Higher Dietary Intake of Lignans Is Associated with Better Cognitive Performance in Postmenopausal Women[1]

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ABSTRACT Data on the relation between phytoestrogens and cognitive function are still sparse. The purpose of this study was to examine the relation between the dietary intake of phytoestrogens and cognitive function in healthy postmenopausal women consuming a Western diet. We conducted a community-based survey among 394 postmenopausal women. Isoflavone and lignan intake was calculated from a validated FFQ. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE). Data were analyzed using logistic regression with intact cognitive function defined as a score ≥ 26 as the outcome variable. After adjustment for confounders, increasing dietary lignans intake was associated with better performance on the MMSE [OR and (95%CI): 1.49 (0.94–2.38)]. Results were most pronounced in women who were 20–30 y postmenopausal [2.02 (1.11–3.71)]. Isoflavone intake was not related to cognitive function. From our results we conclude that higher dietary intake of lignans is associated with better cognitive function in postmenopausal women. J. Nutr. 135: 1190–1195, 2005.

KEY WORDS: • *diet* • *lignans* • *global cognitive performance* • *postmenopausal women*

Estrogen receptors have been found in the central nervous system, suggesting a role for estrogens in cognitive function (1,2). This finding stimulated studies that showed a positive effect of estrogen replacement therapy (ERT)[3] on memory, executive functioning, and risk of Alzheimer's disease (3,4). However, ERT is not innocuous and its use has been related to increased risk of breast cancer, recurrent vaginal bleeding (5), and lately also increased risk of cardiovascular disease (6).

There is growing literature that diet is involved in the development of Alzheimer's disease, for which cognitive decline is often considered part of the road (7–12) This has promoted the interest in the effects of phytoestrogens, dietary components that may share the benefits of estrogens, but not the risks (13).

Phytoestrogens are natural compounds found in plants, with a diphenolic structure similar to that of natural and synthetic estrogens (14). There are 3 major categories of phytoestrogens: isoflavones, lignans (as found in plant food and as produced by intestinal microflora), and coumestans (15,16). Isoflavones, like genistein, daidzein, and formononetin, are found especially in soy products, beans, peas, nuts, tea, and coffee. The main dietary sources of lignans are oilseeds, linseeds, broccoli, and berries. Coumestans are found mainly in alfalfa and broccoli (15,16) The 3 major types of phytoestrogens are all considered agonists of estrogen receptors, especially the β form, and may thus mimic the effects of estrogens (17).

A recent study suggested that isoflavones may indeed positively affect cognition without substantial side effects (18). However, data on the relation between phytoestrogens and cognitive function are still sparse and far from sufficient to become conclusive.

The aim of this study was to quantify the effect of lignans and isoflavones within the range of intake typical for Western diets on cognitive performance in postmenopausal women.

METHODS

Participants. The selection process of the study population is illustrated by a flowchart (**Fig. 1**). Participants were recruited from the PROSPECT study, which is 1 of the 2 Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) (19). In PROSPECT, a total of 17,357 healthy women, participants in a breast-cancer screening program, 49–70 y old and living in Utrecht and the surrounding areas, were enrolled between 1993 and 1997. The main objective of the PROSPECT-EPIC study was to assess the relation between nutrition and cancer and other chronic diseases. For the present study 2 groups of women, who had experienced a natural menopause either between 1987 and 1989 or between 1969 and 1979, were selected from the baseline data of PROSPECT. In addition, selected women had an intact uterus and

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[3] Abbreviations used: EPIC, European Prospective Investigation into Cancer and Nutrition; ERT, estrogen replacement therapy; MMSE, Mini-Mental State Examination.

