

Effects of soy isoflavone supplementation on cognitive function in Chinese postmenopausal women: a double-blind, randomized, controlled trial

Suzanne C. Ho, PhD, MSc, MPH,¹ Agnes S. Y. Chan, PhD,² Yee Ping Ho, PhD,³ Edwin K. F. So, BSc,¹ Aprille Sham, MBA,¹ Benny Zee, PhD,¹ and Jean L. F. Woo, MD, FRCP¹

Abstract

Objective: To investigate whether soy-derived isoflavone extract improves performance in cognitive function and quality of life in Chinese postmenopausal women.

Design: The study was a 6-month double-blind, randomized, placebo-controlled, parallel group trial. Participants were community-dwelling women aged 55 to 76 years; 191 eligible women were randomly assigned to receive a daily oral intake of 80 mg soy-derived isoflavones or an identical-appearing placebo for 6 months. Standardized neuropsychological tests of memory, executive function, attention, motor control, language, and visual perception and a global cognitive function assessment were administered face-to-face individually at baseline and at 6-months posttreatment. The validated Chinese version of the Short Form-36 was used for quality of life measurements.

Results: Of the participants, 88% (168 women: 80 among the supplementation group and 88 among the placebo group) completed the trial. Intention-to-treat analysis, conducted for 176 participants with 6-month assessment results, revealed no significant differences in outcome measures between treatment groups. Subgroup analysis among the good compliers only (consumed at least 80% of the supplements or placebo; n = 168) and among the age groups younger or older than 65 years also indicated no significant differences for any outcome measures. Types of complaints of adverse events were similar in both treatment groups and included mainly gastrointestinal and musculoskeletal problems.

Conclusions: This 6-month trial indicates that 80-mg soy-derived isoflavone supplementation did not improve performance on standard neuropsychological tests and overall quality of life in generally healthy Chinese postmenopausal women.

Key Words: Soy isoflavones – Cognitive function – Postmenopausal women – Randomized, controlled trial.

As a population ages, an increasing proportion is affected by age-related cognitive declines. The effect is more severe in elderly women, who generally have a higher risk of developing cognitive impairment than men.^{1,2} Menopause-related estrogen deficiency has been proposed as a contributory cause of age-related cognitive decline in postmenopausal women.^{3,4} Until recently, hormone therapy (HT) was used for its effects on

menopausal symptoms and to prevent stroke, coronary events, osteoporosis, and Alzheimer's disease.

Animal studies, systematic reviews of human studies, and data based on neuroimaging techniques have generally supported the positive role of estrogens on brain functions.^{5,6} However, other investigators and recent studies have reported conflicting results.⁷⁻⁹ HT-related health risks have also posed a concern for its wide application in postmenopausal women.¹⁰

Phytoestrogens are weakly estrogenic, diphenolic compounds found in plant foods. These heterocyclic phenols are structurally similar to mammalian estrogens, and they have weak estrogenic activity attributable to their affinity for estrogen receptors.¹¹ It has been hypothesized that phytoestrogens, particularly soy isoflavones, are effective in the alleviation of estrogen deficiency-related health problems and may be effective in enhancing memory and cognitive functions. Animal studies have indicated that soy phytoestrogens may have a positive effect in the brains of rats and primate models and may protect against postmenopausal

Received June 29, 2006; revised and accepted October 19, 2006.

From the ¹Department of Community and Family Medicine and the School of Public Health, ²Department of Psychology, and ³School of Pharmacy, The Chinese University of Hong Kong, Hong Kong SAR.

Funding/support: This study was supported by the Research Grants Council of Hong Kong (CUHK 4471/03M).

Financial disclosure: None reported.

Address correspondence to: Professor Suzanne C. Ho, PhD, Department of Community and Family Medicine, 4/F School of Public Health, Prince of Wales Hospital, Shatin, N.T., Hong Kong SAR. E-mail: suzanneho@cuhk.edu.hk.

neurodegeneration.^{12,13} However, results of human trials are inconclusive. Although a study in young adults¹⁴ and two studies in postmenopausal women have reported some positive results,^{15,16} a longer-term and larger study has shown no significant positive effect on any neuropsychological test results.¹⁷ There are few available data for Asian populations, among whom soy is a component of a traditional diet. A trial¹⁸ using supplementation with 100 mg isoflavones derived from *Pueraria lobata* showed a significant positive effect on cognitive function for the test group, as measured by the Modified Mini-Mental State Examination (MMSE), compared with the control group, with a magnitude similar to that for the group taking conjugated equine estrogens (0.625 mg).

