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Dietary Phytoestrogen Intakes and Cognitive Function During the Menopause Transition: Results from the SWAN Phytoestrogen Study

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Abstract

Objective—Phytoestrogens, which consist mainly of isoflavones, lignans and coumestans have estrogenic and anti-inflammatory properties. Prior research suggests that higher dietary or supplemental intakes of isoflavones and lignans are related to better cognitive performance in middle aged and older women.

Methods—We conducted longitudinal analysis of dietary phytoestrogens and cognitive performance in a cohort of African-American, white, Chinese and Japanese women undergoing the menopause transition (MT). Tests were: Symbol Digit Modalities, East Boston Memory and Digits Span Backward. Phytoestrogens were assessed by Food Frequency Questionnaire. We modeled each cognitive score as a function of concurrent value of the primary predictors (highest tertile of isoflavones, lignans or coumestrol) and covariates including MT stage.

Results—Coumestrol and isoflavone intakes were 10 and 25 times greater, respectively, in Asian *versus* non-Asian participants. During late perimenopause and postmenopause, Asian women with high isoflavone intakes did better on processing speed, but during early perimenopause and postmenopause, high isoflavone Asian consumers performed worse on verbal memory. The highest isoflavone consumers among non-Asians likewise posted lower verbal memory scores during early perimenopause. A verbal memory benefit of higher dietary lignan consumption was apparent only during late perimenopause, when women from all ethnic/racial groups who were in the highest tertile of intake demonstrated a small advantage. Coumestrol was unrelated to cognitive performance.

Conclusions—Cognitive effects of dietary phytoestrogens are small, appear to be class-specific, vary by menopause stage and cognitive domain and differ among ethic/racial groups (but whether this is related to dose or to host factors cannot be discerned).

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Keywords

menopause transition; cognitive function; phytoestrogen; isoflavone; lignan; coumestrol

INTRODUCTION

Phytoestrogens are heterocyclic phenols contained in plants. The 3 major phytoestrogen classes are isoflavones, lignans and coumestans. Initial interest in phytoestrogens (mainly isoflavones) stemmed from observational studies linking them to lower rates of hormone-dependent cancers; subsequent research also implicates isoflavones and lignans in the prevention of other chronic diseases. [1–3]

Recent years have witnessed a growth of interest in the possible cognitive benefits of phytoestrogens, largely due to their estrogenic and anti-oxidant properties. Phytoestrogens share some of estrogen's genomic and non-genomic effects throughout the central nervous system, and could facilitate attention, executive function and episodic memory. [4,5] Overall, isoflavones, lignans and coumestrol bind to α and β estrogen receptors and are predominantly agonists, based on transcriptional activation assays. [6–8] However, phytoestrogens' ultimate effects on the estrogen pathway are likely to be influenced by complex factors: compounds vary in relative affinity for α and β estrogen receptors (for example, isoflavones affinities for ERβ are 7 to 30 fold higher than for ERα) and have different conformational effects on estrogen receptors; tissue specific-concentrations of ER subtypes differ; phytoestrogens' agonist or antagonist properties depend on circulating estradiol levels or concentrations of the phytoestrogens; and isoflavones, lignans and coumestrol each modify the metabolism and bioavailability of endogenous sex steroids in ways that may either increase or decrease endogenous hormones' levels or bioavailability. [2,3,6–10] Some isoflavones, lignans and coumestans are potent antioxidants. [3,11] The anti-oxidant characteristics of phytoestrogens could promote better cognitive function, because more oxidation and higher levels of inflammation contribute to decline in synaptic plasticity with aging. [12]

Although many mechanisms by which phytoestrogens could benefit brain function have been proposed, interventional and observational studies of their cognitive effects have had mixed results. [13–23] Most investigations have been clinical trials of one year's duration or less and used high-dose soy isoflavone supplements, the results of which may not represent the cognitive outcomes of long-term, usual dietary exposure to these compounds. [16–23] Reports of the relation between dietary phytoestrogens and cognitive function are few, in part due to the challenges inherent in measuring phytoestrogen intake, the limited representation in cohort studies of persons with phytoestrogen-rich diets and the rarity of studies that have obtained repeated measures of diet and cognitive performance. Moreover, to our knowledge, no prior study has collected serial measures of diet and cognition in a cohort of women experiencing the menopause transition (MT), which would allow examination of whether the effects of phytoestrogen vary by MT stage (a proxy for endogenous sex steroids).

This analysis, from the Study of Women's Health Across the Nation (SWAN) Phytoestrogen Ancillary Study, examined the relations between longitudinally measured cognitive performance and serial assessments of usual dietary intakes of isoflavones, lignans and coumestrol in a cohort of women who were undergoing the MT. The parent project, SWAN, is a US-based, multi-site, multiethnic, community-based, longitudinal cohort study of the MT and mid-life. [24] SWAN originally estimated dietary isoflavone intake based on the limited databases available through 1994; the SWAN Phytoestrogen Study greatly expanded

ascertainment of dietary phytoestrogen intake, compiling databases through 2008. [25,26] The present investigation addressed the following questions: Are higher dietary intakes of isoflavones, lignans or coumestrol related to cognitive performance over time in midlife women, and do the cognitive effects of each class of phytoestrogens vary by MT stage and cognitive domain tested?