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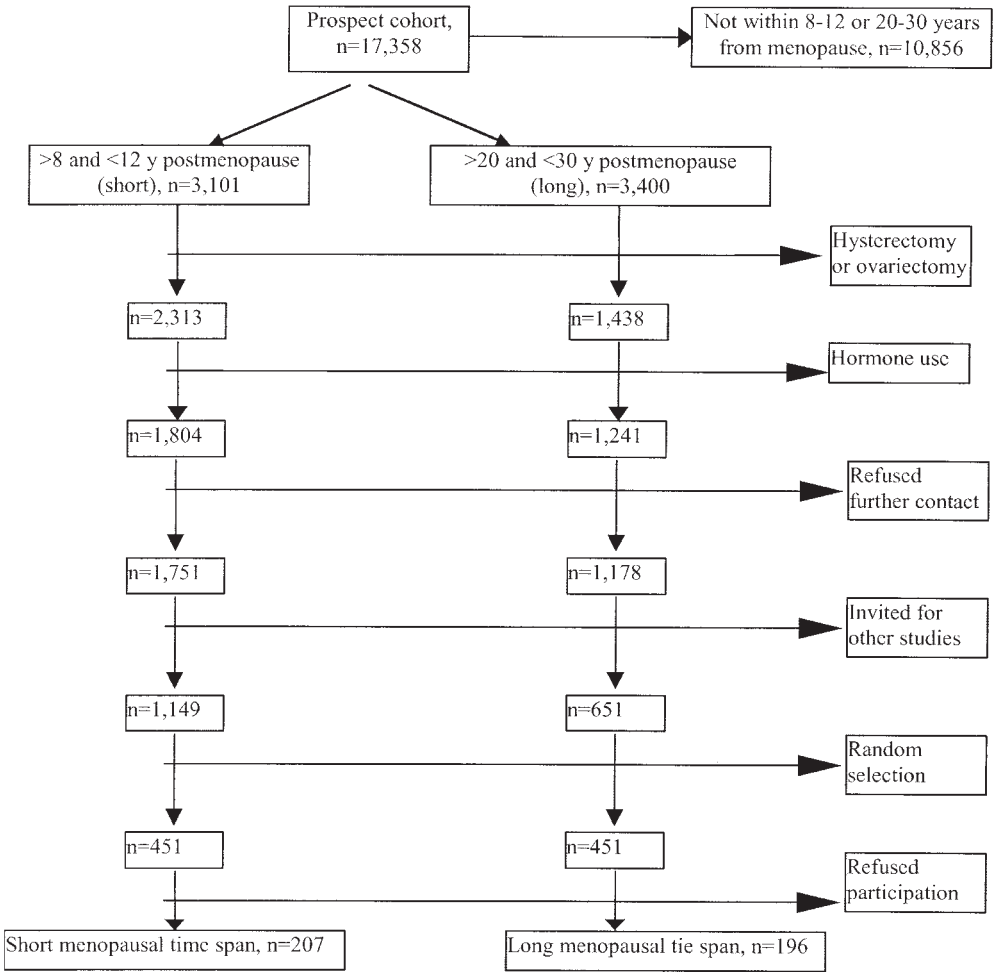

FIGURE 1 Flowchart of participant selection.

at least 1 intact ovary and had not used hormonal replacement therapy after the reported date of last menstruation. These criteria were used because the primary aim of the present study was to elucidate the role of endogenous estrogens on markers of frailty and to determine whether such a role was different for women with different menopausal time span. We compared women with longer menopausal time span (20–30 y) to women with a shorter menopausal time span (8–12 y). These time spans were arbitrarily chosen with a view to contrast the age distribution of the study population. Through personal invitation letters, 902 (451 short time span and 451 long time span) of 1803 (1149 short time span, 653 long time span) were invited, of whom 553 (61%) answered positively. The aim of the present study was to enroll, of these 553 women, 2 random samples of around 200 women: a group with shorter and a group with longer time span since menopause. Eventually, 403 participants were included in the study, 207 with shorter time span since menopause and 196 with a longer time span. Women were considered sufficiently healthy to participate when they were physically and mentally able to visit the study center independently. Each participant underwent all tests and assessments during 2 visits to the study center. The Institutional Review Board of the University Medical Center Utrecht approved the present study. Written informed consent was obtained from all participants. Data collection took place between September 1999 and March 2000.

FFQ and scoring of phytoestrogen intake. At the baseline visit of the PROSPECT study, a validated FFQ was given. This questionnaire was designed to estimate regular intake of 178 food items in the year prior to enrollment (20,21). The method used and the guidelines applied for allocating an individual phytoestrogen intake score for each participant have been described in detail elsewhere (15). Briefly, published laboratory analysis data for the phytoestrogen contents of relevant food items were located by conducting a search on the medical (Medline) (22) and agricultural (Agricola) (23) scientific literature, by contacting experts in the field, and by contacting Dutch food manufacturers. Data regarding the isoflavones daidzein, genistein, formononetin, biochanin A, and the plant lignans matairesinol and secoisolariciresinol were grouped into 7 categories according to their exact values (**Table 1**). One section of the FFQ specifically asked about use of soy-based foods. Subsequently, the phytoestrogen score of each food item was multiplied by its consumption quantity per day per participant. The resulting phytoestrogen score was summed across food items to get a total intake score of each phytoestrogen per each participant per day. We adjusted the dietary intake of all nutrients for total energy intake using the regression residual method (24).