In this 6-month double-blind, placebo-controlled trial, we investigated the effects of soy-derived isoflavone supplementation in Chinese healthy postmenopausal women using standardized tests of memory, executive function, attention, motor control, language, and visual perception and a global cognitive function test. We also assessed quality of life as a secondary outcome measure.

METHODS

Participant recruitment

This 6-month double-blind, placebo-controlled study was conducted at a single site. The potential participants were recruited over a 6-month period from the community through newspaper advertising and health talks. Other print media, such as newsletters, posters, and advertisements at hospitals, health clinics, elderly centers, some associations, churches, and housing estates in Shatin, Hong Kong, were also used. Potential participants were screened for eligibility. Inclusion criteria were Chinese ethnicity with Hong Kong residency; age between 55 and 75 years; postmenopausal status (defined as at least 12 months since the last menstrual cycle) for at least 5 years; body mass index between 18 and 32 kg/m²; no history of mental, neurological, or other chronic disorders, such as chronic renal failure, chronic liver failure, or thyroid disease; no surgery of the gastrointestinal tract; no history of drug or alcohol abuse; no use of HT in the preceding 6 months; no use of medication known to affect the nervous system; and no use of isoflavone and calcium supplements in the past 12 months. Women were excluded if they had dementia, parkinsonism, insomnia of 1 month's duration or longer, known intellectual problems, a history of a venous thromboembolic event, a history of head injury with loss of consciousness, or psychiatric illness, or if they were, for any reason, unable to give informed consent. Women with depression, as assessed by the Center for Epidemiologic Studies Depression scale¹⁹ with a score higher than 16, were also excluded. The study was approved by the ethics committee of the Chinese University of Hong Kong.

A total of 238 potential participants were recruited over a 7-month period from February to August 2004. A 2-week run-in period with the use of placebo supplement was carried

out to familiarize the participants with the trial requirements. Thirty-eight women dropped out or were excluded because of loss of interest during the run-in period or reported side effects. The remaining 200 women who had good adherence to the study protocol were formally recruited into the study.

Participants were stratified by educational level (no formal, primary, secondary, or tertiary education) before random assignment into one of the two study arms, according to a block randomization list developed by one of the coinvestigators (a biostatistician not involved in the administrative aspects of the study). Participants were given soy-derived isoflavones, 80 mg orally daily for 6 months, or a daily placebo for the same length of time. As an incentive for improving the retention rate, bone densitometry tests of the spine and hip were offered to women who completed the trial.

The soy-derived isoflavone extract was supplied by Acacris Holding B.V. (Giessen, The Netherlands). Identical placebo capsules were produced by a local pharmaceutical manufacturer according to good manufacturing practice. The daily dose was 80 mg total soy isoflavones (contained in 250 mg powder) or placebo material (starch). The uniformity of the isoflavone content present in a given sample of capsules by weight and concentration of active ingredients was evaluated using a validated reverse-phase high-performance liquid chromatography method. All participants were supplied with a calcium supplement (containing 400 mg elemental calcium in the form of calcium carbonate, 5 mg zinc, 150 mg magnesium, and 100 IU vitamin D [Osteocare, Vitabiotics Ltd, London, England]), supplied by Mekim Limited (Kowloon, Hong Kong).

Numbered bottles containing isoflavone or placebo capsules were given to the participants at 2-month intervals. Careful instructions on oral intake (once per day with meals) were given. Participants were advised to discontinue the use of other dietary supplements during the trial period. Participants were monitored continuously throughout the study for compliance and reports of adverse events. Compliance was assessed by telephone with reports of the remaining capsules (after 2 wk and at the first, third, and fifth mo) and by counting the capsules at follow-up visits (at the second, fourth, and sixth mo). As an additional measure of compliance, participants were asked to return all bottles at the end of the study. A woman taking at least 80% of the capsules was considered to have good compliance.

