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# Dietary Phytoestrogen Intake and Cognitive Function in Older Women

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***Background.*** Aging is associated with a decline in cognitive function; we explored the possible influence of dietary phytoestrogens on this decline.

***Methods.*** We conducted a cross-sectional study in 301 Dutch women aged 60–75 years. Dietary isoflavone and lignan intake was assessed with a food-frequency questionnaire covering habitual diet in the year preceding enrolment. The endpoints were cognitive function measured in three domains: memory, processing capacity and speed, and executive function. Data were analyzed using linear regression models, after adjusting for confounders.

***Results.*** No association between dietary isoflavone intake and cognitive function was found. High lignan intake was associated with a better performance in processing capacity and speed, and in executive function ($p$ for trend over quartiles = .01 and .02, respectively).

***Conclusions.*** This finding calls for further research to elucidate the relatively underexplored role of lignans within the range of phytoestrogens.

AGING is associated with a decline in some aspects of cognitive function. More specifically, age-related declines have been documented in the realms of mental processing capacity and speed, memory function, and executive functioning, i.e., complex attention processing, planning, and cognitive flexibility (1). In women, this process is accelerated after menopause, and this acceleration could be related to the sharp decline in endogenous estrogen production.

Phytoestrogens are estrogen-like compounds present in several plant foods like soy, beans, and sprouts and are capable of binding to the estrogen receptor (2). They have been claimed to exert various health benefits. The two main groups of phytoestrogens are isoflavones and lignans. In a large cohort of Dutch postmenopausal women, 80% of their isoflavone intake was derived from vegetables, morning cereals, grains, coffee and/or tea, traditional soy foods, and nuts, and 85% of their lignan intake came from grains, vegetables, fruit, coffee and/or tea, and alcoholic beverages (3). As estrogen receptors have been demonstrated in several regions of the brain important for cognitive function (4), we wondered whether phytoestrogens could be effective in reducing the cognitive decline after menopause.

The first trials investigating the effects of high-dose isoflavone supplements or tablets on cognitive function have recently been published but show mixed results (5–8). The effects of relatively low doses through the habitual diet for long periods of time are largely unknown. However, from a public health perspective, the possibility of achieving an improvement in cognitive function by adapting the normal dietary pattern is more attractive than resorting to dietary supplements or pharmaceutical therapy.

We therefore decided to investigate whether a relatively high habitual intake of those isoflavones and lignans commonly seen in a Western diet is associated with better cognitive performance in postmenopausal women.

## Participants and Methods

We recruited women from two sources for this cross-sectional study. The first group 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. Details on the recruitment for this trial have been published previously (9). These 202 women were healthy, aged 60–75 years at baseline in 2000, and living in Utrecht (a medium-sized town) or its surroundings. They had complied with the biannual call to participate in a national screening program for breast cancer in 1999 (the year prior to the start of our study). All had a normal mammogram at that time. Exclusion criteria were a history of malignant disease, active kidney or liver disease, a history of thromboembolism, current estrogen use or estrogen use in the 6 months prior to enrolment, known allergy to soy or milk protein, or endometrial thickness over 4 mm. Only the baseline measurements were used in this cross-sectional study. To increase the power of the study, we recruited more women from a second source (an ongoing cohort study from which we selected participants who fulfilled the same inclusion and exclusion criteria). The ongoing cohort study is one of two Dutch contributions to the European Prospective

Investigation into Nutrition and Cancer (EPIC) cohort (10). 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 (FFQ) (11,12). Habitual phytoestrogen intake was calculated from this questionnaire. To assure a wide range of intake levels, there was a relative oversampling of women with a low intake of total phytoestrogens. The recruitment from the EPIC cohort was similar to that for the trial (9); the women received a letter with information about the study. Those women who were interested returned an answer form and were called by one of the researchers to explain further details and answer questions. When women decided to participate, inclusion and exclusion criteria were checked during the telephone call. Next, an appointment was made to visit our outpatient unit. Although their average intake was lower, women in the second group were represented in all quartiles of isoflavone and lignan intake.

