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# THE EFFECTS OF SOY MILK AND ISOFLAVONE SUPPLEMENTS ON COGNITIVE PERFORMANCE IN HEALTHY, POSTMENOPAUSAL WOMEN

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**Abstract:** *Rationale:* The decline in estrogen concentrations in women after menopause can contribute to health-related changes including impairments in cognition, especially memory. Because of the health concerns related to hormone replacement therapy (HRT), alternative approaches to treat menopausal symptoms, such as nutritional supplements and/or diet containing isoflavones, are of interest. *Objectives:* This study investigated whether soy isoflavones (soy milk and supplement) could improve cognitive functioning in healthy, postmenopausal women. *Participants, Intervention and Design:* A total of 79 postmenopausal women, 48-65 years of age, completed a double-blind, placebo-controlled trial in which they were randomly assigned to one of three experimental groups: cow's milk and a placebo supplement (control); soy milk and placebo supplement (soy milk, 72 mg isoflavones/day); or cow's milk and isoflavone supplement (isoflavone supplement, 70 mg isoflavones/day). *Measurements:* Cognitive functioning was assessed using various cognitive tasks before the intervention (baseline) and after the intervention (test). *Results:* In contrast to predictions, soy isoflavones did not improve selective attention (Stroop task), visual long-term memory (pattern recognition), short-term visuo-spatial memory (Benton Visual Retention Test), or visuo-spatial working memory (color match task). Also, the soy milk group showed a decline in verbal working memory (Digit Ordering Task) compared to the soy supplement and control groups. *Conclusion:* Soy isoflavones consumed as a food or supplement over a 16-week period did not improve or appreciably affect cognitive functioning in healthy, postmenopausal women.

**Key words:** Soy isoflavones, phytoestrogen, menopause, cognition, memory.

## Introduction

The decline in estrogen concentrations in women after menopause can contribute to health-related changes including impairments in cognition, especially memory (1,2). Research suggests that hormone replacement therapy (HRT), which consists of estrogen and progestin or estrogen alone, may improve or protect memory function in postmenopausal women and eliminate or slow the progression of other physical symptoms, such as bone loss, which often accompany menopause (1,3). However, many women are reluctant to accept HRT because of potential health concerns including increased risk of breast cancer, stroke, coronary heart disease, pulmonary embolism, and uterine bleeding (2,4,5,6) Furthermore, despite the wealth of literature on the positive benefits of HRT on cognition, some recent evidence suggests HRT may increase the risk of cognitive impairment and dementia (7,8,9). Therefore, alternative approaches to treat menopausal symptoms, such as nutritional supplements and/or diet, are of considerable interest to researchers, clinicians and consumers.

Isoflavones, plant-derived compounds with a chemical structure similar to endogenous estrogen (17ß-estradiol), show promise as a safe alternative to HRT although more research is needed. In Asian countries where women consume on average 20 to 60 mg of isoflavones a day, less severe menopausal symptoms have been reported (10). Also, isoflavones have been shown to protect against several hormone-dependent diseases and cancers (11,12,13,14). Isoflavones including genistein and daidzein, which are found predominantly in soy foods, appear to have both pro-estrogenic and anti-estrogenic functions (15,16,17,18). The structural similarity between isoflavones and estrogen, as well as evidence indicating that estrogen can improve or protect some aspects of cognitive health have been the rationale for investigating whether soy isoflavones can also improve cognitive health.

Recent studies suggest that soy isoflavones can activate ERß receptors (19) prevalent in both the hippocampus and frontal cortex of the brain (20,21,22,23) and alter metabolism in these areas (24). Isoflavones can also increase choline acetyltransferase and mRNA levels of neurotrophins in the hippocampus and frontal cortex (25). In humans, the hippocampus and surrounding cortex play vital roles in explicit encoding and consolidation of verbal and visual-spatial memories (26,27). The frontal cortex is important for working memory (28), inhibiting irrelevant information (29), and other cognitive executive functions (30).

Behavioral evidence from animal and human studies suggests that isoflavones may improve or protect some cognitive functions associated with these brain areas. For example, ovariectomized female rats fed high soy protein diets showed improved visual-spatial memory and visual reference

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memory compared to those fed low soy protein diets (31,32). Also, an ovariectomy-induced, spatial memory impairment in rats was prevented by soy isoflavones (33). Neuroprotective effects were also found in ovariectomized animals fed high soy protein diets (34,35). There is also evidence that isoflavones may improve cognitive functions associated with hippocampal and frontal cortex function in humans. However, there are only five studies published investigating the effects of isoflavones on human cognition, and they report inconsistent results (36,37,38,38,40).