Outcome measures

Standardized neuropsychological tests of memory, executive function, attention, motor control, language, and visual perception and a global cognitive function test were administered face-to-face individually at the baseline and then at 6 months posttreatment by an independent tester who had been blinded to the group assignment of women.

Tests of learning and memory were based on (1) the Hong Kong List Learning Test,²⁰ in which the rate of learning, rate of forgetting, encoding and retrieval deficits, and learning strategies were assessed, and (2) the Rey-Osterrieth

Complex Figure Test and Wechsler Memory Scale–Revised,²¹ which assessed visuospatial constructional ability and visual memory. Tests of executive function were based on (1) the Trail Making Test,²² designed to assess speed for attention, sequencing, mental flexibility, visual search, and motor function, and (2) the Verbal Fluency Test,²³ in which language ability in two categories of objects (animals and transportation) was tested. Tests of attention and concentration included the Digit Span Tests in the Wechsler intelligence (Wechsler Adult Intelligence Scale–Revised) and memory (Wechsler Memory Scale–Revised) scales^{24,25} to assess the span of immediate verbal recall and the Digit Vigilance Test²⁶ to assess the capacity for sustained attention. The Finger Tapping Test²⁷ was used to measure simple motor speed of the index fingers of both hands. The Boston Naming Test (Modified Short-Form, 30 items)²⁸ was used to assess the ability to name picture objects with a wide range of degree of difficulty. Tests of visual perception and constructional ability were based on the Rey-Osterrieth copy trial of the visual reproduction subtest of the Wechsler Memory Scale–Revised.²⁵ A composite score of the overall test results for individual participants was also calculated as the sum of the *z* scores of the 13 neuropsychological test metrics.

A global cognitive function test was performed using the MMSE.²⁹ The test, which measures general intelligence and global cognitive level, consists of oral responses for orienta-

tion, memory, and attention and the ability to name objects and follow verbal and written commands. The MMSE has been validated for use in the Chinese population (Cronbach’s $\alpha = 0.86$, test-retest reliability correlation = 0.78).³⁰ Women found to have a score of less than 23 for the baseline MMSE were excluded from analysis. The validated Chinese version of the Short Form-36 (SF-36)³¹ was used for quality of life measurements as a secondary outcome measure.

Other measurements

Structured and previously validated questionnaires on sociodemographic data and on factors that may have possible confounding effects on the relation between soy isoflavones and cognitive function were also administered at baseline and at 6 months posttreatment. The information included smoking and alcohol intake, dietary intake of soy phytoestrogens on the basis of a quantitative food frequency questionnaire,³² menopausal symptoms,³³ and sleeping difficulty.³⁴

Statistical analysis

Intention-to-treat analysis was used as the primary analysis and performed for those participants who were randomly assigned to receive treatment, had received at least one dose of the trial supplement, and had returned for the 6-month posttreatment evaluation. Further analysis was also performed separately for participants with good compliance, defined as those consuming at least 80% of the supplement