For the present study all the participants filled in a more detailed FFQ (see Dietary assessment section). In total, the study population consisted of 301 women, aged 60–75 years. The Institutional Ethics Review Board of the University Medical Center Utrecht approved the study protocol, and all participants gave written informed consent.

*General Information*

All the participants had a physical examination, during which 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 assessed by using a Critikon Dinamap (Critikon Corp., Tampa, FL) on the right arm. Waist and hip circumferences (in cm) were measured to obtain an indication of upper body adiposity. All the participants filled in a general and health questionnaire. This yielded health information on age at menarche, age at menopause, history of oral contraceptive use, use of hormone replacement therapy and cholesterol lowering and antihypertensive medication, level of education, and smoking history. Level of education was divided into two categories: ''lower'' (comprising primary school, lower vocational training, lower general secondary education) and ''higher'' (comprising higher general secondary education, higher vocational training, and university). Physical activity was determined by the Questionnaire on Mobility in Elderly, which has been validated in apparently healthy people living independently, aged 63–80 years (13). Classifications based on activity scores showed Spearman's correlations of 0.78 and 0.73, with classifications being obtained by repeated 24-hour activity recalls and pedometer measurements, showing that the questionnaire provided a reliable and valid method for assessing physical activity in this age group. The women were divided into three activity groups: low, medium, and high by dividing the scores generated from this questionnaire into population tertiles.

*Dietary Assessment*

All women underwent the same measurements, including filling in a new FFQ to calculate their phytoestrogen intake when we measured our endpoints of interest. For the present study, data on nutrient intake in the year prior to enrollment were derived from an FFQ, administered using a two-step approach comprising a simple questionnaire (20 minutes) filled in by the participant and followed by a structured interview with a trained dietician (20 minutes) based on the completed questionnaire (14). This FFQ has been validated for nutrients (14), and was slightly modified to capture dietary estrogen intake.

From the FFQ we calculated average intake of alcohol, saturated fat, monounsaturated fat, polyunsaturated fat, fiber, fruits, vegetables, folate, vitamin E, and vitamin C by using national Dutch food composition data. Phytoestrogen intake was calculated as follows: through medical (Medline) and agricultural (Agricola) scientific literature and contacts with several experts in the field of phytoestrogens we retrieved laboratory analysis data for the phytoestrogen content of relevant food items. We searched for data on measurements of the phytoestrogens daidzein, genistein, formononetin, biochanin A, matairesinol, and secoisolariciresinol in foods and drinks (15). First, we assigned a value for the different phytoestrogens in milligrams per 100 g of food for all the relevant food items in our FFQ, including beverages. Based on the content, the foods were grouped into seven categories. The median of phytoestrogen content in the respective food group was used as a score to avoid implying a higher degree of accuracy than the current data warrant, e.g., for all the foods in the group with a phytoestrogen content of 0.1–0.99 mg/100 g, we used a score of 0.05 rather than the actual value. For each participant we calculated a score for the different phytoestrogens by multiplying food items $\times$ phytoestrogen score $\times$ frequency $\times$ portion size. This method was also used in a study by Franco and colleagues (16). All nutrient values were adjusted for total energy intake by means of the regression residual method (17).

*Cognitive Testing*

The participants were tested during a morning visit in a quiet room by staff trained in neuropsychology. Because performance in cognitive tests can be influenced by concomitant depression (18), we assessed the presence of depression using the self-rated Geriatric Depression Scale (GDS) (19). Depression was defined as a GDS score $\geq$11.