Measurements. Information on health was obtained by taking the medical history, registration of current medication, and physical

TABLE 1

Scoring of phytoestrogen concentration of food items

Phytoestrogens, *mg/100 g wet wt*	Scoring value, *mg/100 g*
Undetectable, 0	0
$0 < * < 0.001$	0.0005
$0.001 \leq * < 0.01$	0.005
$0.01 \leq * < 0.1$	0.05
$0.1 \leq * < 1$	0.5
$1 \leq * < 10$	5
≥10	50

TABLE 2

Characteristics of the women studied[1]

	Short postmenopausal time span (8–12 y)	Long postmenopausal time span (20–30 y)
n	201	193
Age, *y*	63.4 ± 2.1	69.2 ± 2.9
MMSE, *score*	27.03 ± 1.8	26.5 ± 2.1
BMI, *kg/m*[2]	25.9 ± 4.4	26.3 ± 4.3
Smoking, *pack-years*	13.1 ± 16.5	15.3 ± 19.7
Physical activity,[2] *Voorrips score*	14.4 ± 6.9	12.3 ± 6.9
Follow-up time, *mo*	46.4 ± 8.7	46.1 ± 9.1
Duration of fertile life, *mo*	39.4 ± 2.5	32.5 ± 4.1
Glucose, *mmol/L*	5.26 ± 1.11	5.28 ± 1.25
Cholesterol, *mmol/L*	6.36 ± 1.04	6.27 ± 1.01
HDL cholesterol, *mmol/L*	1.53 ± 0.4	1.53 ± 0.4
Estradiol, *pmol/L*	20.8 ± 15.1	19.8 ± 11.6
Mean arterial pressure, *mm Hg*	98.2 ± 14.1	101.9 ± 15.6
Energy intake, *kJ/d*	7527.7 ± 1663	7176.7 ± 1577
Fat intake, *g/d*	71.1 ± 21.9	66.1 ± 18.5
Protein intake, *g/d*	71.1 ± 17.4	68.3 ± 16.1
Dietary fiber, *g/d*	23.9 ± 5.61	22.4 ± 6.08
Alcohol intake, *mg/d*	8.27 ± 10.4	7.59 ± 12.2
Education,[3] *levels*	1.50 ± 0.80	1.47 ± 0.77
Saturated fat, *g/d*	30.6 ± 9.91	29.1 ± 9.25
Monounsaturated fat, *g/d*	26.1 ± 8.51	24.1 ± 6.96
Polyunsaturated fat, *g/d*	13.9 ± 5.38	12.3 ± 4.38
Fish consumption, *g/d*	10.5 ± 10.4	10.9 ± 11.3

[1] Values are means ± SD.
[2] See ref. (25).
[3] Adjusted for educational level [primary; lower vocational; advanced elementary; intermediate vocational; higher general secondary (uncompleted); higher general secondary; (completed); higher vocational; university (uncompleted); university (completed)].

examination. A standardized history of estrogen use, alcohol consumption, and smoking was obtained from all women as part of the medical history. Anthropometric measures included height, weight, and waist and hip circumferences. From these measures, BMI (kg/m^2) and body fat distribution were calculated. Physical activity was assessed using a questionnaire that has shown to be valid in an elderly population (25). Blood pressure and heart rate were measured during the first visit by an oscillometric-automated device (DINAMAP 8,100, Critikon). Measurements were conducted before 1100 h after an overnight fast. After 5 min of rest, blood pressure was taken at the right brachial artery simultaneously with heart rate measurement, twice with the participant in supine position, with 1 min between each measurement. Systolic and diastolic blood pressures were taken as the mean of the 2 measurements. Mean arterial pressure was calculated as diastolic blood pressure + 1/3 × (systolic blood pressure − diastolic blood pressure). Venous blood samples from fasting subjects were obtained between 0800 and 1100 h. Serum total cholesterol, HDL cholesterol, triglyceride, and glucose were reflectometrically measured using commercial enzymatic kits with a Vitros 250 (dry chemistry; Johnson & Johnson). Glucose was measured by the glucose oxidase/peroxidase method. Total cholesterol was measured by adaptation of the cholesterol oxidase/peroxidase method (fixed time). Triglycerides were measured by the lipase/glycerolkinase/GPO/POD method (fixed time). HDL cholesterol was measured after precipitation with dextran sulfate/Mg^{2+}. The LDL cholesterol concentration was estimated using the Friedewald formula (26).