METHODS

Study sample

The SWAN Phytoestrogen Ancillary Study was conducted within SWAN. [26] SWAN has 7 clinical sites: Boston, Chicago, Detroit, Los Angeles, Newark, Oakland and Pittsburgh. Each site obtained Institutional Review Board Approval and participant consent. SWAN cohort entry criteria were: age 42 to 52 years; having at least one ovary and an intact uterus; no current use of estrogens or other medications known to affect ovarian function; having had least one menstrual period in the 3 months prior to screening; and self-identification as white, African American, Hispanic, Chinese, or Japanese. SWAN collected dietary data at baseline and at annual follow-up visits 5 and 9. The SWAN Phytoestrogen study excluded the Newark site because of high attrition and lack of dietary data at visit 9. Participants from the remaining 6 sites [N=2870] were included. These diet-based exclusions were applied at baseline: no dietary assessment (N = 17); intake of less than 4 or greater than 17 solid foods daily (N = 130); skipped more than 10 food items on the Food Frequency Questionnaire (FFQ) N = 1); calculated daily energy intake of <500 kcal or >5,000 kcal (N = 24). If any dietary exclusion were met at later visits, we censored participants at that time. The SWAN Phytoestrogen Study baseline sample consisted of 2721 women, 1905 at follow-up visit 5, and 1677 at follow-up visit 9.

Cognitive testing was first administered at SWAN follow-up visit 4 and was repeated at follow-up visits 6, 7, 8, 9 and 10; all visits were used herein (see cognitive tests below). Inclusion in this analysis of phytoestrogens and cognitive function required that participants had: 1) cognitive tests performed according to protocol at ≥1 visit; 2) no self-reported history of stroke prior to the first cognitive test; 3) determinable MT stage at the time of cognitive testing; and 4) no use of menopausal hormone therapy (HT) between SWAN cohort baseline and the first visit at which cognitive testing was performed. Thus, of the 2721 women in the Phytoestrogen Study sample, 1616 were eligible for this analysis. We censored participants if they began using HT during follow up, had a hysterectomy prior to the occurrence of their final menstrual period (making MT stage indeterminate) or reported a new stroke.

Primary Exposure: Phytoestrogen Intakes

The SWAN dietary assessment has been detailed previously. [25] In brief, SWAN used an interviewer-administered dietary assessment to assess usual food consumption during the past year, consisting of three components, tailored to language/ethnicity: 1) a full food frequency questionnaire (FFQ); 2) an “Ethnic Foods Page”, and 3) open-ended questions. The SWAN FFQs were based on the Block FFQ. [27] The English-language version contained a 103-item food list, based on Second National Health and Nutrition Examination Survey (NHANES II). [28] The Chinese and Japanese ethnic group versions included the same 103-item food list plus 12 to 16 foods appropriate for each group (Ethnic Foods Page). Finally, all women were asked an open-ended question about other foods eaten at least weekly. The SWAN Phytoestrogen Study created a phytonutrient database using all available phytonutrient data through 2008 and computed usual daily intakes of 4 isoflavones (daidzein, genistein, formononetin, glycetin), 4 lignans (lariciresinol, pinoresinol, secoisolariciresinol, matariesinol) and coumesterol, used in the current analyses. [26]

Primary Outcome Variables: Cognitive Assessment

SWAN used the Symbol Digit Modalities Test (SDMT) to assess processing speed. [29] Verbal episodic memory (immediate and delayed recall) was evaluated using the East Boston Memory Test (EBMT), similar to the Logical Memory subtest of the Wechsler Memory Scales. [30,31] Digit Span Backward (DSB) tested working memory. [32] Tests were professionally forward and back translated; an adjudication panel resolved discrepancies. Bilingual participants were always tested in the same language. SWAN visits occur in the morning, commencing almost entirely between 0600 and 1000 hours. Because SWAN visits consist of many measurements (besides cognition), to ensure cross-site comparability, the protocols are administered in the same order at each site.

Covariates

Time-invariant covariates, measured at the first cognitive testing visit were: age (years), educational level (less than high school, high school, some college, college or greater), difficulty paying for basics (food, heat and housing costs, classified as not hard, somewhat hard, very hard), race/ethnicity (self-designated white, African American, Japanese, or Chinese), testing language (English *vs.* non-English), cigarette smoking (current, former, never, using American Thoracic Society Questions), alcohol consumption (number of standard drinks per day, coded as abstinent, 1–7 drinks per week and more than 7 drinks per week), current use of central nervous system (CNS) active medications (medications for anxiety, sleep or depression, yes/no), (weight (kilograms), height (meters) assessed by certified staff, using a standard protocol for all sites with calibrated scales and stadiometers and SWAN site. Body mass index (BMI, [weight in kilograms/(height in meters)^2]) was calculated. We computed total calorie intake (time varying) for each woman from the FFQ. Menstrually-defined menopause transition (MT) stages (time varying) were: premenopausal (regular menses), early perimenopausal (menses within the prior 3 months but less predictable), late perimenopausal (at least 3 months but less than 12 consecutive months of amenorrhea) and postmenopausal (12 or more months without menses). All multivariable models were adjusted for each of these covariates.