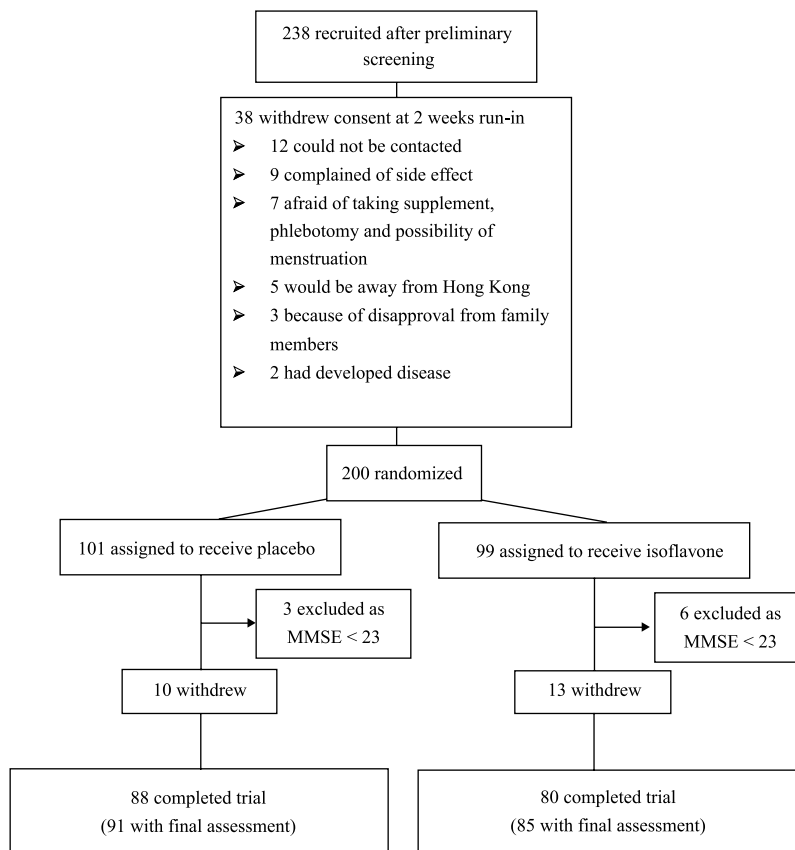


FIG. 1. Flowchart of cognitive function. MMSE, Modified Mini-Mental State Examination score.

capsules. Subgroup analysis by age groups (55-65 and 66-76 y) was also conducted.

Comparisons of the baseline characteristics of the participants receiving the two treatments were done by using *t* tests for the continuous variables and a chi-square test for the categorical variables. For the estimation of treatment effect, a calculation was done for the mean differences and 95% CIs of the change values from baseline to posttreatment between the treatment arms. The changes from baseline to 6 months were compared between treatment arms using the repeated-measures analysis of variance method. Effects of treatment on neuropsychological test results were also assessed after controlling for covariates (age, education, sleep, vasomotor symptoms, and dietary isoflavone intake over the period of intervention) using the general linear model approach.

RESULTS

Two hundred women who had successfully completed the run-in were randomly assigned to the treatment and placebo arms. Three women from the placebo group and six women from the treatment groups were excluded from analysis

because they had MMSE scores lower than 23 at the baseline assessment. Of the 191 participants, 168 (88%) completed the trial. Ten members of the placebo group and 13 members of the treatment group withdrew from the study, but 3 and 5 of these, respectively, returned for the 6-month assessment (Fig. 1).

The baseline sociodemographic characteristics were similar among the participants in the two study arms (Table 1). About half completed primary education or less; 64.8% were aged 55 to 65 years. Except for a longer time since menopause, women lost to follow-up (*n* = 15) were also similar to those who remained in the study (Table 1). Other than the two current smokers and four ex-smokers in the placebo group, all the participants were nonsmokers. About 20% of the women in each of the treatment groups claimed to have some sleep problems. Anthropometric and blood pressure measurements were similar between the groups. Approximately 12% of the participants in either group reported cold sweats/hot flushes at baseline, and the mean number of vasomotor symptoms was low (Table 2). An increase in the estradiol concentration over the treatment period in the supplementation group and a reduction in the

TABLE 1. Baseline characteristics by intervention and lost to follow-up groups (*n* = 191)