Four of these studies examined whether postmenopausal women receiving isoflavone supplements in a double-blind, placebo-controlled, intervention trial showed improvements on several different neuropsychological tests. Kritz-Silverstein et al. (40) showed improvements for postmenopausal women (aged 55-74 years receiving 110 mg/day of isoflavones for 6 months) on a verbal memory task (category fluency) associated with semantic memory mediated by the hippocampus, (41,42) but not on several other neuropsychological tasks assessing verbal memory. Duffy et al. (36) showed improvements for postmenopausal women (aged 50-65 receiving 60 mg/day of isoflavones for 12 weeks) on a long-term memory, picture recall task associated with hippocampal function and on tasks that required ignoring distractor items, learning rule reversals, and planning which are associated with frontal lobe function. Similarly, File et al. (37) showed improvement on learning rule reversals and planning for postmenopausal women of the same age consuming the same amount of isoflavones after only a 6-week intervention. Finally, a study by Kreijkamp-Kaspers et al. (39) showed no improvements in cognitive performance for postmenopausal women (aged 60-75 years receiving 99 mg/day of isoflavone over 12 months) when using similar types of neuropsychological tests as Kritz-Silverstein et al. (40).

Importantly, the Duffy et al. (36) study used cognitive tests that are typically more difficult to perform and that require frontal lobe function (see also File et al.) (37) Using more difficult tests may have increase the likelihood of finding significant effects since they are less susceptible to ceiling effects. Also, according to Duff & Hampson (1), the prefrontal cortex may be a principle target for estrogen and estrogen may modulate the prefrontal cortex relatively more than other parts of the adult, human brain. Furthermore, the Duffy et al. study sample consisted of younger, postmenopausal women compared to the other two clinical studies. Because the most pronounced effects of estrogen on cognitive function have been reported in perimenopausal women (43,44), younger, postmenopausal women may more likely show improvements in cognition with isoflavone consumption as opposed to older postmenopausal women (39).

The purpose of this 16-week, placebo-controlled, double-blind, clinical intervention trial was to assess the effects of soy isoflavones (in food and dietary supplements) on cognitive functioning in relatively young, healthy, postmenopausal women. To our knowledge, this is the first study to examine the effects of dietary isoflavones on cognitive function in postmenopausal women and the first to compare the efficacy of soy isoflavones in dietary and supplement form. This experimental design was chosen for two reasons. First, soy milk is considered to be a functional food, containing a variety of bioactive compounds, including isoflavones. Thus, it is possible that some of the putative effects of isoflavones are dependent on their interactions with other compounds within the soy milk food matrix. For this reason, it was important to have a "dietary" intervention group. Second, this design allowed us to compare effects found in the dietary treatment group (i.e., soy milk) to those in the supplement group (i.e., purified isoflavones), and hence draw conclusions about how the consumption of soy milk might influence human health. For example, if similar cognitive effects are found between dietary and supplement treatments, these effects could be attributed to isoflavones.

The cognitive tasks used in this study were similar to those used in previous studies which showed better or improved performance by women receiving HRT compared to those not receiving HRT (1,45). Our sample consisted of relatively young postmenopausal women (age range of 48-66 years) because, as mentioned earlier, they may be more likely to show cognitive improvements with isoflavones due to a shorter period of estrogen deprivation and hence possibly less irreversible cognitive damage (39). It was hypothesized that treatment with either the dietary or supplemental soy isoflavones would improve cognitive performance (i.e., selective attention, as well as short-term, long-term, and working memory) over the course of the study, whereas the placebo treatment would result in no change in cognitive performance over the course of the study.

## Materials and methods

### *Participants*

The 79 participants reported in this study were part of a larger project (n=117), approved by the Washington State University Internal Review Board, designed to investigate the effects of soy isoflavones and HRT on cognitive and immune function. Among the original 117 participants, five discontinued due to reasons unrelated to the study. Also, 33 women were receiving HRT, and their data will be reported elsewhere. Participants in this study were between 48 and 65 years of age, did not menstruate for at least one year, and did not receive HRT within the last six months. Of the 79 women in our sample, 9 women had surgical menopause (due to random assignment to treatment groups, 5 women with surgical menopause were assigned to the control, 4 were assigned to the supplement, and 0 to the soy milk groups) and 19 had previously received HRT (8 received HRT more than two years ago, 9 received HRT 1-2 years ago, and 2 received HRT 6 months to 1 year ago). Random assignment to the different treatment groups resulted in 11 previous users of HRT assigned to the control, 4 assigned to the the soy milk, and 4 assigned to

the soy supplement group. Unfortunately the duration of HRT use was not known, but all women reported mild and moderate physical symptoms associated with menopause. Removing these women from the data set did not alter the conclusions of this study, and hence their data were included in all analyses. Also, one woman was a regular consumer of soy. All women were free of major health conditions, were non-smokers, and did not have legume allergies, recent antibiotic therapy, or a history of kidney stones. Further, none had a history of dementia, psychiatric disorders, or movement disorders. All women had normal color vision and corrected-to-normal visual acuity. Participants were recruited within two small communities where two large universities are located by responding to local advertisements that appeared in newspaper, radio, pharmacies, physician offices, retail stores, churches or university news announcements. Participants received $100 upon completion of the study.