Interpolation of Dietary Variables

SWAN measured dietary exposures at baseline and follow up visits 5 and 9, and cognitive outcomes at follow-up visit 4 (cognitive baseline) and follow-up visits 6, 7, 8, 9 and 10. To handle the differences in measurement schedules, we interpolated dietary variables (one-at-a-time) using random effects modeling; dietary variables were log transformed due to right-skewness and then modeled as a function of time on study. [33] We stratified models by race/ethnicity, due to differences in phytoestrogen consumption. Loess curves indicated linear time trends, thus each model included a random (woman-specific) intercept and slope for time on study. The resulting woman-specific regression coefficients were weighted averages of the coefficients from the full sample and the coefficients from each participant's data only. [34] We did not use predictors other than time-on-study in the final interpolation, because they did not improve prediction, but missing data reduced sample size. To assess the performance of interpolation models, we compared fitted values with observed values for the 3 visits when diet was actually assessed (baseline and follow-ups 5 and 9). Pearson correlations between fitted and observed, accounting for within-woman correlation, ranged from 0.978 to 0.996, indicating excellent agreement. [35] Linear regressions of observed values on fitted values indicated no systematic bias: intercepts were close to 0 and slopes were close to 1. Finally, loess curves for observed dietary variable values in relation to time-on-study overlapped considerably with corresponding curves for fitted values. We interpolated (i.e., imputed) logged dietary variables for visits at which diet was not assessed, using the participant-specific intercept and slope coefficients and the relevant value of time on study for each visit at which diet was not measured. Due to the high agreement between

observed and fitted values, we did not employ multiple imputation. Moreover, the impact of categorizing dietary variables based on tertiles (see Data Analysis) would be to improve agreement between observed and imputed values.

Data Analysis

In the entire sample and in each ethnic/racial group, we plotted distributions of the logged values of each class of phytoestrogen (total isoflavones, total lignans and coumestrol). For lignans and coumestrol, ethnic/racial distributions overlapped, allowing creation of tertiles based on all participants (i.e., women from all ethnic/racial groups were well-represented in each tertile). In contrast, the distribution of isoflavones was strongly bimodal, with almost no overlap between the Chinese and Japanese intakes and the white and African American intakes. Therefore, for isoflavones, we constructed Asian and non-Asian tertiles and ran relational analyses in stratified samples of Asian and non-Asian women.

Using mixed-effects linear models, we first explored the relation between change in cognitive scores between each testing occasion and length of time elapsed between testing (range, 0.3–3.0; median, 1.0; interquartile range, 0.9–1.3). *P* values ranged from 0.25 for EBMT delayed to 0.59 for DSB, indicating no age-related decline or improvement in cognition scores. Therefore, longitudinal gains mainly reflected learning effects. To capture learning effects, we modeled cognition scores as increasing linearly with number of previous exposures to the test. To allow for a decline in the magnitude of learning after repeated tests, we fit 3 candidate mixed-effects null models, with only intercept, number of previous testing occasions (*n*), and a spline with knot fixed at $n = 1$, $n = 2$, or n=3 (to assess whether learning fell after the first, second, or third testing session, respectively). For SDMT and DSB, there was a decrement in learning after the 2nd occasion ($P < 0.001$). Therefore, we modeled each cognitive test score as a function of the concurrent value (at each cognitive testing visit) of the primary predictors (highest tertile of isoflavones, lignans or coumestrol), covariates, number of previous exposures to the cognitive test (*n*), and a spline with knot fixed at $n = 2$ (to allow learning to fall after the second test). We used mixed-effects modeling with random intercept and random effects for both *n* and the spline at $n = 2$ to account for within-woman correlation between repeated measurements. We modeled the initial learning effect as varying by the value of the primary predictor (and the covariates of age, educational level, difficulty paying for basics, race/ethnicity, testing language and menopause transition stage covariates). To assess whether the effect of phytoestrogens on cognitive performance depended on MT stage, we included an interaction term between MT stage and phytoestrogen tertile. We also ran models adjusting for the additional covariates of smoking, alcohol use and CNS-active medication use, allowing each covariate to affect the concurrent cognitive score as well as the learning effect. Because the distributions of EBMT scores were left skewed, we used robust, empirical estimates of standard errors for all analyses. [36] Information on difficulty paying for basics was missing for 30 women; the modal value (not very difficult) was used. Tests were conducted in 2 languages for 18 women, and we used data from only the language used most often. We did not adjust for multiple comparisons. Analyses were performed using SAS (v9.1.3) software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Characteristics of participants who comprise the analysis sample are summarized in Table 1. In general, they were similar to women in the SWAN Phytoestrogen Study who were not included; however more in-analysis women were premenopausal at baseline. There was also a slightly lower representation of whites and African-Americans and higher representation of Chinese and Japanese women among women in-analysis.

When SWAN initiated cognitive tests at follow-up visit 4, the mean age of women in-analysis was 49.74 years (range, 45–57); 154 (9.5%) were premenopausal, 903 (55.9%) were early perimenopausal, 192 (11.9%) were late perimenopausal, 283 (17.5%) were naturally menopausal and 6 (0.4%) were surgically postmenopausal. At annual follow up visit 10, the last testing included in these analyses, the mean number (and standard deviation) of prior SDMT testing visits (representing learning opportunities; range, 0–4) that occurred during each MT stage was 2.57 (1.50) in premenopause, 3.49 (0.96) in early perimenopause, 3.42 (0.96) in late perimenopause, and 3.29 (1.10) in postmenopause. Numbers of visits that took place during each MT stage were similar for the other cognitive tests. At follow-up visit 10, 7 (0.4%) of the women were premenopausal, 136 (8.4%) were early perimenopausal, 105 (6.5%) were late perimenopausal, and 1089 (67.38%) were postmenopausal (natural or surgical, the former vastly predominant).

