main groups of phytoestrogens are isoflavones and lignans. Isoflavones are predominantly found in soybeans and other legumes. Lignans are found mostly in oil seeds (i.e. flaxseed), whole grains, legumes, vegetables, berries and other fruits [6–9].

A meta-analysis comprising 38 trials has reported a significant lipid-lowering effect of isoflavones from soy [10]. Studies in non-human primates showed positive effects of isoflavones on atherosclerotic plaque formation and on functional measures like endothelium-dependent dilatation [11,12]. The trials on endothelial function published so far are inconclusive, with some finding improvements in endothelial function with isoflavones [13–15], while others do not report any changes [16–19]. These trials were performed supplementing large quantities of isoflavones for a limited period of time. Lignans have less frequently been studied in trials but they are potent antioxidants and have been shown to decrease *in vivo* lipid peroxidation [20]. Furthermore, it was demonstrated that lignans can inhibit the Na^+-K^+-ATP-ase activity through the

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digitalis receptor [21], and can inhibit the blood pressure decrease after mental stress [22]. Reduction of oxidative stress [23] and of vascular superoxide production [24] and a nitric oxide-dependent pathway [25] have been suggested as mechanisms of action.

The long-term effects of low-dose exposure through the habitual diet are largely unknown: a higher dietary soy intake has been reported to be associated with decreased cardiovascular mortality in Japanese women [26], but the consumption of soy and its associated isoflavones is 10-fold to 40-fold higher in Asian countries as compared with Western countries [27,28]. Some studies suggested an improvement of vascular function even in the low range of intake normal for Western countries [29,30]. In an observational study in Finland, high blood levels of lignans were associated with decreased cardiovascular mortality and morbidity [31,32].

The purpose of this cross-sectional study was to investigate whether relatively high habitual phytoestrogen consumption, within the Western diet, results in a better vascular profile as compared with low phytoestrogen consumption in postmenopausal women. As measures of vascular function we used blood pressure, endothelial function and ankle–brachial blood pressure index (ABI).

Subjects and methods

Subjects for this study consisted of 202 women who attended screening and baseline visits for a double blind, randomized, placebo-controlled trial assessing the effect of an intervention with phytoestrogens on bone mineral density, cardiovascular disease risk factors, cognitive function, well-being and physical performance. These 202 women were healthy, aged 60–75 years at baseline in 2000 and living in Utrecht or the surroundings. They complied with the biannual call for participation in a national screening program for breast cancer in the year prior to the start of our study. All had a normal mammogram in the year prior to enrolment. Exclusion criteria were a history of malignant disease, active renal or liver disease, a history of thromboembolism, current estrogen use or estrogen use in the 6 months prior to enrolment, known allergy for soy or milk protein and endometrial thickness over 4 mm. Only the baseline measurements were used in this cross-sectional study. To increase the power of the study, we additionally recruited women from an ongoing cohort study, fulfilling the same inclusion and exclusion criteria as the participants who were recruited via the trial. The ongoing cohort study is one of two Dutch contributions to the European Prospective Study into Nutrition and Cancer, the Prospect-EPIC cohort [33]. This cohort consists of 17 357 women recruited between 1993 and 1997 through the regional breast cancer-screening program. At baseline (1993–1997), women filled in a food frequency questionnaire. Usual phytoestrogen intake was calculated from this questionnaire [34,35]. To assure a wide range of intake levels, there was a relative oversampling of women with a low intake of phytoestrogens. In total, the study population consisted of 301 postmenopausal women, aged 60–75 years.

All women underwent the same measurements, including the administration of a new food frequency questionnaire to calculate the phytoestrogen intake at time of the measurement of our endpoints of interest.

The Institutional Review Board of the University Medical Center Utrecht approved the study protocol and all participants gave written informed consent.