***Procedure***

Prior to the intervention, participants who provided informed consent adhered to a 4-week adjustment diet that minimized intake of foods containing isoflavones. Following this, a 16 week intervention began. Groups of 20-25 participants began the study at the same start date (periods), and a new group of participants started every four weeks, creating five periods. Participants in each period were matched by age and IQ (assessed using the Shipley Institute of Living Scale) (46) and then randomized to one of three groups: 1) cow's milk and placebo supplement (control); 2) soy milk and placebo supplement (soy milk); or 3) cow's milk and isoflavone supplement (supplement). Only one participant was a regular consumer of soy, and was assigned to the soy milk group.

Participants consumed 706 mL of milk daily (soy milk or cow's milk) for 16 weeks. Milk was consumed in the morning (353 mL) and evening (353 mL). Cow's milk was treated with flavoring and color agents to resemble the soy milk. Supplements (isoflavone or placebo tablet) were taken with the milk. The isoflavone content (70 mg/day) and composition of the supplements (30 mg daidzein, 33 mg genistein, and 7 mg glycitein) were formulated and verified by Archer Daniels Midland Co. (Novasoy®; Decatur, IL). The isoflavone content of the soy milk was determined by HPLC. The dosage of isoflavones was chosen based on three factors: 1) this dosage was consistent with the typical isoflavone intakes reported in Asian countries that consume soy on a regular basis, 2) it was consistent with isoflavone dosages (i.e. 60-100 mg/day) reported in similar studies, and 3) we believed that it was not reasonable to expect participants to consume more than 24 oz of milk per day. Placebos were composed of maltodextrin. The energy and nutrient composition of the soy milk and cow's milk were similar (Table 1). A dietitian provided individual instruction and written guidelines to the women regarding replacement of usual dairy or other similar food items with the study milk to allow for consistent macronutrient intake and prevention of weight gain during the intervention. Compliance to the study protocol was assessed via personal communication, dietary records, and the appearance of isoflavone metabolites in the urine.

**Table 1**
Energy and nutrient composition of cow's milk and soy milk

| Nutrient | Cow's Milk[a] | Soy Milk[b] |
|---|---|---|
| Carbohydrate (g/day) | 36 | 30 |
| Fat (g/day) | 6 | 10 |
| Protein (g/day) | 24 | 18 |
| Energy (kcal/day) | 294 | 282 |
| Calcium (mg/day) | 900 | 900 |
| Vitamin D (IU/day)[c] | 300 | 360 |
| Isoflavone (mg/day)[d] | | |
| Daidzein (mean±SEM) | --- | 30.9±1.5 |
| Genistein (mean±SEM) | --- | 37.4±1.3 |
| Glycitein (mean±SEM) | --- | 3.6±0.5 |
| Total (mean±SEM) | --- | 71.6±3.1 |

a 1% low-fat cow's milk, 706 mL/day; b Vanilla Silk Soy Milk, White Wave™ , Inc., 706 mL/day; c Expressed in International Units; d Calculated total daily amounts of isoflavone for 706 mL/day soy milk. Analysis on 30 pooled soy milk samples.

***Isoflavone concentration***

A 24-hour urine collection was obtained at baseline (0 week) and test (16 week). Total urine volume was recorded and aliquots frozen at -20 °C. Urinary isoflavone concentration was measured using HPLC (48,49).

***Cognitive assessment***

Cognitive functioning was assessed using several tasks that measure behavioral responses (accuracy and reaction time, RT). All of these tasks were performed at baseline and test, and were administered in a random order across participants and testing sessions. Each testing session required approximately two hours to complete and included a minimum 15 min break. Because cognitive performance can be influenced by depression, the Beck Depression Inventory (BDI) (50) was administered at baseline and test to screen for depression. Measures of memory span described below served as a control measure for the working memory tasks. No differences in memory span were predicted for group or testing session (1).

***Selective Attention***

The Stroop task (51) is a test of selective attention shown to activate the prefrontal cortex (29). Stimuli consisted of color-words that were the same as the color in which the word was drawn (compatible; e.g., the word "red" in red letters), color-words that were different than the color in which the word was drawn (incompatible; e.g., the word "red" in green letters), or a string of X's that were colored (neutral; e.g., the word "shoe" in blue letters). Each stimulus was presented on a computer

screen for 2 sec at an inter-stimulus interval of 3 sec. The task was to report the stimulus color as quickly as possible into a microphone, while ignoring the word. Compatible, incompatible, and neutral conditions occurred equally and randomly across 3 blocks of 36 trials. The dependent variables (DVs) were vocal RT and percent correct. Longer RTs and/or lower accuracy for the incompatible relative to the other conditions indicate a failure to ignore the word.