At the first cognitive test visit, mean values SDMT and DSB scores were at the midpoints of their ranges and their distributions were symmetrical (Table 2). Distributions of the EBMT-immediate recall and EBMT-delayed recall were skewed, with mean values of approximately 10 (of 12). Approximately 33% of participants scored at the EBMT maximum. Cross-sectional crude mean values of each cognitive test were stable across follow-up visits (Table 2).

Coumestrol intakes were approximately 10 times greater in Asian women compared to non-Asian women (Table 3). Compared to non-Asians, Asian women also consumed about twice the amount of lignans. Nonetheless, coumestan and lignan tertiles based on the entire sample included adequate numbers women from each ethic/racial group to allow the use of aggregated tertiles in relational analyses. In contrast, isoflavone intakes of the Asian women were roughly 25 times greater than those of non-Asians. The distribution of isoflavone intakes in the entire study sample was bimodal: lowest tertiles of Chinese or Japanese isoflavone intake barely overlapped with the highest tertiles of white or African American intake. For relational analyses, therefore, we created isoflavone tertiles for Asian and non-Asian groups.

During late perimenopause, women in the highest tertile of lignan intakes (294 to 2018 μg/day) scored ~0.4 points higher on the EBMT than the remainder of same-MT-staged women, roughly 4% better than the overall mean of 10 on that test (Table 4). This result was unaltered by additional adjustment for total dietary fiber intake (data not shown).

The relations between greater intakes of isoflavones and cognitive performance differed by cognitive domain and also by Asian vs. non-Asian heritage (Table 5). During late perimenopause and postmenopause, Chinese and Japanese women with diets highest in isoflavones (top tertile ranging between 18 and 87 g/day) achieved 3.6 and 1.7 more points, respectively, on the test of processing speed (SDMT) than their same MT-staged Asian counterparts with lower isoflavone consumption. The SDMT scores of high isoflavone consuming Asian women were about 3% to 6% better than the average mean score of 58.4. Results for verbal episodic memory (EBMT, immediate and delayed) were the opposite of the SDMT findings: in early perimenopause and postmenopause, Asian women in the highest isoflavone consumption category posted verbal memory scores that were ~0.4 and ~0.5 points less than same MT-staged Asian women whose diets contained lesser amounts of isoflavones, roughly 4% to 5% lower than the average EBMT score of 9.8. The highest isoflavone consumers among non-Asian women, with intakes ranging between ~0.5 and ~12 grams per day, also had slightly lower (by about 0.2 points) verbal episodic memory scores during early perimenopause compared to their lower intake counterparts.

We found no evidence for an association between being in the highest category of coumestan intake (between ~12 and ~170 μg/day) and performance in any of the cognitive domains tested in either racial/ethnic group (Table 6).

Additional adjustment of each model for concurrent smoking, alcohol consumption or use of CNS- active medications (soporifics, anxiolytics or antidepressants) did not alter the estimated relations between each class of phytoestrogen and each cognitive test (data not shown).

DISCUSSION

This study investigated whether dietary intakes of 3 classes of phytoestrogens--lignans, isoflavones and coumestrol--were associated with longitudinally measured cognitive performance in a midlife, multiethnic cohort of women and whether differential effects of phytoestrogens were observed in each MT stage. We found evidence for MT stage-, cognitive domain-, phytoestrogen class-, and ethnic-specific cognitive effects. During late perimenopause and postmenopause, Asian women with high isoflavone intakes did better on the test of processing speed, but during early perimenopause and postmenopause, the high isoflavone Asian consumers performed worse on the verbal memory test. The highest isoflavone consumers among non-Asians similarly posted lower verbal memory scores during early perimenopause. A verbal episodic memory benefit of higher dietary lignan consumption was apparent only during late perimenopause, when women from all ethnic/racial groups who were in the highest tertile of intake demonstrated a small advantage. Coumestrol was unrelated to cognitive performance.

That dietary isoflavones were unrelated to cognitive function in non-Asian women during postmenopause agrees with limited information from cross-sectional observational studies. [13–15] In Dutch postmenopausal women aged between 40 and 75 years, with isoflavone intakes that were similar to those of SWAN's non-Asians, no relation was observed between isoflavones and tests of memory, processing speed or executive function [14] or intact mini-mental state score. [13] Unlike our current finding that early perimenopausal Asian women in the highest tertile of isoflavone intake did slightly worse on the verbal memory test, SWAN's baseline cross-sectional analysis of genistein and cognitive function in pre- and early perimenopausal Asian women found no association; but, our former study used a limited isoflavone data base and assessed cognitive performance only once. [15]

