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Associations of Urine Excretion of Isoflavonoids with Cognition in Postmenopausal Women in the Women's Isoflavone Soy Health Clinical Trial

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Abstract

Background/Objectives—Results from randomized trials of soy supplements on cognition in postmenopausal women are equivocal. We sought to determine associations of change in urine excretion of isoflavonoids on cognitive change.

Design—Post hoc analysis of isoflavonoid exposures (mean 2.7 years) during the randomized, placebo-controlled, double-blind Women's Isoflavone Soy Health trial.

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Setting—General community.

Participants—350 healthy postmenopausal women.

Intervention—25 g of isoflavone-rich soy protein (91 mg of aglycone weight isoflavones: 52 mg genistein, 36 mg daidzein, 3 mg glycitein) or milk protein-matched placebo, provided daily.

Measurements—Overnight urine excretion and fasting plasma levels of isoflavonoids, and cognitive function, measured at baseline and endpoint.

Results—300 women (mean age = 61 years, range 45-92 years) completed both cognitive assessments and did not use hormone replacement therapy during the trial. Mean on-trial change from baseline in urine excretion of isoflavonoids was not significantly associated with change in a composite score of global cognition ($p=0.39$). Secondary analyses indicated that change in urine excretion of isoflavonoids was inversely associated with change in a factor score representing general intelligence ($p=0.02$), but not with factor scores representing verbal or visual episodic memory. Mean differences in this general intelligence factor score among women in the first compared to highest quartile of isoflavonoid change are equivalent to an approximate 4.4 year age-associated decline. Analyses based on plasma isoflavonoid levels yielded similar but attenuated results.

Conclusion—Among healthy postmenopausal women, long-term changes in isoflavonoids are not associated with global cognition, supporting clinical trial results. Increasing isoflavonoid exposure from dietary supplements is, however, associated with decrements in general intelligence but not memory; this finding requires confirmation in future studies.

Keywords

Cognition; isoflavones; menopause; soy; women's health

INTRODUCTION

While two large randomized clinical trials of soy isoflavone supplements in postmenopausal women discerned no important effects on cognition ^{1, 2}, other isoflavone trials and observational studies on soy product consumption suggested cognitive benefit 3-7 or harm ⁶⁸⁻¹⁰, often within specific domains of cognitive function. Examination of the associations between biologic exposure — inferred from urine excretion or plasma levels of isoflavones — and cognition might help resolve discrepancies, provide insight regarding mechanisms by which soy isoflavones might influence cognitive function, and guide decisions on the optimal dose of soy isoflavone formulations.

The Women's Isoflavone Soy Health (WISH) trial, designed to assess health effects of dietary supplementation with isoflavone-rich soy protein (ISP), was conducted in 350 healthy midlife and older postmenopausal women randomized to placebo or to daily ISP in a dose comparable to that of a traditional Asian diet. One outcome of the WISH trial evaluated the ISP effect on cognitive change ². The primary intent-to-treat analysis showed no overall cognitive benefit after more than 2.5 years of daily dietary ISP, but in secondary analyses women receiving ISP showed significantly greater improvement in visual memory compared to women receiving placebo. Herein, we report associations of urine excretion and

plasma levels of isoflavones and their metabolites on cognitive change during the course of the WISH trial. Primary analyses based on overnight urine excretion were validated in secondary analyses of plasma levels.

METHODS

The WISH trial was conducted as a single-center randomized, double-blind, placebo-controlled trial. 350 healthy postmenopausal women were randomly assigned to daily 25 g ISP or to daily total milk protein matched placebo (0 mg isoflavones), offered in a powder or bar form. Women who had used hormone therapy or consumed isoflavone supplements during the preceding month of screening were ineligible. ISP contained 91 mg aglycone weight naturally occurring isoflavones (154 mg total isoflavone equivalents), composed of genistein (52 mg aglycone equivalents), daidzein (36 mg aglycone equivalents) and glycitein (3 mg aglycone equivalents). Solae LLC (St. Louis, MO) supplied study products without charge. The planned treatment period was 2.5 years.