Cognitive tests were selected that have been documented as sensitive to the effects of aging and that have been included in previous trials of estrogen treatment (20–22). Folstein's Mini-Mental State Examination (MMSE) (23) was used as a screening test for Alzheimer's disease or dementia from other causes. Rey's Auditory Verbal Learning Test was used to measure verbal episodic memory (24). In this test the participants were asked to immediately recall a 15-word list (immediate recall) five times consecutively (maximum score = 75), and again after 25–30 minutes (delayed recall, maximum score = 15). Participants were also asked to recognize the words out of a list of 30 (recognition, maximum score = 30). The Doors Test was used to assess visual memory (25). Participants were shown two series of 12 photographs of doors, which they subsequently have to recognize from arrays of four pictures

Table 1. Average Daily Intake of Phytoestrogens

| Phytoestrogens | Median Intake* (mg/d) | 25%–75% Range | |
|---|---|---|---|
| Isoflavones | | | |
| Lowest quartile | 0.18 | 0.14 | 0.21 |
| 2nd quartile | 0.34 | 0.28 | 0.46 |
| 3rd quartile | 2.99 | 1.41 | 5.20 |
| 4th quartile | 14.64 | 10.3 | 21.8 |
| Lignans | | | |
| Lowest quartile | 0.65 | 0.49 | 0.85 |
| 2nd quartile | 1.39 | 1.26 | 1.54 |
| 3rd quartile | 1.80 | 1.70 | 1.93 |
| 4th quartile | 2.29 | 2.16 | 2.67 |

*Note*: *Energy adjusted.

of doors. In the Digit Span test, a subtest of the Wechsler Adult Intelligence Scale (WAIS) (26), participants were asked to repeat a string of digits in the original order (digit span forward [DSF]) and in the reversed order (digit span reversed [DSR]), to give an impression of short-term memory and working memory. To test verbal fluency, participants were asked to list as many nouns, and to name as many animals and occupations, as possible beginning with the letters ''N'' and ''A,'' each in a period of 1 minute. In the Boston naming test for verbal competence and semantic retrieval, participants were shown 60 line drawings, which had to be properly named. The maximum score was 180 (3 points for a correct answer) (27). The digit symbol substitution test (DSST), also from the WAIS (26), measures cognitive and perceptual speed. Participants were given a code that pairs symbols with digits. The test consists of pairing as many digits as possible to their corresponding symbols in 90 seconds. The Trail-Making Test parts A1, A2, and B were complex attention and mental flexibility tasks in which pseudorandomly placed circles with numbers (Trail-Making A1), letters (Trail-Making A2), and with both letters and numbers (Trail-Making B) have to be connected by a line as fast as possible in a fixed order (28). At baseline we also assessed the verbal intelligence quotient using the Dutch Adult Reading Test [DART, a Dutch version of the National Adult Reading Test (29,30)] in which participants had to read out loud a list of words with irregular pronunciation. Completion of the entire test battery took 1 hour on average.

To assess cognitive domain scores and to minimize misclassification, average or compound cognitive test scores were made by transforming individual test scores into standardized $z$ scores ($z$ score = test score − mean test score/*SD*) (31). By pooling $z$ scores, compound scores for the following domains could be estimated: memory, processing capacity and speed, and executive function. Rey's Auditory Verbal Learning Test and the Doors Test were included in the ''memory'' domain. Processing capacity and speed comprised the DSF, DSR, DSST, and Trail-Making Test parts A1 and A2. Executive function comprised the Trail-Making Test part B, the Boston naming test, and verbal fluency. The sign was reversed before calculating the pooled $z$ score for tests in which a higher score denotes worse performance (Trail-Making).

*Data Analysis*

The energy-adjusted dietary intake of total phytoestrogens, lignans, and isoflavones was divided into quartiles. Because of the skewed distribution of isoflavone and lignan intake, we report the median and interquartile range per quartile of intake. After adjusting for potential confounders in a two-step approach, we evaluated the relationship between isoflavone and lignan intake and our endpoints, the results on the different cognitive domains, and the MMSE, using linear regression analysis. Potential confounders included in the limited regression model were age (in years), education level (high vs low), and verbal intelligence (DART score), whereas in the extensive model we also corrected for the number of postmenopausal years (years), systolic and diastolic blood pressure (mmHg), body mass index (kg/m$^2$), waist–hip ratio, smoking status (years), physical activity [Voorrips score (13)], and intake of total energy (kcal/d), alcohol (g/d), saturated fat (g/d), monounsaturated fat (g/d), polyunsaturated fat (g/d), fiber (g/d), folic acid (mcg/d), vitamin E (mg/d), fruit (g/d), and vegetables (g/d). The results were analyzed both including and excluding depressed participants (GDS $\geq$ 11).