Measurements

General

At the physical examination we measured height, without shoes, to the nearest 0.5 cm and weight to the nearest 0.5 kg. Blood pressure and heart rate were measured with a Critikon Dinamap (Critikon Corporation, Tampa, Florida, USA) at the right arm in sitting position. The Critikon Dinamap was calibrated every 6 months, according to the manufacturer's guidelines. Blood pressure was measured once. Hypertension was defined as systolic blood pressure $\geqslant$ 165 mmHg or diastolic blood pressure $\geqslant$ 95 mmHg in accordance with the guidelines of the Dutch college of general practitioners [36] or an affirmative answer on the question 'are you taking drugs for hypertension?' Also waist circumference, just above the crista iliaca, and hip circumference at the trochanter major (cm) were measured to estimate upper body adiposity. The body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). From the health questionnaire we obtained information about age at menarche, age at menopause, history of oral contraceptive use, use of hormone replacement therapy, cholesterol lowering and antihypertensive medication and smoking history. Physical activity was determined through the validated Questionnaire on Mobility in Elderly [37].

Ankle–brachial index

Measurements were performed in a supine position. Systolic blood pressure at the dorsal pedic artery and the posterior tibial artery was measured using a Doppler device. Blood pressure of both arms was assessed with a Critikon Dynamap. For each leg the higher of the two pressures was divided by the mean systolic pressure of both arms [38]. The left and right ABI were summed and divided by two to calculate the mean ABI. Peripheral arterial disease is generally defined as an ABI lower than 0.9.

Brachial endothelial function

Endothelial function was measured with B-mode ultrasound imaging of the brachial artery assessing the increase in the artery diameter during reactive hyperemia (with increased flow leading to endothelium-dependent dilatation as detailed elsewhere) [39,40]

In short, with the participants in a supine position, a pediatric blood pressure cuff was positioned around the right forearm just below the elbow and electrocardiogram electrodes were placed. Blood pressure was measured. Participants were instructed not to talk during the measurements. With an ultrasound probe (7.5 MHz; Acuson Aspen, Mountain View, California, USA) the brachial artery was visualized. When a satisfactory longitudinal image of the brachial artery was obtained, the position of the transducer was secured. Three B-mode images showing the lumen diameter were frozen on the R-wave of the electrocardiogram for off-line measurement of the 'baseline' lumen diameter. Subsequently, the blood pressure cuff was inflated up to 50 mmHg above the participant's systolic blood pressure. After 4 min the cuff was deflated.

During the subsequent phase of reactive hyperemia, the image of the brachial artery was recorded every 15 s for 5 min. The images were digitized and subsequently analyzed with dedicated software [41]. The dilatation was measured as an increase in diameter relative to the baseline diameter. According to the formula (maximum diameter during reactive hyperemia − mean diameter)/mean diameter × 100, this gives the percentage change in diameter during the reactive hyperemia. One person, blinded to the intake levels, performed all the analyses and a random sample of 10% was analyzed twice to assess reproducibility of the analyses. The Spearman correlation coefficient for repeated analyses was 0.81.

Dietary measurements

The Food Frequency Questionnaire (FFQ) used in this study [42] was slightly modified to capture dietary estrogen intake. The two-step dietary assessment comprised a simple self-administered questionnaire, followed by a structured interview with trained dieticians.

From the FFQ we calculated the average intake of alcohol, saturated fat, mono-unsaturated fat, polyunsaturated fat, fiber, fruit, vegetable and vitamin C using national Dutch food composition data. Phytoestrogen intake was calculated as follows. Through medical (Medline, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) and agricultural (Agricola, http://agricola.nal.usda.gov/) scientific literature and contacts with several experts in the field of phytoestrogens, we retrieved laboratory analysis data for the phytoestrogen content of food items. We searched for data on measurements of the phytoestrogens daidzein, genistein, formononetin, biochanin A, matairesinol and secoisolariciresinol in foods. Subsequently, phytoestrogen intake was scored as described in detail previously [27]. Briefly, we calculated and assigned, for each food item in the FFQ, values for the isoflavones daidzein, genistein, formononetin and biochanin A, and for the lignans matairesinol and secoisolariciresinol. Each phytoestrogen content of a food item was then scored in seven categories. We multiplied the score of each food item by the daily consumption of that food (g) and then summed across foods to get the total individual intake of each phytoestrogen.

All nutrient values were adjusted for total energy intake by means of the regression residual method [43].