The primary WISH trial endpoint was the effect of ISP compared to placebo on progression of subclinical atherosclerosis measured by carotid artery intima-media thickness ¹¹. A secondary trial endpoint was the ISP effect on cognitive change, determined among 313 women who had both baseline and endpoint cognitive test data ². Planned ancillary analyses reported herein were associations between urinary excretion and plasma levels of isoflavonoids and cognitive test performance, conducted within the entire randomized sample.

Cognitive Assessment

Neuropsychological tests were selected to measure a broad spectrum of cognitive abilities, as described ² (Supplemental Table 1). Cognitive ability (verbal intelligence quotient) was estimated at baseline with the Wechsler Test of Adult Reading ¹²; mood was assessed with the Center for Epidemiological Studies Depression scale (CES-D) ¹³. Participants were tested prior to randomized intervention and at the study end point, approximately 2.5 years later (mean 33 months; range 24-41 months).

Demographic and Clinical Variables

Demographic information (age, education and race/ethnicity), smoking history, medication and nutritional use, and reproductive history were obtained by structured questionnaires. Baseline vasomotor symptoms were assessed with a hot flash diary beginning at least 2 weeks prior to randomization (median duration of recording = 31 days). Women recorded the number and rated the intensity of hot flashes experienced daily, classified as mild: warm sensation, no perspiration, no disruption of activity; moderate: warm sensation, with perspiration, no disruption of activity; severe: hot sensation with perspiration, disruption of activity ¹⁴. Body mass index was calculated as weight divided by height squared (kg/m²).

Isoflavonoids

Urine excretion and plasma levels of soy isoflavones (genistein, daidzein, and glycitein) and their metabolites (equol, dihydrogenistein, dihydrodaidzein, and O-desmethylangolensin)

were assessed at baseline and six-month intervals¹⁵. Plasma was collected after an overnight fast, and overnight urine collection began the night of the overnight fast. Isoflavonoids (isoflavones and metabolites) were quantified as previously described¹⁵. Plasma levels of isoflavonoids were expressed in nmol per liter and urinary excretion of isoflavonoids were adjusted for urine volume using creatinine concentrations and expressed in nmol per mg creatinine; the latter were measured with a Roche-Cobas MiraPlus CC clinical chemistry autoanalyzer¹⁵.

Changes in isoflavonoids were summarized as average on-trial values minus baseline values. Overnight urinary excretion of isoflavonoids were significantly correlated at baseline and during the course of the trial with fasting plasma levels¹⁵. Because overnight urine excretions are more valid measures of cumulative isoflavonoid exposure¹⁵, our primary analyses focused on urine excretion; findings were confirmed in secondary analyses of plasma levels.

Statistical Analysis

350 women were randomized into the WISH trial; 313 women completed cognitive assessments at baseline and at the end of the trial. Seven women who reported use of hormone therapy during the trial were excluded; 6 women without overnight urine measures of isoflavonoids were excluded, leaving 300 women (150 randomized to ISP, 150 randomized to placebo) for the present analysis.

The primary cognitive outcome was the change in global cognition, a composite score calculated at baseline and study end point as a weighted average of the standardized scores for each of 14 individual neuropsychological tests (weighted by the inverse of the correlations between tests)². Standardization used test means and standard deviations of baseline neuropsychological test data from the entire sample. So that an association with a specific cognitive domain did not go undetected due to the use of a global composite measure, secondary analyses used change scores for cognitive factors and for individual tests, described previously². The first factor represented aspects of executive function (including working memory), verbal expression, and visuospatial skills (general intelligence factor). The three other factor scores represented aspects of episodic memory: a verbal learning factor from list-learning tasks, a verbal logical memory factor from paragraph recall tasks, and a visual memory factor from facial recognition tasks (Supplemental Table 1).

Cognitive change scores (endpoint minus baseline) were computed for the global composite, the four cognitive factors and, if a significant association was found for global cognition or a specific factor score, individual neuropsychological tests. Age, BMI, systolic blood pressure, estimated verbal intelligence, mood (CES-D), education and race were considered as possible confounders. Only age and education changed the regression coefficient of interest (the association of isoflavonoid with cognitive change) by more than 10% and were included in the final models.