## Results

The median intake of isoflavones was 0.18 mg/d in the lowest intake quartile and 14.6 mg/d in the highest quartile. For lignans, intake was 0.65 mg/d and 2.3 mg/d for the lowest and highest quartiles (Table 1). General and dietary characteristics are reported relative to the intake of isoflavones and lignans in Table 2 (intake quartiles 1 and 2 vs quartiles 3 and 4). As nutrient intake tended to follow a skewed distribution, we report medians and interquartile ranges in Table 3. The women with high isoflavone intake were somewhat younger and more physically active, consumed more vegetables and fruits but less fat, and consumed slightly more alcohol.

In Tables 4 and 5 we present the relationship between the different domains of cognitive function on the one hand, and the intake of isoflavones and lignans, respectively, on the other hand. We only present the fully adjusted model, including all participants. No significant differences were found in memory, processing capacity and speed, or executive functions for the different levels of isoflavone intake. In contrast, we did see a better performance in two domains of cognitive function (notably, processing capacity and speed, and executive function) related with higher lignan intake, but saw no differences in memory. The difference between the extreme quartiles of lignan intake in processing capacity and speed was approximately one-third of an *SD* for the $z$ score distribution and for executive function one-quarter *SD*. This reflects a 4- to 8-second faster performance on the Trail-Making Test parts A and A1, respectively, the pairing of four more digits on the DSST, and the retrieval of two more words on the verbal fluency test for the women in the highest quartile of lignan intake compared to those in the lowest level of intake.

The differences remained statically significant after adjusting for multiple potential confounders, with a significant trend over the quartiles (processing capacity and speed

Table 2. Characteristics of the Study Population Relative to Either Isoflavone or Lignan Intake (Low vs High Intake)