	Intervention (<i>n</i> = 85)	Placebo (<i>n</i> = 91)	Lost to follow-up (<i>n</i> = 15)	<i>P</i>
Age group				
55-65 y	55 (64.7)	59 (64.8)	6 (40.0)	0.163
66-76 y	30 (35.3)	32 (35.2)	9 (60.0)	
Education				0.987
No formal	17 (20.0)	18 (19.8)	3 (20.0)	
Primary	28 (32.9)	34 (37.4)	4 (26.7)	
Secondary	26 (30.6)	25 (27.5)	5 (33.3)	
Postsecondary	14 (16.5)	14 (15.4)	3 (20.0)	
Occupation				0.552
Housewife	73 (85.9)	69 (75.8)	13 (86.7)	
Professional and administration	2 (2.4)	1 (1.1)	0 (0)	
Clerical/sales/services	3 (3.5)	7 (7.7)	1 (6.7)	
Others/unclassified	7 (8.2)	14 (15.4)	1 (6.7)	
Sources of income				0.136
Salary/pension	9 (10.6)	11 (12.1)	1 (6.7)	
Public assistance	5 (5.9)	5 (5.5)	0 (0)	
Relatives	67 (78.8)	59 (64.8)	13 (86.7)	
Savings/rental/investments/others	4 (4.7)	16 (17.6)	1 (6.7)	
Smoking and drinking habits				
Smoking				0.032
Never	85 (100.0)	84 (93.3)	15 (100.0)	
Current/ex	0	6 (6.7)	0	
Drinking				0.976
Never	80 (94.1)	84 (93.3)	14 (93.3)	
Occasional	5 (5.9)	6 (6.7)	1 (6.7)	
Sleeping problems: difficulty sleeping				0.682
No	63 (74.1)	70 (76.9)	10 (66.7)	
Yes	22 (25.9)	21 (23.1)	5 (33.3)	
Age, y	63.4 ± 5.67	63.5 ± 6.01	66.0 ± 6.49	0.280
Time since menopause, y	13.6 ± 6.33 ^a	13.9 ± 7.01 ^a	18.7 ± 7.00	0.083
Anthropometric measurements				
Height, cm	152.0 ± 5.37	151.2 ± 6.87	150.6 ± 4.31	0.605
Weight, kg	56.1 ± 8.67	56.5 ± 8.16	56.2 ± 5.22	0.928
Body mass index, kg/m ²	24.3 ± 3.37	24.7 ± 3.28	24.8 ± 2.14	0.594
Systolic blood pressure, mm Hg	126.1 ± 19.13	127.3 ± 17.89	129.3 ± 18.06	0.807
Diastolic blood pressure, mm Hg	72.2 ± 11.01	73.3 ± 12.75	67.0 ± 7.85	0.161

Data are *n* (%) or mean ± SE.

^a*P* < 0.05 by multiple range test compared with the lost to follow-up group.

TABLE 2. Baseline and posttreatment values of hormonal measurements, vasomotor symptoms, and dietary intake

	Intent-to-treat analysis						Evaluable participant analysis: intervention (n = 80), placebo (n = 88)	
	Baseline		Posttreatment		Mean difference (95% CI) ^a	<i>P</i> ^b	Mean difference (95% CI) ^a	<i>P</i> ^b
	Intervention (n = 85)	Placebo (n = 91)	Intervention (n = 85)	Placebo (n = 91)				
Menopausal symptoms								
Vasomotor	0.14 ± 0.44	0.16 ± 0.40	0.24 ± 0.59	0.23 ± 0.54	0.03 (-0.16-0.21)	0.756	0.04 (-0.15-0.24)	0.658
Hormonal measurements								
FSH, IU/L	69.9 ± 22.0	65.3 ± 21.8	67.8 ± 22.8	63.5 ± 19.9	-0.06 (-2.47-2.36)	0.963	0.02 (-2.42-2.46)	0.989
LH, IU/L	30.0 ± 10.2	28.4 ± 9.8	30.5 ± 11.3	28.1 ± 9.3	0.97 (-0.51-2.44)	0.198	1.02 (-0.44-2.48)	0.171
Estradiol, pmol/L	47.1 ± 6.8	48.2 ± 9.8	48.0 ± 8.9	46.9 ± 11.0	2.09 (-0.59-4.76)	0.126	1.79 (-0.90-4.49)	0.191
Dietary intake per day over the past 6 mo								
Isoflavones, mg	16.7 ± 22.0	17.1 ± 18.3	16.4 ± 17.3	19.0 ± 18.3	-2.18 (-7.80-3.45)	0.446	-2.38 (-8.24-3.48)	0.425
Soy protein, g	7.4 ± 9.9	7.7 ± 8.2	7.4 ± 8.0	8.4 ± 8.0	-0.76 (-3.34-1.82)	0.563	-0.83 (-3.51-1.86)	0.543

Data are mean ± SD unless noted otherwise. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

^aMean difference is the difference in change values from baseline to follow-up between the intervention and placebo groups.