We used multivariable linear regression to evaluate the associations of baseline and change in overnight urine excretion of individual isoflavones and individual metabolites, total isoflavones (genistein + daidzein + glycitein), and total isoflavonoids (total isoflavones +

equol + dihydrogenistein + dihydrodaidzein+ O-desmethylangolensin), all modeled as continuous independent variables, with change scores for global cognition or cognitive factors (dependent variables). Regression analyses were conducted within the combined treatment groups, unless otherwise specified. In addition to age and education, regression models adjusted for the baseline value of the cognitive score and the baseline level of the isoflavonoid measure under consideration.

Pre-planned analyses included evaluation of the associations of isoflavonoid changes within subgroups defined by age (< 60 years or ≥ 60 years), time since menopause (< 5 years; 5-10 years; >10 years), menopause type (natural or surgical), vasomotor symptoms at baseline (any or none)² and past use of hormone therapy (yes or no). For these analyses effect modification was tested by adding subgroup-by-total isoflavonoid interaction terms. Significance was set at $p < 0.05$ for analyses based on global cognition and cognitive factor change scores and $p < 0.004$ (0.05/14) for change scores based on individual cognitive tests. Data were analyzed using SAS statistical software, 9.2, SAS Institute Inc., Cary, NC, USA.

RESULTS

Participants were primarily non-Hispanic White (62%) of above average intelligence, ranging in age from 45 to 92 years (mean age = 61 years). More than half were college graduates. Most participants did not smoke, were on average mildly overweight (mean BMI = 26.6 kg/m²) and were normotensive. Clinical and cognitive factors at baseline did not differ between treatment groups (Table 1).

Isoflavonoids and Associations with Global Cognition and Cognitive Factors

Baseline overnight urine excretions of individual isoflavones, total isoflavones, or total isoflavonoids were not significantly associated with baseline measures of global cognition or with any baseline cognitive factor score (all p -values ≥ 0.17, data not shown).

Change in overnight urine excretion of individual isoflavones, total isoflavones or total isoflavonoids were not significantly associated with the 2.5-year change in the global cognition change score or with changes on the three cognitive factors measuring aspects of episodic memory (Table 2). However, changes in each were significantly negatively associated with change on the general intelligence factor. In post hoc analyses of individual tests comprising this factor, each of the eight tests showed negative associations with change in total isoflavonoids, although none of the individual associations were statistically significant (all p -values > 0.004; Supplemental Table 2). Larger effects were seen for tests assessing working memory and other aspects of executive functions (Letter-Number Sequencing, Category Fluency, Shipley Abstraction, and the Trail-Making Test, part B). To help place this result in a clinical context, the cross-sectional baseline association between general intelligence and age was -0.143 units per year of age. For women in the upper quartile of isoflavonoid change compared to the lowest quartile, the mean difference in 2.5-year change in general intelligence was -0.625; this difference is therefore equivalent to age-associated declines of 4.4 years.

There was no evidence of a quadratic relationship between change in overnight urine excretion of total isoflavonoids and changes on global cognition or any of the cognitive factor scores (all p-values = 0.44). Change in plasma isoflavonoids showed similar but somewhat smaller associations as for change in overnight urine excretion of isoflavonoids (Supplemental Table 3).

Linear regression model assumptions regarding homoscedasticity and normality of residuals were met. No collinearity was present among model covariates.

Subgroup Analyses

We examined whether total isoflavonoid effects on change in the general intelligence factor were modified within defined subgroups (Table 3). Type of menopause significantly modified this association; the inverse association between change in isoflavonoids and change in this factor score was of greater magnitude in women who had undergone surgical menopause compared to women who experienced natural menopause. Although this association was not significantly modified by other subgroup factors, the inverse association was somewhat stronger in older women, in women without vasomotor symptoms at baseline (who tended to be older), and in women who had never used hormone therapy.