| | Low Isoflavone Intake (<0.8 mg/d) | | High Isoflavone Intake (≥0.8 mg/d) | | Low Lignan Intake (<1.7 mg/d) | | High Lignan Intake (≥1.7 mg/d) | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | Mean | *SD* | Mean | *SD* | Mean | *SD* | Mean | *SD* |
| Age, y | 67.6 | 4.7 | 65.7 | 4.2 | 67.0 | 4.7 | 66.2 | 4.4 |
| BMI, kg/cm$^2$ | 26.7 | 4.2 | 26.2 | 3.8 | 26.9 | 4.2 | 26.0 | 3.8 |
| Waist-to-hip ratio | 0.8 | 0.1 | 0.8 | 0.1 | 0.8 | 0.1 | 0.8 | 0.1 |
| Years since menopause | 19.0 | 6.8 | 16.9 | 7.2 | 18.6 | 7.3 | 17.3 | 6.9 |
| Systolic blood pressure, mmHg | 149.5 | 22.6 | 141.8 | 20.2 | 148.3 | 22.4 | 143.0 | 20.8 |
| Diastolic blood pressure, mmHg | 78.1 | 14.2 | 77.2 | 13.4 | 78.7 | 13.6 | 76.5 | 14.0 |
| Physical activity, Voorrips score | 13.6 | 7.4 | 15.8 | 8.5 | 13.5 | 7.3 | 15.9 | 8.6 |
| Verbal intelligence, DART score | 78.3 | 17.5 | 82.0 | 15.2 | 79.9 | 16.5 | 80.5 | 16.3 |
| Cognitive test scores | | | | | | | | |
| Rey immediate recall | 39.3 | 9.3 | 41.5 | 8.3 | 39.5 | 9.3 | 41.5 | 8.4 |
| Rey delayed recall | 8.1 | 2.9 | 8.3 | 2.5 | 8.0 | 2.8 | 8.4 | 2.6 |
| Rey recognition | 28.2 | 1.9 | 28.4 | 1.6 | 28.1 | 1.8 | 28.5 | 1.6 |
| Digit Span forward | 5.6 | 1.1 | 6.0 | 1.1 | 5.7 | 1.1 | 5.9 | 1.2 |
| Digit Span reverse | 4.2 | 1.1 | 4.5 | 1.2 | 4.3 | 1.1 | 4.4 | 1.2 |
| Doors test | 18.2 | 3.0 | 19.1 | 2.9 | 18.2 | 3.0 | 19.1 | 2.8 |
| Trail-Making A1 | 46.5 | 17.7 | 40.9 | 14.3 | 45.4 | 18.5 | 42.0 | 13.5 |
| Trail-Making A2 | 49.8 | 26.5 | 44.1 | 24.3 | 51.8 | 31.7 | 42.3 | 16.3 |
| Trail-Making B | 99.4 | 42.5 | 84.2 | 33.9 | 96.3 | 39.1 | 87.9 | 39.0 |
| Digit Symbol Substitution | 46.3 | 11.5 | 50.4 | 10.3 | 46.9 | 11.3 | 49.8 | 10.7 |
| Verbal fluency N | 5.2 | 3.3 | 6.4 | 3.5 | 5.7 | 3.3 | 6.0 | 3.5 |
| Verbal fluency A | 7.4 | 3.4 | 8.3 | 3.3 | 7.3 | 3.0 | 8.4 | 3.7 |
| Verbal fluency animals | 19.7 | 4.8 | 21.2 | 5.3 | 19.4 | 4.6 | 21.4 | 5.4 |
| Verbal fluency occupations | 14.2 | 4.4 | 15.8 | 4.3 | 14.3 | 4.2 | 15.7 | 4.5 |
| Boston naming test | 153.4 | 16.9 | 156.3 | 15.0 | 153.4 | 18.0 | 156.4 | 13.7 |
| MMSE | 26.8 | 2.1 | 27.6 | 1.8 | 27.0 | 2.1 | 27.3 | 1.9 |
| Other scores | *N* | % | *N* | % | *N* | % | *N* | % |
| Higher education | 19 | 12.7 | 37 | 24.7 | 23 | 15.3 | 33 | 22.0 |
| Depression (GDS ≥ 11) | 20 | 13.3 | 15 | 10.0 | 20 | 13.3 | 15 | 10.0 |
| Smoking status | | | | | | | | |
| Current | 35 | 23.3 | 19 | 12.7 | 36 | 24.0 | 18 | 12.0 |
| Past | 47 | 31.3 | 49 | 32.7 | 38 | 25.3 | 59 | 39.3 |

*Note*: *SD* = standard deviation; BMI = body mass index; DART = Dutch Adult Reading Test; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.

$p = .01$, executive function $p = .02$), indicating a dose–response relationship. Analyses excluding depressed participants did not change our findings.

## Discussion

Our results show a statistically significantly better cognitive performance, notably in processing capacity and speed, and in executive function, in participants who have a higher lignan intake. Intake of isoflavones was not associated with cognitive performance.

To appreciate these results, we should first address some strengths and limitations. Our study population consisted of women who volunteered to take part in a trial on phytoestrogens and women participating in an ongoing cohort study into the effects of nutrition on cancer and recruited through a breast cancer screening program. This way of recruitment may limit how much we can generalize our findings to the general population, as women willing to take part in these kinds of studies are generally more health conscious and may well adhere to a healthier diet and lifestyle. Observational studies may also suffer from confounding and bias. We applied a stepwise approach to our data analyses and included a wide range of potential confounders, including lifestyle and dietary factors, in the full model. We were able to include factors such as intelligence and depression, as both are related to dietary pattern and strongly related with cognitive performance. In an attempt to correct for a ''healthy lifestyle'' effect, we included physical activity, alcohol intake, and fruit and vegetable intake. However, confounding by other, unrecognized factors is always a concern in this type of study.