Asian women who were in the late perimenopausal and postmenopausal stages and whose diets were highest in isoflavones performed better on the SDMT, an assessment of cognitive processing speed. Verbal episodic memory (tested by the EBMT), a hippocampal function, was slightly worse in Asian women during early perimenopause and postmenopause and in non-Asian women during early perimenopause. Comparisons of our observational study finding to the results of 8 randomized controlled trials of soy isoflavone supplements with cognitive performance outcomes must be made cautiously, because the trials were mostly short-term (6 of 8 lasted ≤ 6months), administered higher isoflavone doses (60 to 110 mg) than those found even in Japanese diets and some used proportions of isoflavones uncharacteristic of those that occur in foods. [5,16–23] The SDMT was assessed in two soy isoflavone trials: one reported a cognitive benefit[18] while the other did not. [23] Participants in the negative trial were women aged 60 years or greater, older than those in both the positive trial and our study sample. [22,23] Verbal episodic memory was evaluated by 5 of the 8 trials. [16,17,19,22,23] In only one trial was a benefit of soy isoflavone supplementation on verbal memory observed, [17] whereas we witnessed a slightly negative association between isoflavones and the EBMT scores in both Asian and non-Asian women. The isolated clinical

trial finding of verbal memory benefit of isoflavones and our negative verbal memory findings may be chance events. Or, these contrary verbal memory findings could represent differences between the effects of isoflavones from supplements and food sources. In a single trial that administered soy supplement or soy milk, each dosed to deliver ~70 mg/day of isoflavones, soy milk led to worse verbal working memory, while the supplements had no effect on any domain. [21]

Our 6-year longitudinal study, which tracked 4 racial/ethnic groups of women as they progressed through MT and obtained repeated measures of dietary intake and cognitive function, enabled us to probe some previously proposed theories about how menopause might modify the biological impact of phytoestrogens. Notably, we observed a processing speed benefit of high dietary isoflavones, limited to postmenopause in Asian women, consistent with the thesis that agonist properties of isoflavones may depend not only on the compound and dose, but also on host factors such as circulating estradiol levels (which decline as women advance to postmenopause). [2,3,6–10] A different pattern of association between isoflavones and the SDMT compared to the EBMT is also consistent with the idea that isoflavones influence brain regions differentially, due to varying estrogen receptor distributions, distinctive neurophysiological pathways or differential susceptibility of specific brain regions to age-or menopause-related changes. [37,38]

Higher dietary lignans were related to slightly higher verbal episodic memory scores during late perimenopause in both racial groups. This isolated finding for lignans, especially in the context of multiple tests, may be due to chance. Prior lignan studies have been confined to cross-sectional analyses of Dutch women who were largely older than SWAN participants and who had higher lignan intakes, [13,14] These studies reported better prefrontal function [14] and a greater likelihood of having a mini-mental state exam score of greater than 26 (out of 30) was among older women with higher lignan intakes. [13,14]

A brief overview of the leading dietary sources of the 3 classes of phytoestrogens studied and the phytoestrogen content of these foods may help the reader contextualize the exposures[26]. Soybeans, tofu and soy milk were leading sources of isoflavones in Asian women while soy milk, tofu and meat substitutes were the highest ranking isoflavone sources in the non-Asian participants. One glass of soy milk contains 55 mg. of isoflavones, thus the median intakes of the highest Asian and non-Asian isoflavone tertiles are roughly equal to 0.5 and 0.02 cups of soy milk daily, respectively. For lignans, coffee and teas were among the commonest sources in all race/ethnicities. The lignan content of one cup of coffee is 0.04 mg; the median intake of the highest aggregated lignan tertile translates to approximately 10 cups of coffee. Finally, bean sprouts were the highest ranking food source of coumestrol in all women. About 0.03 cup of bean sprouts would equal the median of the highest aggregated tertile of coumestrol.

Limitations of our study include that we conducted multiple statistical tests; thus, our findings may result from chance. We faced unavoidable measurement error in estimating nutrient intakes. Phytonutrient databases, while expanding exponentially, remain incomplete, resulting in underestimation; small-area variation in isoflavone content of soy crops can lead to inaccuracies. [26,39] While absolute nutrient intakes cannot be calculated from FFQs, relative rankings of nutrient intakes are robust; importantly, differential misclassification is minimized in SWAN because its diet assessment was designed to accommodate mixed dishes and account for ethnic foods. [26,40] Underestimation was minimized by using our Phytoestrogen Study database to compute coumestrol, lignan and isoflavones; values were as comprehensive as possible, based on currently available sources. [26] Another study limitation is our small cognitive battery, a consequence of SWAN's large, multifaceted protocol, balancing depth against burden. In the context of

phytoestrogen research, a notable omission in the SWAN battery is a test of executive function, a domain that may be sensitive to soy isoflavone supplementation. [16, 17, 19, 20] We also had a ceiling effect on the EBMT, minimizing ability to detect improvement with time. Finally, we faced statistical methodological challenges due to the large differences in consumption of soy-based foods in Eastern and Western diets; Asian isoflavone intakes were vastly greater than those of non-Asians. Collinearity between race and intake would have resulted if we had created isoflavone tertiles based on the entire sample. Therefore, we created Asian and non-Asian tertiles and used stratified models. But we cannot escape the fact that exposure levels in Asian and non-Asian strata were unequal: the highest isoflavone tertile in non-Asians was roughly equivalent to the lowest in Asians. The reader is cautioned, that dissimilar findings for isoflavones in Asian and non-Asian women could represent racial and/or "dosage" differences, dissimilarities in food sources (for example, aglycone forms of isoflavones found in fermented soy foods may be more biologically active) and/or varying capacity to metabolize isoflavones. The capacity to metabolize isoflavones to their "mammalian" forms (e.g., equol and p-ethyl phenol, which are bioactive) varies among individuals. On the whole, racial/ethic differences in metabolic capacity may be one source of the apparent disparities in the effects of these compounds: ~30% to 60% of Asians produce equol, while only ~20% to 40% of Westerners do so [41–50]