Sensitivity Analyses

Primary endpoint analyses were repeated using change in total isoflavonoids, controlling additionally for randomized treatment group as well as total number of visits with overnight urine excretion samples; results were not altered. Analyses were also repeated using area under the curve of overnight urine excretion measured over the trial¹⁶ and average on-trial plasma levels (Supplemental Table 3); results remained essentially the same.

DISCUSSION

The randomized WISH trial conducted among healthy postmenopausal women provided soy isoflavones in quantities within the upper range of traditional Asian diets¹⁷. This was the longest and largest trial of isoflavone supplementations with a high rate of adherence to study intervention (median compliance was 90%). WISH is the only such trial to have obtained repeated samples of overnight urinary excretion and plasma levels of the three primary soy isoflavones and their principal metabolites, and to examine their associations with cognition. Supporting the main finding from the WISH trial of no ISP effect on global cognition when compared to placebo², we found no significant association between change in urinary excretion or plasma levels of individual isoflavones, total isoflavones, or total isoflavonoids and change in global cognition over a 2.5-year period.

We also found that changes in isoflavonoids were significantly negatively associated with changes in general intelligence but not with changes in memory. Episodic memory depends particularly on function of the hippocampus and other medial temporal lobe structures¹⁸, whereas general intelligence depends more on function of association cortex in other regions of the cerebrum¹⁹. This novel finding was driven largely by relative reductions in scores on neuropsychological tests assessing executive functions (Letter Number Sequencing, category fluency, Shipley Abstraction, and the Trail-Making Test, part B) thought

particularly to involve frontal cortex, although associations with individual test change scores were not themselves significant. These results fail to support inferences from small clinical trials in postmenopausal women that soy isoflavone supplements might benefit aspects of executive function^{3, 6} but are consistent with results of a small trial of older men and women where placebo-treated subjects performed better than isoflavone-treated subjects on two tests measuring executive function: Trail Making Test part B and Stroop Color-Word test⁶.

Although age did not significantly modify the association between change in general intelligence and urinary excretion of isoflavonoids, the negative association was significant only in older postmenopausal women. Similarly, subgroup analysis in the WISH clinical trial indicated that women age 60 years and over randomized to ISP performed significantly worse on the general intelligence factor than older women in the placebo group; this difference was not evident among women below the age of 60 years (p for interaction=0.06; unpublished data).

In subgroup analyses that examined the relation between changes in total isoflavonoid excretion and general intelligence, surgically menopausal women showed significantly greater cognitive decline in relation to isoflavonoid increases than naturally menopausal women. This finding is consistent with WISH clinical trial findings of a decline in global cognition among surgically menopausal women assigned to ISP relative to placebo, a difference representing about three-fourths of a standard deviation in cognitive performance². However, the finding was unanticipated, and the potential significance of this finding is tempered by the relatively small size of this subgroup. In other subgroup analyses, there were no significant interactions based on time since menopause, the presence of vasomotor symptoms, or prior use of hormone therapy.

WISH participants randomized to receive ISP showed significant improvement in visual (but not verbal) memory compared to placebo-treated participants². Visual memory changes, however, were only weakly and nonsignificantly associated with changes in isoflavones or total isoflavonoids. In post hoc exploratory analyses, changes in visual memory were positively associated only with changes in O-desmethylangolensin (β (CI) = 0.017 (0.002 to 0.033), p = 0.03), a daidzein metabolite produced by about 80-90% of the population²⁰. O-desmethylangolensin change was not significantly associated with change in other cognitive factors, and the potential clinical relevance of this association requires independent confirmation.

Soy isoflavones bind estrogen receptors, with greater affinity for the beta receptor than alpha receptor^{21, 22}. Transcriptional activation may involve mechanisms that differ from those of its natural ligand estradiol²³. Within human brain, estrogen receptor-beta expression is relatively high in the hippocampus and cerebral cortex²⁴. Putative cognitive effects are usually ascribed to receptor binding within the brain, although soy isoflavones may act as selective estrogen receptor modulators rather than as pure agonists²⁵. Estrogenic activity of selective estrogen receptor modulators may be regionally specific within the brain²⁶. Non-estrogenic properties of soy isoflavones have the potential to influence cognition as well,

including antioxidative effects, regulation of cerebral blood flow, and effects on cholinergic, dopaminergic, and GABAergic neurotransmitter systems²⁷.