Data analysis

The energy-adjusted dietary intake of total phytoestrogens, lignans and isoflavones was divided into tertiles. Because of the skewed distribution of isoflavone and lignan intake we report the median and interquartile range per tertile of intake. We evaluated the relation between isoflavone and lignan intake and our endpoints (i.e. systolic and diastolic blood pressure, endothelial function and ABI) using linear regression, after adjusting for potential confounders. Potential confounders considered in the regression model were age (years), cholesterol lowering medication (yes/no), use of antihypertensives (yes/no), BMI (kg/m^2), waist/hip ratio, smoking (no/past/current), physical activity (Voorrips score), and time postmenopausal (years). In the limited model we adjusted only for those factors that, in our study population, were related to both phytoestrogen intake and the endpoints of our study, resulting in a model including age, years postmenopausal and BMI. In the full model we included all potential confounders and several dietary parameters namely: total energy intake (kJ/day), alcohol intake (g/day), saturated fat (g/day), mono-unsaturated fat (g/day), polyunsaturated fat (g/day), fiber intake (g/day), fruit intake (g/day), vegetable intake (g/day) and vitamin C intake (mg/day). In the analyses of systolic and diastolic blood pressures, women using blood pressure-lowering medication ($n = 73$) were excluded. Logistic regression models were used to investigate the association between lignan and isoflavone intake and hypertension.

To control for the effect baseline arterial diameter may have on endothelial function, we performed analyses with baseline diameter as a covariate and absolute increase in diameter as a dependent variable.

The associations of vascular functions with isoflavones and lignans were also investigated in the following predetermined subgroups; ever smokers/never smokers, BMI $\leqslant 25$/BMI > 25 and short ($\leqslant 17$ years)/long (> 17 years) menopausal. To test statistical significance of the

subgroup effects, multiplicative interaction terms of phytoestrogen intake with smoking, BMI and menopause, respectively, were added to the regression model.

Results

General characteristics and dietary characteristics of the study population are presented in Tables 1 and 2, respectively.

The median intake of isoflavones in the lowest tertile was 0.2 mg/day and in the highest tertile was 11.4 mg/day. For lignans the median intake was 0.8 and 2.2 mg/day, respectively (see Table 3). The women with high isoflavone intake were somewhat younger and more physically active, consumed more vegetables and fruits, and used somewhat more alcohol.

Table 1 Population characteristics of 301 women aged 60–75 years

Characteristic	Mean	Standard deviation
Age (years)	66.6	4.5
Body mass index (kg/cm^2)	26.5	4.0
Waist-to-hip ratio	0.8	0.1
Years postmenopausal (years)	17.9	7.1
Total cholesterol (mmol/l)	6.2	1.0
Fasting glucose (mmol/l)	5.6	1.3
Fasting insulin (mmol/l)	9.9	8.0
Physical activity (Voorrips score)	14.7	8.1
Systolic blood pressure (mmHg)	145.6	21.7
Diastolic blood pressure (mmHg)	77.6	13.8
Endothelial function (FMD%)	4.6	4.2
Ankle–brachial index (mmHg/mmHg)	1.17	0.12
	n	%
Smoking		
Current	54	17.9
Past	97	32.2
Cholesterol-lowering medication	45	15.0
Antihypertensive medication	73	24.3
Hypertension[a]	113	37.5

FMD, flow mediated dilatation. [a]Hypertension defined as systolic blood pressure $\geqslant$ 165 mmHg or diastolic blood pressure $\geqslant$ 95 mmHg or self-reported use of medication for hypertension.

Table 2 Dietary characteristics of 301 women aged 60–75 years

Characteristic	Mean	Standard deviation
Energy (kcal/day)	2037.1	450.8
Protein (g/day)	94.8	24.0
Plant protein (g/day)	36.6	11.5
Total fat (g/day)	75.2	23.6
Saturated fat (g/day)	31.1	11.3
Mono-unsaturated fat (g/day)	27.4	9.3
Polyunsaturated fat (g/day)	16.1	6.5
Dietary fiber (g/day)	34.8	10.6
Vitamin C (mg/day)	133.2	62.7
Alcohol (g/day)	9.2	10.7
Fruit (g/day)	289.6	172.0
Vegetables (g/day)	222.6	102.7

Table 3 Daily dietary intake of phytoestrogens by tertiles of isoflavones and lignans

Intake	Median intake[a] (mg/day)	25–75% range
Isoflavone		
Low isoflavone tertile	0.20	0.15–0.24
Middle isoflavone tertile	0.76	0.40–1.77
High isoflavone tertile	11.43	7.59–19.63
Lignan		
Low lignan tertile	0.75	0.53–1.14
Middle lignan tertile	1.63	1.51–1.74
High lignan tertile	2.21	2.02–2.53

[a]Energy-adjusted.