CONCLUSIONS

In conclusion, this novel, longitudinal study of the relation between cognitive function and usual dietary intakes of 3 different classes of phytoestrogens in a multiethnic cohort of midlife women undergoing the MT suggests that the cognitive effects of these compounds are phytoestrogen class-specific, vary by menopause stage (a proxy for endogenous sex steroid milieu), vary by cognitive domain and differ among the ethic/racial groups (but whether this is related to dose and/or host factors is not discernable). The differences in cognitive test results reported here are small and of scientific interest rather than having immediate clinical relevance. Whether small differences in trajectories cognitive performance during mid-life predict later-life clinical cognitive outcomes is not known at this time. Future work will continue to follow this cohort's longitudinal cognitive performance, will incorporate estimates of phytoestrogen metabolic capacity (i.e., metabolites of isoflavones and lignans) and will consider food sources of phytoestrogens (a proxy for bioavailability).

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Table 1

Demographic, behavioral, anthropometric and menopause transition stage characteristics of Study of Women's Health Across the Nation (SWAN) Phytoestrogen Study participants in the current analysis[a, b]

Participant Characteristics	Analysis Sample (N = 1586–1616)[c]
Categorical Variables, percent	
Menopause Transition Stage	
Pre	59.55
Early Peri	40.45
Race	
Black	30.69
Caucasian	47.15
Chinese	11.14
Japanese	11.01
Educational Level	
Less than high school	3.87
High school	15.97
Some college	32.69
College	23.39
More than college	26.08
Difficulty paying for basics	
Very hard	7.00
Somewhat hard	28.31
Not hard at all	64.69
Language used in reading/speaking	
Other than English	4.96
Bilingual	7.56
English only	87.48
Current cigarette smoking	14.68
Alcohol use in past year	
Abstinent	51.18
1–7 drinks per week	41.40
7+ drinks per week	7.43
Current use of a CNS-active medication[d]	8.17
Continuous variables, mean (SD)	
Age, years	45.64(2.61)
Body Mass Index (kg/m^2)	27.94(7.43)

[a]Eligibility criteria for inclusion in analysis sample were: 1) Part of SWAN Phytoestrogen Study cohort (see methods for derivation); 2) Cognitive data collected according to protocol standards at one or more visits (follow-ups 4, 6, 7, 8, 9 or 10); 3) No self-reported stroke through the 4th follow-up visit; 4) No self-reported hormone use from SWAN baseline through the 4th follow-up visit; 5) Menopause status able to be determined (see methods for explanation); Women who reported a stroke, started hormones or whose menopause status became unclassifiable were censored from analysis at the time of occurrence of these events.

[b] Values in table are based on data from cohort baseline data, rather than visit 4, because 10 women in analytic sample did not attend the 4th follow-up visit and because some characteristics were measured only at cohort baseline.

[c] Of the 1616 women in the analytic sample, 1467 began the study at the 4th follow up visit and 149 entered the study at a later visit (visit 6, 7, 8, 9 or 10).

[d] Central nervous system (CNS) active medicines included: soporifics, anxiolytics and antidepressants.

Table 2

Mean values of measured cognitive test performance at each study visit[a] [b]

	Crude Mean (Standard Deviation) of Cognitive Measure and Sample Size at Each Visit					
Cognitive Tests (score range)[c]	**Visit 4**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Symbol Digit Modalities (0 – 110)	55.88 (11.08) N = 1,464	56.84 (10.97) N = 1,251	57.82 (11.13) N = 1,175	59.77 (11.76) N = 711	56.71 (11.50) N = 383	57.25 (11.71) N = 1,018
East Boston Memory Test						
Immediate (0 – 12)	10.16 (1.73) N = 1,466	10.18 (1.80) N = 1,255	10.35 (1.65) N = 1,181	10.51 (1.56) N = 711	10.22 (1.74) N = 387	10.32 (1.67) N = 1,023
Delayed (0 – 12)	9.99 (1.80) N = 1,464	10.01 (1.87) N = 1,255	10.21 (1.72) N = 1,181	10.34 (1.67) N = 710	10.02 (1.84) N = 387	10.17 (1.77) N = 1,023
Digit Span Backward (0 – 12)	6.70 (2.32) N = 1,452	6.80 (2.39) N = 1,237	6.92 (2.32) N = 1,152	6.97 (2.37) N = 695	6.63 (2.22) N = 379	6.78 (2.30) N = 991

[a] First cognitive assessment was conducted during the 4th annual SWAN follow-up visit. Therefore SWAN follow-up visit 4 is the cognitive assessment baseline; however, women who elected to initiate cognitive tests at a later visit could join the cognitive cohort.

[b] Cognitive tests were not taken at visit 8 by 552 women from the entire SWAN sample; only women not tested at visit 8 were tested at visit 9.

[c] Cognitive test scores shown are means (standard deviations). The number of cognitive tests taken at visit 4 is less than the number of in-analysis participants (1,616) because some women did not contribute cognitive data at follow-up visit 4 but did so at subsequent visits.