Strengths of this study are the relatively large sample of healthy women that included both midlife and older postmenopausal women, repeated urine excretion and plasma levels of several isoflavonoids over a 2.5-year period, and use of a comprehensive battery of neuropsychological tests. Sample sizes were limited for subgroup analyses, and we did not assess dietary phytoestrogens more abundant in non-soy food products. Findings do not generalize to people who were not eligible for the WISH trial, including men, women of reproductive age, or women with cognitive disorders such as Alzheimer's disease.

Macronutritional benefits of soy are well recognized. Soy is an important source of high-quality protein, low in saturated fat and high in fiber content. For postmenopausal women, present findings indicate that dietary soy supplements intended to increase isoflavonoid exposure do not improve global cognition. Secondary analyses, which suggest decrements in general intelligence of more than 4 age-associated years with relatively large increases in isoflavonoid exposure over the course of 2.5 years, should be confirmed in future studies and can be weighed against clinical trial evidence for improved visual memory. However, based on limited evidence, postmenopausal women considering long-term soy isoflavone dietary supplements should consider a lower dose than that studied in the WISH trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1Participant Characteristics at Baseline (n=300)^a

Characteristic ^b	ISP Group (n=150)	Placebo Group (n=150)
Age, y	61 ± 7	61 ± 7
Race or ethnicity, n ^c (%)		
White, non-Hispanic	89 (60%)	98 (65%)
Black, non-Hispanic	11 (7%)	9 (6%)
Hispanic	28 (19%)	21 (14%)
Asian	21 (14%)	22 (15%)
Education, n (%)		
Less than high school	2 (<1%)	1 (<1%)
High school or some college	65 (43%)	55 (37%)
College graduate	83 (55%)	94 (63%)
Smoking history, n (%)		
Current	3 (2%)	4 (3%)
Former	62 (41%)	52 (35%)
Never	85 (57%)	94 (63%)
Age at menopause, y ^c	49.5 ± 4.7	49.6 ± 4.8
Time since menopause, y		
Mean, y	11 ± 8	11 ± 8
< 5y, n (%)	29 (19%)	31 (21%)
5 to 10 y, n (%)	45 (30%)	42 (28%)
> 10 y, n (%)	64 (43%)	58 (39%)
Unknown ^c	12 (8%)	19 (13%)
Type of menopause, n (%) ^c		
Natural	140 (93%)	134 (90%)
Surgical	10 (7%)	15 (10%)
Past use of hormone therapy, n (%)		
Yes	113 (75%)	103 (69%)
No	37 (25%)	47 (31%)
Hot flashes within previous month, n (%) ^c		
None, n (%)	71 (50%)	65 (46%)
Any, within previous month, n (%)	70 (50%)	77 (54%)
Body mass index, kg/m ²	26.6 ± 5.1	26.6 ± 5.0
Systolic blood pressure, mm Hg	117 ± 13	119 ± 14
Diastolic blood pressure, mm Hg	75 ± 9	75 ± 9
Verbal intelligence quotient estimate	107 ± 13	108 ± 12
Mood (CES-D)	6.8 ± 6.4	7.3 ± 7.1