***Memory***

*Working Memory*. Digit Ordering (52) is a verbal working memory task assumed to activate the prefrontal cortex (1). The task was to verbalize the numbers 1 to 10 in a random order, without repeating or omitting any digits. Ten digit ordering trials were completed, each with a unique digit order. The DV was the total number of errors, including inappropriately repeated digits and omissions, summed over the 10 trials.

Color Matching is a spatial working memory task also assumed to activate the prefrontal cortex (1,53). The task was to find all 10 matching pairs of colored dots that were hidden behind a 4 x 5 array of hinged doors, in as few choices as possible, by opening two doors at a time. A trial was completed when all 10 matching colors were found. Participants completed two consecutive trials and a third trial 30 min later. Color locations were constant within a session, but differed between baseline and test, the order of which was counterbalanced across participants. Performance was videotaped and scored later. The DVs were 1) the number of trial errors (choosing a pair of locations that had already been searched but did not match, and revisiting an already matched pair) and 2) the trial completion time (i.e., RT, in min).

*Memory Recall and Recognition*. The Benton Visual Retention Test (BVRT) is a test of visual-spatial, short-term memory recall (54,55), shown to activate the frontal lobe (45). In each of 10 trials, a line drawing (containing multiple shapes and/or line segments in different spatial locations and orientations) is presented for 10 sec, and the task was to reproduce the drawing from memory on paper. Stimulus complexity increased across the 10 trials. The DV was the total number of errors (based on both the shapes of all objects as well as the spatial relations among them), scored according to standard procedures. A different drawing set was used for the baseline and test, the order of which was counterbalanced across participants.

Visual Pattern Recognition is a long-term memory task shown to rely on the right, medial temporal areas (56). (Technically, the cognitive assessment literature considers any delay greater than 30 sec in recall of recognition after stimulus presentation to represent long-term memory). Ten different colored, abstract patterns were presented in a series (2 sec each, with an inter stimulus interval of 1 sec) on a computer screen (memory phase). When the series ended, 10 pairs of abstract patterns appeared one at a time. The task was to select which pattern of each pair appeared in the memory phase. Participants completed 2 blocks of 10 memory phase and recognition trials. Memory and recognition patterns differed between blocks and between baseline and test, the order of which was counterbalanced across participants. The DV was percent correctly recognized.

*Memory Span (Control for Working Memory Tasks)*. Forward Digit Span, Wechsler Adult Intelligence Scale—Revised (57), is a verbal, memory span task that requires the inferior posterior parietal cortex (58). Participants verbally repeated sequences of digits of progressively increasing length (from 3 to 12 digits) that were verbally presented by the examiner. The DV was the number of digit sequences repeated correctly (scored according to standard procedures). A different set of random sequences was used at baseline and test, the order of which was counterbalanced across participants. This task required passive retention of information and was a control task to quantify any group differences in the ability to temporarily store verbal information in the Digit Ordering task.

Corsi Block-Tapping, Wechsler Adult Intelligence Scale—Revised (57), is a spatial analogue of the Forward Digit Span task (59). Ten identical blocks were fixed in a random arrangement on a platform. Participants observed as the examiner tapped progressively longer spatial sequences on the array of blocks (1 to 12 tapped blocks). The task was to reproduce the sequence tapped by the examiner, immediately after each sequence. The DV was the number of blocks tapped in the correct order. A different set of random sequences was used during the baseline and test, the order of which was counterbalanced across participants. This task required passive retention of spatial information and was a control task to quantify any group differences in the color matching task.

***Statistics***

All analyses were conducted using SAS, version 8.2 (SAS Institute Inc., Cary, NC). First, isoflavone concentration and the study population [age, IQ, BDI, education, number of years since last menstruation, body mass index (BMI), and exercise] were characterized using descriptive statistics, and group comparisons were conducted using a one-way, between subjects, analysis of variance (ANOVA) for unbalanced design or a chi square analysis. (To ensure that the BDI and BMI did not change across testing session, an ANOVA was conducted with group as a between subject's factor and testing as a within subjects factor). Second, to discern unadjusted differences between test and baseline measures within each group for each cognitive test, paired-difference t-tests were used. Third, to evaluate whether there was a differential improvement in cognitive function for women in the different treatment groups, a between subjects multivariate ANOVA was conducted on the difference scores between test and baseline means for each treatment group. This multivariate ANOVA was carried out on each cognitive task except for the Stroop task. Stemming from this ANOVA, a two-way least square-means (LSM) analysis was conducted using PROC GLM. LSMs were adjusted for

age, IQ, period (start date of intervention), education, and current exercise level. In the BVRT task, models also adjusted for drawing set order. (One or more of each of these control variables was significantly correlated with performance on each of our cognitive tests when evaluating our sample as a whole and when treatment sample was used as an independent variable). Finally, to evaluate mean correct RT and accuracy for the Stroop task, a mixed design ANOVA with one between-subjects factor (group) and two within-subject factors (test session and Stroop condition) was used.