Cognitive function assessment. Participants had a Mini-Mental State Examination (MMSE) at their second visit. The MMSE assesses different areas of cognition with questions and tasks: orientation, registration, attention, calculation, recall, and language. Its score ranges from zero to 30, with 30 indicating maximum cognition. In our study a score ≥ 26 was considered intact cognitive function (27,28). The choice of the cutoff was made prior to the analyses.

Statistical analysis. To analyze the relation between phytoestrogen (lignans and isoflavones) consumption as a continuous variable and cognitive performance we used a logistic regression model where the outcome was intact cognitive functioning. The possibility of a U- (or inverse U) shape relation between phytoestrogen consumption and intact cognitive function was tested by adding quadratic terms to the regression model. Potential confounders were age; age at menopause; duration of fertile life; smoking pack-years; mean arterial pressure; BMI; physical activity score; total energy intake; dietary protein intake; dietary intake of saturated fat; dietary intake of monounsaturated fat; dietary intake of polyunsaturated fat; dietary fiber intake; alcohol intake; fruit intake; vegetable intake; fatty fish intake; glucose levels in serum; serum lipid profile; estradiol levels in serum; level of education; dietary intake of vitamins A, B-6, B-12, C, D, and E; and dietary intake of calcium, iron, β-carotenes, and folate. Because dietary intake of phytoestrogens was calculated from the baseline FFQ of PROSPECT and the MMSE was assessed in the present study a few years later, follow-up time was considered a potential confounder.

In the eventual regression models only those confounders that materially changed the regression coefficients for phytoestrogens intake were included, with the exception of level of education, which was controlled for in all analyses.

The analyses were repeated for phytoestrogen intake, isoflavone intake, and lignan intake in the total population. Because the relative importance of premenopausal estrogens may diminish with age, the analyses were redone in prespecified subgroups of postmenopausal time span (short, 8–12 y since menopause, and long, 20–30 y since menopause). Differences among groups were considered significant at a 2-sided $P < 0.05$. The analyses of the data were performed using the Statistical Package for the Social Sciences version 10 for Windows. Values in the text are means ± SD.

TABLE 3

Dietary phytoestrogen intake by women with short or long postmenopausal time spans

Phytoestrogen intake	All (IQR)	Short postmenopausal time span	Long postmenopausal time span
n	394	201	193
		mg/d	
Total	0.86 (0.51–1.08)	0.8 (0.63–1.11)	0.76 (0.41–1.04)
Isoflavones	0.14 (0.09–0.24)	0.15 (0.09–0.24)	0.13 (0.08–0.22)
Lignans	0.62 (0.32–0.86)	0.71 (0.44–0.91)*	0.52 (0.25–0.77)

[1] Values are medians (IQR).
* Different from women with a long postmenopausal time span, $P < 0.05$.

TABLE 4

Phytoestrogen intake and cognition: results for the women studied

Phytoestrogen intake	OR for intact cognition (95% CI)[1]	OR for intact cognition (95% CI)[2]
	mg/d	
Total phytoestrogens	1.77 (1.22–2.55)	1.59 (0.99–2.58)
Isoflavones	1.29 (0.99–1.67)	1.12 (0.82–1.53)
Lignans	1.55 (1.07–2.24)	1.49 (0.94–2.38)

[1] Crude (unadjusted) OR.
[2] Adjusted for duration of fertile life (mo), dietary intake of saturated fat, dietary intake of monounsaturated fat, dietary intake of polyunsaturated fat, fatty fish intake, energy-adjusted fiber intake, energy-adjusted alcohol intake, and serum levels of estradiol (pmol/L).

RESULTS

Data on dietary intake of phytoestrogens were not available for 3 women. Data on smoking were not available for 5 women. One outlier in serum estradiol level was detected and this record was deleted. This left 394 women for the analysis (201 of the short time span since menopause group and 193 of the long time span since menopause group). The mean age of the total study group was 66.3 y old (SD 3.8 y). The mean age for the group with short postmenopausal time span was 63.5 y old and that for the group with long postmenopausal time span was 69.2 y old. The mean follow-up of the total population was 46.3 mo. Ninety-nine percent of the subjects (389 of 394) were Caucasians, 68% (267 of 394) had only a primary level education, and 5.4% (21 subjects) reached a university level of education (**Table 2**). The mean MMSE score was 26.7 ± 1.9 (SD) and 77% (n = 303) had intact cognitive function (MMSE ≥ 26) (Table 2).