Intake of phytoestrogens was estimated using an FFQ covering the year preceding the measurements. The accuracy of an FFQ depends on the participants' recall. An alternative, not depending on recall, is to measure biomarkers in blood or urine. Unfortunately, these biomarkers only reflect intake in the last 24–48 hours prior to collecting the sample (32). This would be a problem, especially for less frequently consumed items like soy or beans. The FFQ we used was validated only for nutrients, by comparing the data collected from the questionnaire with those drawn from 15 daily dietary records, with the age-, sex-, and energy-adjusted Spearman rank correlation coefficients ranging from 0.44 to 0.85, which is good (14).

More precise knowledge is needed on the phytoestrogen content of different products to be able to make a valid

Table 3. Nutrient Intake Relative to Either Isoflavone or Lignan Intake (Low vs High Intake)

| | Low Isoflavone Intake (<0.8 mg/d) | | | High Isoflavone Intake (≥0.8 mg/d) | | | Low Lignan Intake (<1.7 mg/d) | | | High Lignan Intake (≥1.7 mg/d) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Interquartile Range | | | Interquartile Range | | | Interquartile Range | | | Interquartile Range | |
| Nutrients | Median | 25% | 75% | Median | 25% | 75% | Median | 25% | 75% | Median | 25% | 75% |
| Energy, kcal/d | 2001 | 1714 | 2301 | 2042 | 1726 | 2377 | 2085 | 1766 | 2453 | 1929 | 1710 | 2278 |
| Protein, g/d* | 90 | 71 | 106 | 98 | 84 | 114 | 95 | 75 | 111 | 92 | 80 | 110 |
| Plant protein, g/d* | 35 | 27 | 42 | 36 | 29 | 46 | 34 | 26 | 42 | 36 | 31 | 45 |
| Total fat, g/d | 78 | 61 | 91 | 73 | 57 | 91 | 85 | 66 | 99 | 66 | 54 | 79 |
| Saturated fat, g/d | 31 | 24 | 40 | 29 | 21 | 37 | 35 | 27 | 44 | 26 | 19 | 31 |
| Monounsaturated fat, g/d | 28 | 21 | 33 | 26 | 20 | 33 | 31 | 24 | 36 | 24 | 19 | 29 |
| Polyunsaturated fat, g/d | 16 | 12 | 20 | 15 | 11 | 21 | 16 | 13 | 21 | 14 | 11 | 19 |
| Dietary fiber, g/d* | 33 | 26 | 39 | 37 | 28 | 43 | 30 | 23 | 39 | 37 | 31 | 44 |
| Vitamin C, mg/d* | 111 | 85 | 145 | 141 | 99 | 176 | 117 | 84 | 153 | 133 | 96 | 168 |
| Alcohol, g/d* | 3 | 0 | 12 | 8 | 1 | 20 | 3 | 0 | 13 | 8 | 1 | 18 |
| Fruits, g/d* | 237 | 154 | 335 | 306 | 196 | 427 | 240 | 153 | 332 | 289 | 191 | 399 |
| Vegetables, g/d* | 176 | 129 | 235 | 251 | 185 | 318 | 194 | 134 | 259 | 232 | 168 | 285 |

*Note*: *The difference in intake between the two groups was statistically significant ($p < .05$).

estimation on intake, but phytoestrogen content in food items may also differ between brands and methods of preparations (33). We used categories rather than absolute content to reduce any measurement bias, but this resulted in a lower power to detect possible associations. Several studies have investigated the relationship between isoflavones and cognitive function, but only one study has been performed for lignans (16).

The observed effects in our study did not include the memory domain (verbal or visual), a domain that has generally been associated with conventional estrogen supplementation (21,34). However, the observed effects of conventional estrogens on verbal memory were also not confirmed in subsequent trials (35,36).