## Results

Study population characteristics are summarized in Table 2 by treatment group. No significant differences were found by group with respect to age, IQ, levels of depression (BDI), education, number of years since last menstruation, BMI, and level of exercise. On average, women were 56.1 years of age (range was 48-65 years), had an IQ of 100.6, and had not menstruated over the last 8 years (range was 1-35 years). Also, 62% had a college degree or beyond. Levels of depression were low, with an average BDI score of 7.0 which did not differ between baseline and test [$F(2,78)=1.19$, $p=0.31$]. Average BMI was 28.1 kg/m2 which did not differ between baseline and test [$F(1,78)=0.09$, $p=.76$]. In terms of exercise, 78.5% exercised 0-2 hours/week and 20.3% exercised 3-5 hours/week.

### *Isoflavone concentration*

Total isoflavone concentration in the urine was analyzed on a subset of 45 women (soy milk n=15; supplement n=15; control n=15) who completed the intervention first. At baseline, total isoflavone concentration was not detectable in each group. At test, a significant main effect of group was found for total isoflavone concentration [$F(2,42)=18.24$, $p<0.0001$]. The total isoflavone concentrations were not statistically different between the soy milk and supplement groups (M=36.5±6.3 and 52.2±6.3 $\mu$mol/L, respectively; $p=0.08$), but these concentrations were significantly greater compared to the control group (M=undetectable for control; $p<0.0001$, respectively).

### *Cognitive Assessment*

Performance in the selective attention (Stroop) task conditions for each treatment group at both baseline and test is presented in Table 3. A summary of performance differences on each of the memory tasks at test relative to baseline for each of the treatment groups is presented in Table 4.

### *Selective Attention*

A main effect of condition in the Stroop task was found for RT and accuracy [Mixed design ANOVAs: $F(2,152)=334.02$, $p<0.0001$ for RT and $F(2,152)=60.84$, $p<0.0001$ for accuracy]. Mean correct RT (in milliseconds, ms) was slower for the incompatible (M=804 ms) compared to the compatible (M=643 ms) and the neutral (M=634 ms) conditions ($p<0.01$), and there was no significant difference in correct RT between the

**Table 2**
Characteristics of postmenopausal women by treatment group

| Characteristic | Treatment Group | | | P-value |
|---|---|---|---|---|
| | Soy Milk (n = 25) | Supplement (n = 27) | Control (n = 27) | |
| Age (mean±SEM) | 56.1±0.9 | 55.7±0.7 | 56.4±0.8 | 0.80 |
| Range | (48-65) | (48-65) | (49-61) | |
| IQ (mean±SEM) | 99.9±1.7 | 100.8±2.3 | 101.0±2.3 | 0.93 |
| BDI[a] (mean±SEM) | | | | |
| Baseline score | 7.8±1.3 | 5.7±0.8 | 7.7±1.3 | 0.31 |
| Test score | 6.0±1.4 | 4.4±1.1 | 6.6±1.2 | 0.43 |
| Education, No., (%) | | | | |
| 12 – 15 years | 8 (32.0) | 9 (33.3) | 13 (48.1) | 0.41 |
| ≥ College graduate | 17 (68.0) | 18 (66.7) | 14 (51.9) | |
| Number of years since last menstruation (mean±SEM) | 7.4±1.3 | 6.0±1.0 | 9.6±1.37 | 0.16 |
| BMI[b] (mean ± SEM) | 26.8±1.2 | 28.2±0.9 | 28.5±1.3 | 0.52 |
| Exercise: Number, (%) | | | | |
| 0-2 hours/week | 20 (80.0) | 20 (74.1) | 22 (81.5) | |
| 3-5 hours/week | 5 (20.0) | 6 (22.2) | 5 (18.5) | 0.92 |
| Not reported | --- | 1 (3.7) | --- | |

a. Beck Depression Inventory; b. Body mass index: weight(kg)/height($m^2$)

**Table 3**

Mean±SEM reaction time (RT; in ms) and percent accuracy (AC) performance in the selective attention (Stroop) task conditions for each treatment group at both baseline and test. Only the main effect of condition was significant for RT and AC.