The dietary intake of phytoestrogens for the total study population and for each postmenopausal time span group separately is presented (**Table 3**). In general, the intake of phytoestrogens was low among the study population compared to Asian populations (29–31). Vegetables (mainly peas and beans), breakfast cereals, and bread were the most important food groups contributing to isoflavones, whereas grain products (mainly bread), coffee and tea, and vegetables contributed most to the lignans (32).

Phytoestrogen intake and cognition. The final model in the logistic regression analyses included the following variables: duration of fertile life, dietary intake of saturated fat, dietary intake of monounsaturated fat, dietary intake of polyunsaturated fat, fatty fish intake, educational level, dietary fiber intake, alcohol intake, and serum levels of estradiol. Other variables (nutrients) that have been previously linked with cognition like vitamins E and C and β-carotene did not alter the relation between phytoestrogens (lignans and isoflavones) with cognitive function and therefore they were not included in the final model.

In general, a high intake of phytoestrogens was associated with a higher probability of intact cognitive function, particularly a higher intake of lignans. Contrary to lignan intake, a high dietary intake of isoflavones was not associated with performance on the MMSE (**Table 4**). The relations between phytoestrogens and intact cognition did not differ.

Subgroup analysis. In women with the longer postmenopausal time span, a higher dietary intake of phytoestrogens, and particularly lignans, resulted in a higher MMSE score (**Table 5**). In women with a shorter postmenopausal time span, a high dietary level of lignans did not materially improve the performance on the MMSE. A high dietary intake of isoflavones did not improve the performance on the MMSE in either group (Table 5).

DISCUSSION

The results of this study suggest that a higher dietary intake of phytoestrogens and particularly lignans in Western diets is associated with a better cognitive performance in postmenopausal women. This relation was more pronounced among women with a relatively long postmenopausal time span. Dietary intake of isoflavones showed no association with cognition.

To appreciate the results obtained in this study, some issues must be addressed. This study was performed among a relatively healthy population because women had to be physically and mentally able to visit the study center independently. As a consequence, women with intact cognitive function were probably overrepresented in the present study. Also, women in our study may have had higher than average phytoestrogen intake. Although prevalences of cognitive impairment or high phytoestrogen intake may not be representative, it is not likely that associations are any different between responders and nonresponders (33).

TABLE 5

Phytoestrogen intake and cognition by women with short or long postmenopausal time spans

	Short postmenopausal time span (8–12 y), n = 201		Long postmenopausal time span (20–30 y), n = 193	
Phytoestrogen intake	OR for intact cognition (95% CI)[1]	OR for intact cognition (95% CI)[2]	OR for intact cognition (95% CI)[1]	OR for intact cognition (95% CI)[2]
		mg/d		
Total phytoestrogens	1.31 (0.75–2.31)	1.25 (0.58–2.71)	1.97 (1.97–3.21)	2.16 (1.11–4.21)
Isoflavones	1.31 (0.85–2.03)	1.21 (0.71–2.03)	1.21 (0.89–1.74)	1.14 (0.76–1.71)
Lignans	0.93 (0.48–1.80)	0.93 (0.41–2.15)	1.84 (1.14–2.99)	2.03 (1.11–3.72)

[1] Crude (unadjusted) OR.
[2] Adjusted for duration of fertile life (mo), dietary intake of saturated fat, dietary intake of monounsaturated fat, dietary intake of polyunsaturated fat, fatty fish intake, energy-adjusted fiber intake, energy-adjusted alcohol intake, and serum levels of estradiol (pmol/L).

We used the MMSE test to evaluate cognitive function because it is widely used, it is simple to perform on a large scale, and subjective interpretation can easily be avoided. A cutoff value of 26 was chosen to mark intact cognition because our objective was to determine cognitive function rather than to diagnose dementia. Although on an individual level the MMSE is probably not a very precise test to assess cognitive function, on a population level it adequately reflects the distribution of cognition (34).