The mechanism of action for phytoestrogens might differ from that for conventional estrogen supplementation. The antioxidant properties of isoflavones have been related to a strong neuroprotective effect (37), but lignans also exhibit antioxidant properties (38); thus, a similar neuroprotective effect could be hypothesized. Furthermore, lignans bind to

Table 4. Cognitive Function and Isoflavone Intake

| Cognitive Function Domains | Difference* | *p* Value | 95% CI | | *p* for Trend |
|---|---|---|---|---|---|
| Memory (*z* score)† | | | | | |
| 2nd quartile of isoflavone intake | 0.065 | .603 | −0.181 | 0.310 | |
| 3rd quartile of isoflavone intake | 0.135 | .264 | −0.103 | 0.374 | .80 |
| 4th quartile of isoflavone intake | −0.077 | .565 | −0.340 | 0.186 | |
| Processing capacity and speed (*z* score)† | | | | | |
| 2nd quartile of isoflavone intake | −0.007 | .946 | −0.209 | 0.195 | |
| 3rd quartile of isoflavone intake | 0.177 | .079 | −0.021 | 0.376 | .19 |
| 4th quartile of isoflavone intake | 0.084 | .448 | −0.134 | 0.302 | |
| Executive function (*z* score)† | | | | | |
| 2nd quartile of isoflavone intake | 0.004 | .968 | −0.192 | 0.200 | |
| 3rd quartile of isoflavone intake | 0.166 | .087 | −0.024 | 0.356 | .29 |
| 4th quartile of isoflavone intake | 0.055 | .606 | −0.155 | 0.265 | |
| MMSE† | | | | | |
| 2nd quartile of isoflavone intake | 0.086 | .798 | −0.578 | 0.751 | |
| 3rd quartile of isoflavone intake | 0.195 | .558 | −0.459 | 0.848 | .07 |
| 4th quartile of isoflavone intake | 0.692 | .059 | −0.026 | 1.410 | |

*Notes*: *Difference in cognitive function relative to the lowest quartile of isoflavone intake.

†Results adjusted for age (years), verbal intelligence (Dutch Adult Reading Test [DART] score), level of education (higher vs lower), number of years since menopause, systolic and diastolic blood pressures (mmHg), body mass index (kg/m$^2$), waist-to-hip ratio, smoking status (years), physical activity [Voorrips (13) score], total energy intake (kcal/d), and intake of alcohol (g/d), saturated fat (g/d), monounsaturated fat (g/d), polyunsaturated fat(g/d), fiber (g/d), folic acid (μg/d), vitamin E (mg/d), fruits (g/d), and vegetables (g/d).

CI = confidence interval; MMSE = Mini-Mental State Examination.

Table 5. Cognitive Function and Lignan Intake

| Cognitive Function Domains | Difference* | *p* Value | 95% CI | | *p* for Trend |
|---|---|---|---|---|---|
| Memory (*z* score)† | | | | | |
| 2nd quartile of lignan intake | 0.027 | .836 | −0.232 | 0.286 | |
| 3rd quartile of lignan intake | 0.181 | .216 | −0.106 | 0.468 | .42 |
| 4th quartile of lignan intake | 0.094 | .580 | −0.240 | 0.428 | |
| Processing capacity and speed (*z* score)† | | | | | |
| 2nd quartile of lignan intake | 0.183 | .089 | −0.028 | 0.394 | |
| 3rd quartile of lignan intake | 0.345 | .004 | 0.110 | 0.580 | .01 |
| 4th quartile of lignan intake | 0.325 | .020 | 0.052 | 0.597 | |
| Executive function (*z* score)† | | | | | |
| 2nd quartile of lignan intake | 0.064 | .546 | −0.143 | 0.270 | |
| 3rd quartile of lignan intake | 0.270 | .020 | 0.043 | 0.498 | .02 |
| 4th quartile of lignan intake | 0.260 | .054 | −0.005 | 0.524 | |
| MMSE† | | | | | |
| 2nd quartile of lignan intake | 0.284 | .420 | −0.410 | 0.978 | |
| 3rd quartile of lignan intake | 0.191 | .625 | −0.577 | 0.959 | .99 |
| 4th quartile of lignan intake | 0.074 | .871 | −0.816 | 0.963 | |

*Notes*: *Difference in cognitive function relative to the lowest quartile of lignan intake.