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| | **Soy Milk (n=25)** | | **Supplement (n=27)** | | **Control (n=27)** | |
| *Testing* | | | | | | |
| Baseline | | | | | | |
| Conditions | RT | AC | RT | AC | RT | AC |
| Incompatible | 821±126 | 97.9±2.3 | 799±91 | 96.7±3.1 | 821±135 | 94.5±9.7 |
| Neutral | 640±73 | 99.6±1.4 | 624±90 | 99.9±0.6 | 642±112 | 99.7±1.0 |
| Compatible | 648±96 | 100±0 | 635±114 | 99.6±1.3 | 645±122 | 99.9±0.6 |
| *Test* | | | | | | |
| Conditions | RT | AC | RT | AC | RT | AC |
| Incompatible | 817±120 | 97.4±3.4 | 801±97 | 97.5±3.8 | 787±123 | 98.1±3.4 |
| Neutral | 634±84 | 99.8±0.8 | 615±63 | 99.8±0.8 | 651±88 | 99.7±1.0 |
| Compatible | 637±92 | 99.8±0.8 | 639±85 | 99.5±1.4 | 640±90 | 99.4±1.4 |

**Table 4**

Mean±SEM performance at baseline and test in the different memory tasks for each treatment group. Only the Digit Ordering task showed a significant change in performance across the treatment groups.

| | Treatment Group | | |
|---|---|---|---|
| **Cognitive Task** | **Soy Milk** | **Supplement** | **Control** |
| *Digit Ordering* | (n=25) | (n=26) | (n=27) |
| Total Error Baseline[a] | 9.8±1.3 | 9.9±1.3 | 9.9±1.3 |
| Total Error Test[a] | 13.1±1.3 | 9.2±1.3 | 8.6±1.3 |
| *Color Matching* | (n=17) | (n=23) | (n=19) |
| Total Error Baseline[a] | 34.1±7.5 | 41.9±7.5 | 35.0±7.5 |
| Total Error Test[a] | 33.1±7.5 | 39.0±7.5 | 31.9±7.5 |
| RT (sec) Baseline[a] | 207±25.9 | 189±25.9 | 188±25.9 |
| RT (sec) Test[a] | 166±25.9 | 150±25.9 | 148±25.9 |
| *Benton Visual Retention Test* | (n=25) | (n=27) | (n=25) |
| Total Error Baseline[a] | 5.2±0.7 | 4.8±0.7 | 3.8±0.7 |
| Total Error Test[a] | 4.4±0.7 | 4.4±0.7 | 3.6±0.7 |
| Total Correct Baseline[b] | 6.3±0.4 | 6.9±0.4 | 7.4±0.4 |
| Total Correct Test[b] | 6.7±0.4 | 7.1±0.4 | 7.5±0.4 |
| *Visual Pattern Recognition* | (n=25) | (n=27) | (n=25) |
| Percent Correct Baseline[b] | 80.0±2.5 | 85.9±2.5 | 87.8±2.5 |
| Percent Correct Test[b] | 93.4±2.5 | 95.0±2.5 | 94.8±2.5 |
| *Forward Digit Span* | (n=25) | (n=27) | (n=27) |
| Total Correct Baseline[b] | 8.3±0.5 | 8.5±0.5 | 8.2±0.5 |
| Total Correct Test[b] | 8.3±0.5 | 8.9±0.5 | 8.6±0.5 |
| *Corsi Block-Tapping* | (n=25) | (n=27) | (n=27) |
| Total Correct Baseline[b] | 4.8±0.3 | 4.9±0.3 | 4.7±0.3 |
| Total Correct Test[b] | 4.9±0.3 | 4.8±0.3 | 4.9±0.3 |

a. Smaller values reflect better performance, b. Larger values reflect better performance

compatible and neutral conditions. Also, accuracy was less ($p<0.01$) for the incompatible (97.3%) compared to the compatible and the neutral conditions (99.7%, respectively), which did not significantly differ. In contrast to predictions, there was no significant group x testing interaction found for RT [$F(2,76)=0.13$, $p>0.05$] or accuracy [$F(2,76)=2.51$, $p>0.05$]. There was also no group x testing x condition interaction found for RT [$F(4,152)=0.74$, $p>0.05$] or accuracy [$F(4,152)=3.23$, $p>0.05$]. Furthermore, there was no significant main effect of group for RT [$F(2,76)=0.26$, $p>0.05$] or accuracy [$F(2,76)=0.63$, $p>0.05$] nor was there a significant main effect of testing for RT [$F(1,76)=2.28$, $p>0.05$] or accuracy [$F(1,76)=1.44$, $p>0.05$]. Thus, the three groups did not differ in performance, and performance within each group did not change from baseline to test.

***Memory***

*Working Memory*. In the Digit Ordering task, error rate at test relative to baseline was significantly greater than zero within the soy milk group only [$T(24)=2.66$, $p<0.05$], but did not significantly differ from zero within the supplement or control groups [$T(25)=-0.74$ and $T(26)=-1.17$, respectively; $p>0.05$]. When evaluating group differences in performance at test relative to baseline, there was a significant effect of group on error rate [$F(2,76)=4.30$, $p<0.05$]. In contrast to predictions, the soy milk group showed significantly more errors at test relative to baseline compared to the supplement and the control group (LSM: $p<0.05$). The change in errors between the supplement and control groups at test relative to baseline was not significantly different (LSM: $p>0.05$).