Characteristic ^b	ISP Group	Placebo Group
Baseline isoflavonoids, median (25th, 75th percentile) ^d		
Overnight urine excretion, nmol per mg creatinine		
Genistein	0.23 (0.06, 1.3)	0.19 (0.06, 0.90)
Daidzein	0.76 (0.18, 3.7)	0.61 (0.14, 2.9)
Glycitein	0.08 (0.02, 0.37)	0.05 (0.02, 0.43)
Dihydrogenistein	0.05 (0.02, 0.37)	0.03 (0.12, 0.20)
Dihydrodaidzein	0.12 (0.02, 1.8)	0.13 (0.02, 1.1)
O-desmethylangolensin	0.15 (0.02, 1.01)	0.10 (0.02, 0.92)
Equol	0.02 (0.01, 0.06)	0.03 (0.01, 0.07)
Total isoflavonoids	1.51 (0.34, 9.6)	2.04 (0.51, 11.9)
Plasma levels, nmol/L per liter		
Genistein	12.6 (4.5, 54.3)	7.5 (3.3, 38.2)
Daidzein	16.6 (3.6, 55.6)	11.4 (4.2, 47.4)
Glycitein	1.9 (0.50, 7.6)	2.1 (0.50, 5.3)
Dihydrogenistein	0.50 (0.50, 4.2)	0.50 (0.50, 3.5)
Dihydrodaidzein	5.0 (0.50, 20.5)	4.9 (0.05, 14.6)
O-desmethylangolensin	3.9 (1.0, 20.4)	4.1 (1.0, 15.1)
Equol	4.0 (2.1, 7.1)	3.9 (1.0, 6.7)
Total isoflavonoids	39.7 (16.3, 160.3)	63.3 (17.3, 98.8)
Baseline neuropsychological global composite and factor test scores ^e (sample size)		
Global Cognition	0.005 ± 1.8	0.002 ± 1.7
(150,150)	(-5.9, 4.2)	(-5.5, 4.4)
General intelligence (executive/expressive/visuospatial)	0.44 ± 5.4	0.07 ± 5.7
(144,142)	(-15.3, 10.6)	(-22.2, 11.6)
Verbal episodic memory (list learning) factor	-0.001 ± 1.7	0.06 ± 1.9
(149,148)	(-5.0, 3.7)	(-5.8, 4.4)
Verbal episodic memory (logical memory) factor	-0.05 ± 1.9	0.05 ± 1.8
(150,148)	(-8.1, 2.4)	(-5.5, 2.4)
Visual episodic memory factor	-0.06 ± 2.0	-0.004 ± 1.7
(150,149)	(-5.2, 4.8)	(-3.8, 4.6)

^aData are given as mean (± SD) or number (%).

^bDemographic and clinical characteristics were compared between treatment groups with 2-sample *t* tests (or Wilcoxon rank sum) for continuous variables and χ^2 tests for categorical variables. Between group differences were not significant for any baseline comparison (all *p* > 0.11).

^cRace was unknown for 1 woman (ISP); age at menopause and time since menopause were unknown for 31 women (12 ISP, 19 placebo [hysterectomy without oophorectomy, or hysterectomy where it was not known whether oophorectomy was performed]); type of menopause was unknown for 1 woman (placebo); hot flash information was missing for 17 women (9 ISP; 8 placebo); and intelligent quotient estimates (Wechsler Test of Adult Reading scores) were missing for 4 women (2 ISP; 2 placebo).

CES-D = Center for Epidemiological Studies Depression scale; ISP = isoflavone-rich soy protein.

^dBaseline values are median (25th, 75th percentile).

^eTest scores are weighted sum of z scores. Numbers in parentheses represent the minimum and maximum test scores.

Table 2

Changes^a in Global Cognition Composite Score and Cognitive Factors, by Changes^b in Overnight Urine Excretion of Isoflavonoids