^b*P* value from *t* tests.

placebo group were noted, but the differences in the changes did not achieve statistical significance (Table 2). The dietary intake pattern and mean intakes of soy protein and isoflavones at baseline and over the intervention period, as assessed at follow-up, were similar between the treatment and placebo groups (Table 2). The neuropsychological test results indicated no significant differences between the two groups in any of the objective tests at baseline (Table 3). The mean values of the tests at follow-up and the mean differences in the changes of the scores between the intervention and placebo groups over the treatment period were similar. No significant differences in the changes at the follow-up between the two groups were noted. Similar analyses conducted for the good compliers (consumed >80% of the capsules provided) revealed similar results. The results also remained unchanged after adjustment for the potential covariates: age, education, sleeping problems from baseline, vasomotor symptoms, and dietary isoflavone intakes over the intervention period.

Figure 2 shows the 95% CIs for the differences in the changes of test results between the two test groups (intervention minus placebo). All overlapped zero, indicating that the differences were not statistically significant. Figure 2 also shows that six of the point estimates for the tests were positive (favoring isoflavones), five were negative (favoring placebo), and two were neutral. No particular pattern of favorable effects was noted.

Table 4 shows scores for the SF-36 domains, which were similar for the two groups at baseline. Except for general health, there was a decrease in the other domains in both groups at the 6-month assessment, but no between-group statistically significant differences in the mean changes were noted. No significant differences in the baseline values for any of the eight SF-36 domains between the treatment and placebo groups or in changes in scores over the treatment period were noted (Table 4). Similar findings were noted

after controlling for the same potential covariates as those used for the neuropsychological tests.

Adverse events

Reports of adverse effects were monitored and ranged from gastrointestinal, musculoskeletal, and gynecological problems to nonspecific symptoms, such as headache and hair loss, but the degree of severity did not differ between the treatment groups. Twelve complaints were noted among the 10 women who had withdrawn from the placebo group, and 15 complaints were noted among the 13 women who had withdrawn from the treatment group. Two members of each group had left because they found the study troublesome. Among those who completed the study, 68 complaints from 43 participants and 103 complaints from 58 participants were recorded from the placebo and isoflavone groups, respectively (Table 5). Reports of beneficial effects were also noted, with 17 and 16 reports from the placebo and treatment groups, respectively. The benefits cited included improvements in energy levels, wellness, memory, bowel movement, walking agility, and knee and bone pain.

DISCUSSION

Menopause is associated with an accelerated decline in estrogen. Estrogen deficiency has been proposed as one of the causes of age-related cognitive decline in menopausal women.³⁵ Decreases in memory abilities, in focusing attention,³⁶ and in speed of information processing³⁷ are well documented. Investigations of the effects of HT on cognitive functioning have revealed positive effects, particularly in verbal memory, verbal fluency, perceptual speed, spatial awareness, motor control, and articulation.³⁸⁻⁴¹ Data collected by neuroimaging techniques have also supported the positive role of estrogens on brain functions.⁵ The proposed mechanisms for estrogen effects

TABLE 3. Neuropsychological test results by treatment groups at baseline and posttreatment