Table 3

Dietary intakes of lignans, coumestrol, and isoflavones at cognitive study baseline: tertile medians and cut-points, by ethnic/racial groups and aggregated [a, b, c]

Phytoestrogen Class	Tertile 1	Tertile 2	Tertile 3
	Median (Upper and Lower Bound)	Median (Upper and Lower Bound)	Median (Upper and Lower Bound)
Lignans (μg/day)			
African American	155.1 (88.2 – 176.5)	202.1 (176.9 – 233.7)	278.2 (234.2 – 686.3)
Caucasian	178.4 (76.3 – 215.9)	255.1 (216.0 – 289.5)	345.6 (289.6 – 669.0)
Chinese	247.1 (126.9 – 295.0)	344.0 (298.0 – 398.2)	469.3 (402.9 – 839.3)
Japanese	211.1 (118.2 – 258.9)	320.7 (259.7 – 374.8)	463.3 (378.1 – 2018.5)
Aggregated, all 4 ethnic/racial groups	171.6 (76.3 – 210.1)	250.2 (210.3 – 294.5)	365.1 (294.6 – 2018.5)
Coumestrol (μg/day)			
African American	2.4 (0.6 – 3.9)	5.5 (4.0 – 8.0)	12.1 (8.0 – 62.7)
Caucasian	1.7 (0.4 – 3.3)	4.8 (3.3 – 7.4)	11.6 (7.4 – 48.2)
Chinese	17.2 (2.5 – 26.7)	39.1 (27.7 – 50.3)	66.7 (51.4 – 146.3)
Japanese	19.9 (6.4 – 31.1)	43.6 (31.3 – 58.8)	83.0 (58.9 – 170.6)
Aggregated, all 4 ethnic/racial groups	2.4 (0.4 – 4.4)	7.2 (4.4 – 12.2)	27.7 (12.2 – 170.6)
Isoflavones (μg/day)			
African American	214.3 (64.1 – 289.7)	369.6 (290.8 – 471.3)	810.1 (475.3 – 11998.1)
Caucasian	151.4 (22.4 – 231.7)	332.8 (233.6 – 473.0)	997.9 (475.3 – 8602.4)
Chinese	3875.8 (280.0 – 6797.4)	10037.7 (6827.4 – 13987.2)	24728.2 (14747.7 – 87518.0)
Japanese	6545.9 (1373.2 – 10129.4)	14053.1 (10248.6 – 23590.5)	30476.2 (23656.7 – 70192.7)
Aggregated, Asian groups	5119.4 (280.0 – 8358.2)	11883.4 (8392.6 – 18151.3)	27556.7 (18553.2 – 87518.0)
Aggregated, non-Asian groups	171.7 (22.4 – 259.5)	343.1 (259.6 – 473.0)	944.6 (475.3 – 11998.1)

[a] Study baseline is SWAN follow-up visit 4, because cognitive tests were inaugurated at that visit.

[b] Tertile values are based on SWAN Visit 4; these cut-points for tertiles were maintained throughout the follow-up period. Aggregated tertile values were used as dietary exposures in relational analyses of isoflavones and cognitive function. Sample sizes per tertile in each ethnic group ranged as follows: African-American 152–153; Caucasian 243–244; Chinese 58–59; and Japanese 58–60. Aggregated tertile sample sizes were between 117–118 for Asian, 395–396 for non-Asian and 512–514 for all women combined.

[c] Aggregated tertiles, based on all ethnic/racial groups, were used for relational analyses of coumestrol and lignans. For isoflavones, relational analyses were done using non-Asian (aggregate of African-Americans and Caucasians) and Asian (aggregate of Chinese and Japanese) tertiles. See methods for details.

Table 4

The difference between cognitive test scores among those in the highest tertile of dietary lignan intake and those in the lower two tertiles, stratified by menopause transition (MT) stage

Cognitive Test[a]	*Beta* Coefficient (Standard Error)[b, c]	P value
Symbol Digital Modalities Test (1–110) Mean score = 55.53, N = 1561		
Premenopause	0.21 (1.08)	0.84
Early perimenopause	−0.64 (0.48)	0.18
Late perimenopause	−0.31 (0.64)	0.64
Postmenopause	0.34 (0.40)	0.40
East Boston Memory Test, Immediate Recall (1–12) Mean score = 10.1, N = 1561		
Premenopause	0.29 (0.23)	0.21
Early perimenopause	0.10 (0.08)	0.21
Late perimenopause	**0.39 (0.12)**	**0.002**
Postmenopause	0.13 (0.10)	0.18
East Boston Memory Test, Delayed Recall (1–12) Mean score = 9.95, N = 1560		
Premenopause	0.25 (0.22)	0.24
Early perimenopause	0.03 (0.08)	0.75
Late perimenopause	0.16 (0.13)	0.24
Postmenopause	0.18 (0.10)	0.08
Digit Span Backward Test (0–12) Mean score = 6.65, N = 1556		
Premenopause	0.38 (0.26)	0.15
Early perimenopause	−0.02 (0.11)	0.87
Late perimenopause	−0.02 (0.15)	0.89
Postmenopause	0.11 (0.10)	0.26

[a] Possible range of scores for each test given in parentheses. The mean score for each test is computed from the a model that includes only number of previous exposures to the cognitive tests and, for Symbol Digit and Digit Span tests, a spline knot to allow learning to fall after the second test administration (please see Methods for details). Sample sizes for each cognitive test vary slightly due to missing data.

[b] The beta coefficient shown represents the numbers of points by which scores differ in women in the highest tertile of intake compared to those with lesser intakes (please see Table 3 for tertile ranges). Values in bold are statistically significantly different from the referent group at $p \leq 0.05$.

[c] The model is adjusted for age, race/ethnicity, educational level, difficulty paying for basics, testing language, study site, menopausal status, body mass index and total calorie intake.