No associations were found for systolic and diastolic blood pressures, ABI, endothelial function or hypertension and higher intake of isoflavones (Table 4). For lignans no association was found for ABI or endothelial function, but we did observe a lower systolic blood pressure and diastolic blood pressure, and a lower prevalence of hypertension in the limited model [difference between third versus first tertile, −11.2 mmHg (95% confidence interval, −17.8 to −4.5; P for trend = 0.001) and −3.6 mmHg (95% confidence interval, −7.8 to 0.6; P for trend = 0.08)] for systolic and diastolic blood pressures, respectively, and an odds ratio for the third versus first tertile of 0.41 (95% confidence interval, 0.22–0.76; P for trend = 0.004) for the prevalence of hypertension (Table 5). In the full model the estimates remained comparable with the limited model (systolic blood pressure difference low–high intake, −7.8 mmHg; diastolic blood pressure, −5.2 mmHg; and prevalence of hypertension, odds ratio = 0.49), but the difference did not reach statistical significance anymore. Analysis of variance with BMI, smoking and postmenopausal years showed no significant interaction.

Discussion

This study did not show a relation between high habitual dietary isoflavone intake and several parameters of vascular function. However, dietary lignan intake was related to lower blood pressure and a lower prevalence of hypertension.

To appreciate the results of our study some strengths and limitations have to be addressed. Although this study had an observational design, with the resulting potential for confounding, we were able to consider and, when necessary, adjust for important cardiovascular risk factors, as well as differences in dietary factors.

In the analysis of our data we adjusted in two steps. First, in a limited model with the factors that in our study population were related to both the exposure and the endpoints. Because lignan or isoflavone intake might be related to other dietary factors, especially

Table 4 Multiple adjusted differences between the lowest and highest tertiles of isoflavone intake

Characteristic	Difference[a]	*P* value	95% confidence interval	*P* trend
Systolic blood pressure (mmHg)[b]				
Crude	−7.38	0.03	−14.06 to −0.70	0.03
Limited model[a]	−5.66	0.11	−12.51 to 1.20	0.10
Full model[c]	−1.72	0.66	−9.36 to 5.93	0.58
Diastolic blood pressure (mmHg)[b]				
Crude	−1.72	0.41	−5.82 to 2.39	0.37
Limited model[a]	−0.87	0.69	−5.13 to 3.39	0.63
Full model[c]	1.03	0.67	−3.75 to 5.81	0.80
Ankle brachial index				
Crude	−0.01	0.78	−0.04 to 0.03	0.85
Limited model[a]	−0.01	0.75	−0.04 to 0.03	0.81
Full model[c]	−0.01	0.74	−0.05 to 0.03	0.75
Endothelial function (FMD%)				
Crude	0.84	0.20	−0.44 to 2.12	0.21
Limited model[a]	0.85	0.22	−0.50 to 2.19	0.23
Full model[c]	1.13	0.16	−0.45 to 2.71	0.16
Endothelial function (pimax)				
Crude	0.03	0.23	−0.02 to 0.07	0.24
Limited model[a]	0.03	0.19	−0.02 to 0.08	0.20
Full model[c]	0.04	0.17	−0.02 to 0.09	0.17
Hypertension (odds ratio)				
Crude	0.50	0.02	0.28−0.88	0.01
Limited model[a]	0.57	0.07	0.31−1.05	0.05
Full model[c]	0.56	0.13	0.26−1.19	0.09

FMD, flow mediated dilatation. [a]Adjusted for age (years), body mass index (BMI) (kg/m^2), and time postmenopausal (years). [b]Excluding women using blood pressure-lowering medication (n = 73). [c]Adjusted for age (years), cholesterol lowering medication (yes/no), use of antihypertensives (yes/no), BMI (kg/m^2), waist/hip ratio, smoking (no/past/current), physical activity (Voorrips score), total energy intake (kJ/day), alcohol intake (g/day), saturated fat (g/day), mono-unsaturated fat (g/day), polyunsaturated fat (g/day), time postmenopausal (years), fiber intake (g/day), fruit intake (g/day), vegetable intake (g/day) and vitamin C intake (mg/day).