Endpoint (Sample size = 300)	Genistein			Daidzein			Glycitein			Total Isoflavones			Total Isoflavonoids		
Primary Endpoint	β (CI) ^c	p-value ^d	β (CI)	β (CI)	p-value	β (CI)	β (CI)	p-value	β (CI)	β (CI)	p-value	β (CI)	β (CI)	p-value	
Cognitive composite score (275) ^e	-0.009 (-0.021 to 0.003)	0.151	-0.003 (-0.010 to 0.004)	-0.053 (-0.132 to 0.025)	0.39	-0.003 (-0.010 to 0.004)	-0.003 (-0.007 to 0.002)	0.178	-0.003 (-0.007 to 0.002)	-0.001 (-0.004 to 0.001)	0.25	-0.001 (-0.004 to 0.001)	-0.001 (-0.004 to 0.001)	0.39	
Secondary Endpoints															
Cognitive Factor Scores															
I. General intelligence factor (253)	-0.038 (-0.066 to -0.010)	0.008 ^f	-0.017 (-0.034 to -0.0009)	-0.262 (-0.446 to -0.078)	0.039 ^f	-0.013 (-0.023 to -0.003)	-0.005 ^f	0.014 ^f	-0.007 (-0.013 to -0.001)	0.016 ^f	0.184	-0.002 (-0.006 to 0.001)	-0.002 (-0.006 to 0.001)	0.184	
II. Verbal episodic memory (list learning) factor (269)	-0.01 (-0.028 to 0.006)	0.197	-0.004 (-0.014 to 0.006)	-0.049 (-0.185 to 0.088)	0.47	-0.002 (-0.014 to 0.010)	-0.002 (-0.009 to 0.006)	0.48	-0.002 (-0.009 to 0.006)	-0.0003 (-0.005 to 0.004)	0.68	-0.0003 (-0.005 to 0.004)	-0.0003 (-0.005 to 0.004)	0.91	
III. Verbal episodic memory (logical memory) factor (273)	-0.004 (-0.025 to 0.017)	0.71	-0.002 (-0.014 to 0.010)	0.073 (-0.017 to 0.164)	0.72	0.006 (-0.002 to 0.015)	0.004 (-0.002 to 0.009)	0.113	0.004 (-0.002 to 0.009)	0.002 (-0.0007 to 0.005)	0.176	0.002 (-0.0007 to 0.005)	0.002 (-0.0007 to 0.005)	0.139	
IV. Visual episodic memory factor (273)	0.005 (-0.008 to 0.019)	0.44	0.006 (-0.002 to 0.015)		0.121										

^aEndpoint minus baseline value.

^bOn-trial minus baseline level.

^cCI, 95% confidence intervals. Models adjusted for the baseline cognitive composite or cognitive factor score, baseline isoflavone level, age and education.

^dSignificance was defined as $p < 0.05$ for the cognitive composite score and for cognitive factor scores.

^eTwenty-five subjects did not provide on-trial overnight urine samples. 6 subjects (1 ISP, 5 placebo) provided 1 on-trial overnight urine sample; 7 subjects (4 ISP, 3 placebo) provided 2 on-trial overnight urine samples, 13 (8 ISP, 5 placebo) provided 3; 49 (24 ISP, 25 placebo) provided 4; 200 (104 soy, 96 placebo) provided all 5 on-trial overnight urine samples.

^fStatistically significant

Table 3

Subgroup Analyses: Changes^a in General Intelligence Factor by Changes^b in Overnight Urine Excretion of Total Isoflavonoids

Characteristic	β (CI) ^c	P- valued	P-value, subgroup by isoflavone interaction
Age group — yr			
<60 (121)	−0.003 (−0.012 to 0.005)	0.42	0.202 ^d
60 (132)	−0.012 (−0.021 to −0.004)	0.005	
Time Since Menopause — yr			
<5 (50)	−0.018 (−0.030 to −0.007)	0.003	0.101 ^d
5–10 (78)	0.005 (−0.007 to 0.016)	0.42	
>10 (101)	−0.014 (−0.023 to −0.005)	0.003	
Type menopause			
Natural (233)	−0.004 (−0.010 to 0.001)	0.141	<0.001
Surgical (20)	−0.068 (−0.095 to −0.041)	<0.001	
Vasomotor symptoms, within past month			
Any (130)	−0.002 (−0.011 to 0.008)	0.73	0.107
None (109)	−0.012 (−0.020 to −0.004)	0.005	
Prior use of hormone therapy			
Yes (181)	−0.006 (−0.012 to 0.001)	0.114	0.34
No (72)	−0.01 (−0.022 to −0.0009)	0.033	

^aEndpoint minus baseline value.

^bOn-trial average minus baseline level.

^cCI, 95% confidence intervals. Models adjusted for the baseline cognitive composite or cognitive factor score, baseline total isoflavonoid level, age and education.

^dModeled as a continuous variable.