Table 5

The difference between cognitive test scores among those in highest tertile of dietary isoflavone intake and those in the lower two tertiles, stratified by menopause transition (MT) stage and race/ethnic category

Cognitive Test[a]	Asian		Non-Asian	
	***Beta* Coefficient (Standard Error)[b, c]**	**P value**	***Beta* Coefficient (Standard Error)[b, c]**	**P value**
Symbol Digital Modalities Test (1–110) Asian: mean score = 58.44, N = 354; Non-Asian: Mean score = 54.71, N = 1204				
Premenopause	0.38 (1.90)	0.84	0.66 (1.15)	0.57
Early perimenopause	0.55 (0.73)	0.45	−0.65 (0.56)	0.25
Late perimenopause	**3.14 (1.04)**	**0.003**	−0.62 (0.77)	0.42
Postmenopause	**1.72 (0.68)**	**0.01**	0.41 (0.52)	0.43
East Boston Memory Test, Immediate Recall (1–12) Asian: mean score = 9.87, N = 354; Non-Asian: mean score = 10.19, N =1207				
Premenopause	0.30 (0.32)	0.36	−0.25 (0.27)	0.34
Early perimenopause	−0.27 (0.18)	0.12	**−0.25 (0.10)**	**0.01**
Late perimenopause	−0.12 (0.26)	0.63	−0.04 (0.14)	0.75
Postmenopause	**−0.53 (0.18)**	**0.003**	0.04 (0.10)	0.70
East Boston Memory Test, Delayed Recall (1–12) Asian: mean score = 9.72, N = 354; Non-Asian: mean score = 10.01, N = 1206				
Premenopause	0.20 (0.38)	0.60	−0.18 (0.25)	0.46
Early perimenopause	**−0.41 (0.17)**	**0.02**	**−0.24 (0.10)**	**0.02**
Late perimenopause	−0.23 (0.27)	0.41	−0.10 (0.15)	0.52
Postmenopause	**−0.44 (0.18)**	**0.01**	0.07 (0.10)	0.51
Digit Span Backward Test (0–12) Asian: mean score = 6.37, N = 354; Non-Asian: mean score = 6.72, N = 1202				
Premenopause	0.29 (0.39)	0.47	−0.03 (0.30)	0.93
Early perimenopause	−0.25 (0.17)	0.14	−0.11 (0.13)	0.39
Late perimenopause	0.17 (0.28)	0.53	−0.14 (0.16)	0.38
Postmenopause	−0.26 (0.16)	0.12	0.02 (0.11)	0.83

[a] Possible range of scores for each test given in parentheses. The mean score for each test is computed from the a model that includes only number of previous exposures to the cognitive tests and, for Symbol Digit and Digit Span tests, a spline knot to allow learning to fall after the second test administration (please see Methods for details). Sample sizes for each cognitive test vary slightly due to missing data.

[b] The beta coefficient shown represents the numbers of points by which scores differ in women in the highest tertile of intake compared to those with lesser intakes (see table 3 for tertile ranges). Values in bold are statistically significantly different from the referent group at p≤0.05.

[c] The model is adjusted for age, race/ethnicity, educational level, difficulty paying for basics, testing language, study site, menopausal status, body mass index and total calorie intake.

Table 6

The difference between cognitive test scores among those in highest tertile of dietary coumestrol intake and those in the lower two tertiles, stratified by menopause transition (MT) stage

Cognitive Test[a]	*Beta* Coefficient (Standard Error)[b,c]	P value
Symbol Digital Modalities Test (1–110) Mean score = 55.53, N = 1558		
Premenopause	0.37 (1.04)	0.72
Early perimenopause	−0.56 (0.56)	0.32
Late perimenopause	−0.31 (0.68)	0.65
Postmenopause	−0.20 (0.53)	0.71
East Boston Memory Test, Immediate Recall (1–12) Mean score = 10.1, N = 1561		
Premenopause	0.10 (0.23)	0.64
Early perimenopause	−0.09 (0.10)	0.36
Late perimenopause	0.22 (0.14)	0.11
Postmenopause	−0.10 (0.10)	0.30
East Boston Memory Test, Delayed Recall (1–12) Mean score = 9.95, N = 1560		
Premenopause	−0.14 (0.22)	0.53
Early perimenopause	−0.04 (0.10)	0.70
Late perimenopause	0.19 (0.14)	0.18
Postmenopause	0.06 (0.10)	0.55
Digit Span Backward Test (0– 12); Mean score = 6.65; mean learning = 0.14, N = 1556		
Premenopause	0.41 (0.26)	0.12
Early perimenopause	−0.14 (0.13)	0.29
Late perimenopause	0.06 (0.16)	0.70
Postmenopause	−0.07 (0.12)	0.56

[a] Possible range of scores for each test given in parentheses. The mean score for each test is computed from the a model that includes only number of previous exposures to the cognitive tests and, for Symbol Digit and Digit Span tests, a spline knot to allow learning to fall after the second test administration (please see Methods for details). Sample sizes for each cognitive test vary slightly due to missing data.

[b] The beta coefficient shown represents the numbers of points by which scores differ in women in the highest tertile of intake compared to those with lesser intakes (see table 3 for tertile ranges). Values in bold are statistically significantly different from the referent group at $p \leq 0.05$.

[c] The model is adjusted for age, race/ethnicity, educational level, difficulty paying for basics, testing language, study site, menopausal status, body mass index and total calorie intake.