Table 5 Multiple adjusted differences between the lowest and highest tertile of lignan intake

Characteristic	Difference[a]	*P* value	95% confidence interval	*P* trend
Systolic blood pressure (mmHg)[b]				
Crude	−12.44	0.00	−18.99 to −5.88	0.00
Limited model[a]	−11.15	0.00	−17.81 to −4.49	0.00
Full model[c]	−7.92	0.12	−17.91 to 2.07	0.12
Diastolic blood pressure (mmHg)[b]				
Crude	−4.44	0.03	−8.52 to −0.35	0.03
Limited model[a]	−3.64	0.09	−7.83 to 0.55	0.08
Full model[c]	−5.19	0.10	−11.41 to 1.03	0.07
Ankle brachial index				
Crude	0.00	0.88	−0.03 to 0.04	0.88
Limited model[a]	0.01	0.65	−0.03 to 0.04	0.66
Full model[c]	0.01	0.61	−0.04 to 0.07	0.60
Endothelial function (FMD%)				
Crude	0.29	0.65	−0.98 to 1.56	0.65
Limited model[a]	0.28	0.67	−1.02 to 1.59	0.67
Full model[c]	0.09	0.93	−1.93 to 2.12	0.92
Endothelial function (pimax)				
Crude	0.00	0.98	−0.04 to 0.05	0.98
Limited model[a]	0.00	0.89	−0.04 to 0.05	0.89
Full model[c]	−0.01	0.78	−0.08 to 0.06	0.80
Hypertension (odds ratio)				
Crude	0.37	0.00	0.21 to 0.67	0.00
Limited model[a]	0.41	0.00	0.22 to 0.76	0.00
Full model[c]	0.49	0.15	0.18 to 1.29	0.15

FMD, flow mediated dilatation. [a]Adjusted for age (years), body mass index (BMI) (kg/m^2), and time postmenopausal (years). [b]Excluding women using blood pressure-lowering medication (n = 73). [c]Adjusted for age (years), cholesterol lowering medication (yes/no), use of antihypertensives (yes/no), BMI (kg/m^2), waist/hip ratio, smoking (no/past/current), physical activity (Voorrips score), total energy intake (kJ/day), alcohol intake (g/day), saturated fat (g/day), mono-unsaturated fat (g/day), polyunsaturated fat (g/day), time postmenopausal (years), fiber intake (g/day), fruit intake (g/day), vegetable intake (g/day) and vitamin C intake (mg/day).

vegetables, fruits or fiber, and the risk of confounding by other lifestyle factors that is always present in observational studies, we also used a full model including many dietary and lifestyle factors; namely, age, BMI, waist/hip ratio, smoking, physical activity, years postmenopausal, total energy intake, intake of alcohol, saturated fat, mono-unsaturated fat, polyunsaturated fat, fruit, vegetable and vitamin C. The full model allows us to control for confounding caused by dietary and lifestyle but carries the risk of overcorrection as some factors might be in the causal pathway; for example, lignan intake is strongly related to fruit and vegetable intake. Furthermore, it reduces the power to detect a relation. In this study, the magnitude of the estimates remained the same, but the precision decreased. Therefore it is unlikely that the estimates found with the limited model are biased by lifestyle or dietary factors However, in observational research, we can never entirely rule out the possibility that some other unmeasured factor might have biased the results. Exposure was measured using a FFQ comprising the year prior to enrolment. This allowed us to capture both frequently and infrequently consumed items. Using several-day diaries or 24-h recall interviews, although more precise, would have caused serious misclassification of these infrequently consumed items. Biomarkers like urinary excretion or plasma levels would provide a more objective alternative, not depending on the recall of participants, but biomarkers reflect phytoestrogen intake for only 24 h prior to collection of the sample [44].