The FFQ we used allowed us to quantify the customary dietary intake of phytoestrogens in the previous year. This is important for a study on dietary intake of phytoestrogens because food items containing high amounts of phytoestrogens are more likely to be consumed weekly or monthly and not on a daily basis. Dietary assessment methods such as 24-h dietary recall and food record methods represent a relatively short period of intake and are more difficult to recall. The underlying principle of the FFQ is that a long-term dietary pattern may be more important than the intake of a few days (20,21). By using information from the literature, values for isoflavones and lignans were assigned for each food item in the FFQ. We decided to score the highest value reported in the literature into 7 categories and to use the scores instead of using the exact measurements of phytoestrogen content reported in the literature. By using this method, we avoided the suggestion of a degree of precision for which the reported data in the literature are too limited and too preliminary. In addition, this system decreased the degree of misclassification of our determinant of interest: dietary intake of phytoestrogens.

On the other hand, from a validation study on the FFQ used we concluded that the relative validity for vegetables remains of concern (20). Because dietary phytoestrogens are mainly found in vegetables, some exposure misclassification may have occurred. Because this misclassification is probably independent of our outcome, i.e., cognition, it has most likely resulted in attenuation of the associations observed. Dietary intake of phytoestrogens in our population was low compared to Asian populations, but in agreement with the levels observed in women from other Western populations (32).

We adjusted for other nutrient intake levels like proteins, fruit, fat, and fiber because they might be related to both levels of consumption of phytoestrogens and performance on MMSE. Additional adjustment for alcohol, carbohydrates, and vegetable intake did not change the results. The most important nonnutrient determinants of cognitive function that might confound the association between phytoestrogen intake and cognition were also adjusted. However, as in any observational study, residual confounding due to unmeasured or unknown factors may have affected the results. Further, because the estimation of vitamin E and β-carotene intake with our questionnaire was suboptimal (21), some residual confounding by vitamin E and β-carotene may exist.

Dietary lignans have been suggested to be a proxy for fiber intake. The Pearson correlation coefficient between lignans and fiber in our data was 0.53 ($P < 0.001$). Because it has been shown that correlation between variables up to 0.8 are no problem in regression modeling (35), we took no separate precautions.

A few previous studies investigating the relation between isoflavones and cognition must be discussed. In a clinical trial (18) in which student volunteers were randomly allocated to high-soy and low-soy diet groups, the results showed substantially better cognitive improvement in the high-soy group. However, this study had serious limitations. The number of participants was rather small and the results for both sexes were combined. The most important limitation was that the participants knew which diets they were given. In the KAME study population (36), a longitudinal cohort study of Japanese Americans over 65 y old, high tofu consumers, i.e., with high isoflavone intake, had substantially lower cognitive function scores than low or intermediate consumers, although this was not significant in men or in women who never used ERT. Longitudinally, no associations were observed between tofu consumption and 2-year change in cognitive function score. The Honolulu Asian Ageing Study (37), a large cohort of Japanese American men in Hawaii, also studied spouses of the participants and found an important relation between cognitive impairment and the tofu intake of their husbands. The odds ratios for cognitive impairment comparing the high-intake group with the low-intake group were, depending on the test used, 1.6–2.0. A large placebo-controlled randomized trial among elderly women did not find any change in cognitive performance after 1 y of supplementation (38).

Phytoestrogens were first noted in 1926 to have estrogenic activity (39). Although the isoflavones in particular are known for their estrogenic properties, lignans have also shown estrogenic and antiestrogenic activity, capability of binding to sex hormone binding globulin, inhibition of aromatase, and antioxidant activity (40).

Various mechanisms of action have been proposed for phytoestrogens: they might bind the estrogen receptor, especially the β form, compete with endogenous mammalian estrogens, interfere with the release of gonadotropins, and inhibit aromatase enzyme (15). They may promote vascular health through an antioxidative effect, improve lipid concentration in plasma, diminish thrombus formation, and increase vascular compliance (41). Phytoestrogens may act on cognition through different mechanisms: by increasing vascular compliance, interference with tyrosine-kinase dependent mechanisms, and induction of synaptogenesis in the hippocampus (18). The association between dietary intake of lignans and performance on the MMSE was stronger in women with a longer postmenopausal time span (20–30 y). This association could be affected by some other age-related mechanism because women with a longer postmenopausal time span were older (mean age = 69.2 y) than the women with shorter postmenopausal time span (mean age = 63.5 y). The close relation between age and years since menopause precludes mutual adjustments. An alternative explanation is that the protective effect of endogenous estrogens on the nervous system is dependent on cumulative time of exposure rather than on actual levels of intake.

In summary, the results of the present study provide evidence that higher dietary intake of lignans is associated with better cognitive function in postmenopausal women. This association was not observed for isoflavones.

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