†Results adjusted for age (years), verbal intelligence (Dutch Adult Reading Test [DART] score), level of education (higher vs lower), number of years since menopause, systolic and diastolic blood pressures (mmHg), body mass index (kg/m$^2$), waist-to-hip ratio, smoking status (years), physical activity [Voorrips (13) score], total energy intake (kcal/d), and intake of alcohol (g/d), saturated fat (g/d), monounsaturated fat (g/d), polyunsaturated fat (g/d), fiber (g/d), folic acid (μg/d), vitamin E (mg/d), fruits (g/d), and vegetables (g/d).

CI = confidence interval; MMSE = Mini-Mental State Examination.

sex hormone–binding globulin (SHBG) and are able to reduce the binding of estradiol and testosterone to SHBG leading to a higher free (active) fraction of these hormones (39). Lignans might be able to improve cognitive function through this pathway, although not in all domains.

A few studies on isoflavones and cognition in humans have been published recently. A trial in college students (8) reported statistically significantly better performance on short-term and long-term memory and mental flexibility tasks after an isoflavone-rich diet. The differences in study population, i.e., much younger participants, including men, and the lack of blinding limits the comparison to our study. Two studies performed in postmenopausal women using isoflavone tablets for 3 and 6 months, respectively, found improvements in isolated domains—for example, fluency (6), picture recall, sustained attention, learning rule reversals, and task planning (7). In a larger trial (which used the same tests as our current study) performed by our group, we found no effect on any of the cognitive tests (5).

Data on the effects of low dose, but long-term exposure, as investigated in our study, are scarce. In a study in Chinese and Japanese women living in the United States, genistein intake estimated from FFQs was not related to cognitive function in women aged 42–52 years (40). This finding agrees with those of our study and suggests that dietary isoflavones do not improve cognitive function, at least not at the low levels of intake we studied. The contrast with the positive findings reported by some trials could be due to the amount of isoflavones (a minimum of 60 mg isoflavones per day in trials vs 15 mg/d in the highest quartile of intake in our study). The pattern of consumption is also rather different. In a trial there is a fixed daily dose, whereas the exposure through the habitual diet might be more intermittent, as important sources of isoflavones, like soy, are not likely to be consumed on a daily basis by a Western population.

Lignans are a group of phytoestrogens that have so far received little attention. In Asian populations, isoflavones are the main source of dietary phytoestrogens, but in Western populations the relative contribution of lignans to the total amount of phytoestrogen intake is much larger, and foods rich in lignans are consumed more frequently. This leads to a more or less continuous exposure compared to isoflavones coming from sources like soy, which is only consumed occasionally. As far as we know, only one study on lignan intake and cognitive function has been published (16). In this study in elderly women, only the MMSE was performed, and high lignan intake was associated with a reduced incidence of cognitive impairment, defined as a score below 26 points on the MMSE. However, we found no relationship between lignan intake and MMSE although our average age, the level of correction for potential confounders, and the average test results were similar. We feel that our larger study population should have revealed any effect in this global test. Unfortunately, no other cognitive domains were investigated in this cohort. Our results clearly show an association between higher lignan intake and two domains of cognitive function—processing capacity and speed—and executive function with a dose–response effect ($p$ for trend = .01, both domains).

The results of a cross-sectional study always need to be interpreted with caution, but our results suggest that it may be worthwhile to elucidate the possible role of dietary lignan intake and explore the neurobiological mechanisms through which lignans can act on brain receptors.

## *Conclusion*

This observational study in postmenopausal women suggests that high dietary lignan intake has a beneficial effect on cognitive function, notably on processing speed and capacity, and executive function. We found no apparent relationship between dietary isoflavone intake and cognition in the range of intake common in a Westernized population. This finding calls for further research into the role of lignans.

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