Bias during data collection is always a concern, but women participating in the study were not informed of the study hypothesis and the subgroup with low phytoestrogen intake was not aware of this selection criterion. Furthermore, the reader of the flow-mediated dilatation images was blinded for the exposure and measurements of blood pressure, and ABI was measured before actual phytoestrogen intake was calculated.

Epidemiological studies collecting blood pressure data often prefer automated oscillometric methods over manual methods involving sphygmomanometry. Inaccuracy may arise from random error, systematic error, or both. Systematic error, which may be of great importance in clinical situations involving monitoring of acutely ill patients or treatment decisions for patients with hypertension, may be less critical in epidemiologic studies in that regression coefficients may not be much affected if heteroscedasticity is not present. Random error and observer bias may matter more in epidemiologic studies. The use of an automated device allowed us to remove observer bias [45]. The device we used for blood pressure measurements has been shown to yield valid results in epidemiological surveys [46,47].

After the menopause, the vascular function changes, brachial endothelial function and arterial compliance decrease, and blood pressure increases. Animal research showed that in non-human primates soy isoflavones are also capable of improving endothelial function and decreasing atherosclerotic plaque formation [11,12], and several trials in humans and cross-sectional studies found an improvement in vascular function [30,48]. A large trial, in which 60 postmenopausal women treated with genistein (54 mg/day) or placebo for 6 months, showed a significant improvement in brachial endothelial function [13]. Several other, smaller, trials did not find an effect on brachial endothelial function [16,17,49,50]. The assessment of endothelial function using flow-mediated dilatation is a complex task. Many physiological factors influence endothelial function causing large variability [51]. The lack of an effect in our study could be caused by higher variability in the measurement of endothelial function than anticipated. On the other hand, levels of phytoestrogens in an experimental setting are several fold higher than the habitual intake in our study population. Further studies have to be awaited to reveal the true nature of this relation.

Data regarding blood pressure focused on absolute values of blood pressure, while we also looked at the prevalence of hypertension because it allowed us to include participants using antihypertensive medication. In several rat studies isoflavones exerted a blood pressure-lowering effect [52,53], which was confirmed in human trials. A trial comparing soy milk with cow milk found a reduction in diastolic blood pressure of 15.9 mmHg in the soy group as compared with a 3.7 mmHg reduction in the placebo group. In this trial both men and women participated [54]. Two trials with an isolated soy protein supplement containing isoflavones in perimenopausal women [55] and in men and women combined [18] also found a significant decrease in blood pressure. Two cross-sectional studies looking at habitual dietary intake of phytoestrogen in Western women found no relation between blood pressure and phytoestrogen intake [29,48]. However, only one of these studies looked at lignan intake, and the median lignan intake in this study was only 0.58 mg/day [56], while in our study for the lowest tertile of lignan intake the median intake (0.75 mg/day) already exceeded this level. When we included all participants we found a lower prevalence of hypertension with higher lignan intake. Our findings suggest that within the Western dietary pattern lignans are at least as important as isoflavones. This might be related to the fact that sources of isoflavones, like soy products, tend to be consumed infrequently, on a weekly or even monthly basis, while sources of lignans, oil seeds (i.e. flaxseed), whole grains, legumes, vegetables, berries and other fruits are consumed much more frequently, leading to a more continuous exposure.

With respect to ABI, as far as we know, this study is the first to look at this in relation to estrogens or phytoestrogens. In ovariectomized monkeys, phytoestrogens were found to reduce atherosclerotic plaque formation [11], the main cause of impaired ABI, and a cross-sectional study in postmenopausal women revealed an association between aortic stiffness and dietary phytoestrogen intake [30]. We did not find any effect of dietary phytoestrogen intake on ABI, suggesting that levels of phytoestrogen in the habitual Western diet are not capable of diminishing the amount of arteriosclerosis in peripheral arteries. On the other hand, it is possible that ABI was not sensitive enough to detect smaller differences in arteriosclerosis in our relatively healthy population. Only four women in our study had an abnormal ABI (< 0.9) indicative of peripheral arterial disease.

In conclusion, the results of this study suggest a protective effect of dietary lignan intake on blood pressure and hypertension, even at low levels of intake. No association between dietary intake of isoflavones and vascular function was found. The exact role of lignans within the array of phytoestrogens offers a promising subject for further research.

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