Improvements in Color Match performance at test relative to baseline were not significantly different from zero within any of the groups in terms of error rate [$T(16)= -0.31$ for soy milk, $T(21)= -0.76$ for supplement, and $T(18)= -0.63$ for control, $p>0.05$, respectively]. However, improvements in Color Match performance at test relative to baseline were significantly different from zero in all of the groups in terms of RT [$T(16)= -2.44$ for soy milk, $T(22)= -3.58$ for supplement, and $T(18)= -3.1$ for control, $p<0.05$, respectively], indicating a practice effect. More importantly, when evaluating group differences in performance at test relative to baseline, improvements in performance did not significantly differ among the three groups in terms of total number of errors committed [$F(2, 57) = 0.02$, $p>0.05$] or RT [$F(2, 57) = 0.21$, $p>0.05$]. Unfortunately, due to video recording device errors, we only had complete data sets for 59 women in this task (17 in the soy milk, 23 in the supplement, and 19 in the control group).

*Memory Recall and Recognition*. Improvements in BVRT performance at test relative to baseline were not significantly different from zero within any of the groups for total errors [$T(23)=-1.52$ for soy milk, $T(26)=-0.13$ for supplement, and $T(26)=-0.84$ for control, $p>0.05$, respectively] or total correct [$T(23)=1.12$ for soy milk, $T(26)=0.49$ for supplement, and $T(26)=0.81$ for control, $p>0.05$, respectively]. Also, when evaluating group differences in performance at test relative to baseline, improvements in performance were not significantly different across groups [$F(2,76)= 0.44$ and $0.08$, $p>0.05$, for total errors or total correct, respectively].

In the Pattern Recognition task, improvements in recognition accuracy at test relative to baseline were significantly different from zero in the soy milk [$T(24)=5.68$, $p< 0.001$], supplement [$T(26)=4.32$, $p< 0.001$], and control [$T(24)= 4.24$, $p<0.001$], indicating a practice effect. However, when evaluating group differences in performance at test relative to baseline, there was no significant effect of group [$F(2,75)=2.55$, $p=0.09$].

Memory Span (Control Tasks for Working Memory Tasks). Accuracy for the Digit Span and Corsi Block tasks at test relative to baseline were not significantly different from zero within any group [$T(24)=-0.09$ for soy milk, $T(26)=1.05$ for supplement, and $T(26)=1.28$ for control, $p>0.05$, respectively in the Digit Span task; $T(24)=0.44$ for soy milk, $T(26)=-0.68$ for supplement, and $T(26)=0.69$ for control, $p>0.05$, respectively, in the Corsi Block task]. Also, when evaluating group differences in performance at test relative to baseline, there were no significant differences in Digit Span accuracy or Corsi Block accuracy across groups [$F(2,77)=0.32$ and $0.79$, $p>0.05$, respectively]. These results indicate that verbal memory span and spatial memory span did not differ among groups.

## Discussion

This 16-week, placebo-controlled, double-blind, randomized trial investigated the effects of soy isoflavones (in food and dietary supplements) on cognitive functioning. The total concentration of all three isoflavones (daidzein, equol, and genestein) increased in the urine in response to both the soy milk and isoflavone supplement interventions. However, this study found that consumption of isoflavones in supplement or dietary (soy milk) form over a 16-week period did not have an appreciable effect on attention or memory in healthy, postmenopausal women; postmenopausal women showed no improvement on the cognitive tasks chosen to assess short-term memory, long-term memory, working memory, or selective attention based on the intervention. Our conclusion is consistent with those who showed no cognitive improvements in postmenopausal women consuming isoflavone supplements over a longer intervention (39). However, it is important to note that the small sample size and short intervention used in our study may have contributed to some of the insignificant results.

Soy isoflavones, in contrast to predictions, did not benefit selective attention (assessed by the Stroop task), visuo-spatial short-term memory recall (assessed by the BVRT), or long-term pattern recognition (assessed by the pattern recognition task), or visuo-spatial working memory (assessed by the color match task) in postmenopausal women. No differential improvements in cognitive functioning were found in these tasks at test relative to baseline for women in the soy milk,

supplement, or control groups.

Also, in contrast to predictions, the soy milk group showed poorer performance in verbal working memory (as assessed by the Digit Ordering task), compared to the supplement and control groups (who showed no change in performance). Because no significant differences in verbal memory span (assessed by the Forward Digit Span task) were found among postmenopausal women in the different groups, the decline in digit ordering performance for women consuming soy milk was not due to memory span, but may be attributed to frontally-mediated manipulative functions in working memory (1). However, drawing such a conclusion may be premature since this was the only significant group difference found among all of our cognitive tests and hence this result may have been obtained by chance and has yet to be shown as reliable. Also, at least one study showed that postmenopausal women on HRT performed better on the Digit Ordering task than those not on HRT (1), although this study did not use a pretest-posttest design.

Similar to HRT research (44), soy isoflavones did not improve selective attention in postmenopausal women. However, the attention tasks used in most HRT studies were from neuropsychology test batteries developed to detect extreme disruptions in attention, whereas the Stroop task used in this study is a more sensitive measure of selective attention. Regardless of group, women in our study performed worse in the incompatible relative to the compatible and neutral conditions which is consistent with research on young, healthy adults (60).

In contrast to some HRT research, (1,45) soy isoflavones did not improve visuo-spatial memory including short-term memory (assessed by the BVRT) or long-term memory (assessed by the pattern recognition task), or working memory (assessed by the color match task). A lack of power may have contributed to insignificant findings in the color match task since, due to data loss, the sample size was reduced to 59 women. Also, variability in performance on the color match task was high due to differences in whether speed or accuracy was emphasized among our participants. Performance on the BVRT and pattern recognition tasks were more stable, but were not significantly influenced by soy isoflavones. (Even if the small differences between groups for the pattern recognition task had been significant, the maximum difference in performance was an improvement of the 1.2 pictures recognized out of 20 pictures, which is not a very meaningful improvement).

Similar to reports in the HRT literature, clinical intervention studies examining the effects of soy isoflavones on cognitive functioning in postmenopausal women have reported inconsistent results. The different study outcomes may reflect the age of the sample as well as the type of the cognitive tests used. The present study is most similar to that of Duffy et al. (36) in terms of the mean age (56 years compared to their 57 years), years postmenopausal (8 years compared to their 8 years), and size (n=25-27 per treatment compared to their n=15-18 per treatment) of the sample. Also, the cognitive tests used were less susceptible to ceiling effects and/or showed positive cognitive results for women on HRT. Furthermore, the isoflavone concentrations (70 mg/day compared to their 60 mg/day) and intervention duration (16 weeks compared to their 12 weeks) were comparable.

However, there were several differences between the present study and that of Duffy et al. which may have contributed to the differences found concerning the efficacy of soy isoflavones on cognitive functioning. First, our sample was more educated; 62% of our women completed at least a college degree or more, whereas 48% of the women in Duffy et al.'s study received secondary education. Fewer years of education have been associated with a faster age-related decline in spatial and verbal memory (61). It is suggested that perhaps more educated individuals use different strategies to perform a task and/or recruit different brain regions that benefit cognitive performance when the brain regions that normally mediate the task no longer function as a cohesive unit. Thus, any cognitive deficits present in our sample may have been more difficult to detect and/or the strategies used by our sample may have had a larger impact on task performance than our intervention. Second, the most important difference between the present study and that of Duffy et al. and other clinical studies, were the cognitive tasks used, and hence the cognitive functions assessed. For example, Duffy et al. found positive effects on tasks that required executive function (e.g., mental flexibility, planning), as did File et al. (37,38) but we did not find positive effects on verbal or spatial working memory tasks that also require executive function. Thus, the different conclusions drawn regarding the effectiveness of soy isoflavones in improving cognitive functioning may be dependent on type of cognitive task, even those that are known to activate similar brain regions.

Similar to other clinical interventions, this study has several limitations. First, compliance to the intervention was mainly subjective. Objective compliance was assessed in only a subset of our sample by examining isoflavone concentrations in the urine at baseline and test; thus, it is unknown whether compliance was 100% throughout the intervention. Second, our sample size was small due to the small population of people living in the area where the study was conducted, and a lack of power could have contributed to our insignificant findings. Third, this is a quasi-experimental design, and hence it is difficult to control for other factors (e.g., emotions or stress) that may have influenced cognitive performance on a particular day. Fourth, the intervention was only 16 weeks; results may differ for longer interventions.

Clearly, there is a need for studies to further investigate the effects of soy isoflavones on cognitive functioning, particularly in postmenpausal women who tend to show a decline in cognitive functioning associated with reduced estrogen production. Using a variety of tasks that assess one type of

cognitive process (e.g., spatial working memory) within a single study may be useful to determine whether a particular cognitive process, as opposed to particular task performance, can benefit from soy isoflavones. Also, assessment of several different types of cognitive processes across studies will be particularly useful in understanding the full extent at which soy isoflavones may or may not benefit cognitive processing. At present, for example, it is not clear whether there are any positive effects for verbal memory and picture recall/recognition since positive findings have not been reliable either within and/or between studies (e.g., there were positive effects on category fluency in the Kreitz-Silverstein et al. (40) but not in the Duffy et al. study (36), and there were positive effects on long-term picture recall in the Duffy et al. study but not on long-term picture recognition in our study). Finally, this study as well as the others did not measure estrogen levels of women in the different groups; this is an important factor that may account for the mixed results reported in the literature, and should be examined in future research.

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