	Possible range (mean ± SD)	Intent-to-treat analysis				Mean difference (95% CI) ^d	P ^b	Evaluation based on good compliance: intervention (n = 80), placebo (n = 88)
		Baseline		Posttreatment				
		Intervention (n = 85)	Placebo (n = 91)	Intervention (n = 85)	Placebo (n = 91)			
Memory								
HKLLT (trials 1-5)	0-80 (38 ± 11)	38.3 ± 11.4	36.8 ± 11.1	44.0 ± 13.1	42.5 ± 13.0	-0.16 (-2.53-2.21)	0.90	-0.36 (-2.78-2.05)
HKLLT (short delay recall)	0-16 (8 ± 3)	7.8 ± 3.2	7.4 ± 2.9	9.1 ± 3.2	8.7 ± 3.6	-0.01 (-0.71-0.70)	0.99	-0.04 (-0.76-0.68)
HKLLT (long delay recall)	0-16 (7 ± 3)	7.8 ± 3.2	7.0 ± 3.0	9.0 ± 3.4	8.6 ± 3.3	-0.35 (-1.00-0.31)	0.30	-0.41 (-1.08-0.26)
Visual reproduction								
I (WMS-R)	0-41 (26 ± 7)	26.5 ± 7.0	26.3 ± 6.7	29.3 ± 6.7	28.7 ± 7.0	0.33 (-1.23-1.88)	0.68	0.40 (-1.19-1.99)
II (WMS-R)	0-41 (21 ± 9)	22.3 ± 8.9	20.7 ± 9.3	26.0 ± 9.2	25.4 ± 9.0	-1.07 (-3.50-1.35)	0.38	-0.89 (-3.36-1.59)
Executive function								
Color Trail 1, s ^c	0-? (37 ± 14)	36.1 ± 14.5	38.7 ± 13.9	37.5 ± 14.9	39.4 ± 18.3	0.74 (-3.13-4.60)	0.71	1.07 (-2.92-5.06)
Color Trail 2, s ^c	0-? (83 ± 37)	82.3 ± 38.7	84.6 ± 35.6	83.0 ± 37.9	85.0 ± 47.2	0.38 (-8.80-9.56)	0.94	0.89 (-8.58-10.36)
Verbal Fluency	0-60 (25 ± 5)	25.4 ± 5.2	25.2 ± 5.6	27.1 ± 5.4	26.2 ± 4.9	0.71 (-0.69-2.11)	0.32	0.71 (-0.72-2.14)
Attention								
Digit Symbol (WAIS-R)	0-100 (32 ± 15)	33.0 ± 16.4	31.4 ± 14.2	34.5 ± 17.1	33.4 ± 14.9	-0.63 (-2.33-1.06)	0.46	-0.83 (-2.55-0.88)
Motor								
Finger Tapping, right	0-44 (27 ± 7)	27.0 ± 6.7	26.7 ± 6.6	25.9 ± 6.6	25.0 ± 6.2	0.68 (-1.09-2.44)	0.45	0.90 (-0.90-2.69)
Finger Tapping, left	0-44 (27 ± 6)	27.8 ± 6.3	26.8 ± 5.7	27.1 ± 6.5	26.2 ± 5.7	-0.26 (-1.88-1.35)	0.75	0.09 (-1.47-1.64)
Language								
Boston Naming Test	0-30 (21 ± 4)	21.5 ± 4.1	21.3 ± 4.1	22.3 ± 3.8	22.1 ± 3.4	-0.05 (-0.68-0.58)	0.88	-0.08 (-0.73-0.57)
Visual perceptual and constructional ability								
Visual reproduction								
Copy (WMS-R)	0-41 (33 ± 5)	32.9 ± 5.1	33.0 ± 4.2	34.3 ± 4.3	34.0 ± 4.6	0.31 (-0.73-1.35)	0.56	0.45 (-0.62-1.51)
Composite cognitive score ^d	(0.15 ± 9.59)	0.88 ± 10.21	-0.56 ± 8.95	0.78 ± 9.82	-0.65 ± 9.19	0.01 (-1.18-1.20)	0.99	0.09 (-1.13-1.30)
Global cognitive level								
MMSE	23-30 (28 ± 2)	28.2 ± 1.8	28.1 ± 1.9	27.9 ± 2.0	27.9 ± 1.9	0.06 (-0.45-0.57)	0.81	0.05 (-0.48-0.58)

Data are mean ± SD unless noted otherwise. HKLLT, Hong Kong List Learning Test; I, immediate recall; II, 30-min delayed recall; WMS-R, Wechsler Memory Scale-Revised; WAIS-R, Wechsler Adult Intelligence Scale-Revised; MMSE, Modified Mini-Mental State Examination.

^aMean difference is the difference in change values from baseline to follow-up between the intervention and placebo groups.

^bP value from *t* tests.

^cColor Trail has no end score because of participants' unlimited time to finish the trail. Mean difference was difference of intervention (posttreatment minus baseline) and placebo (posttreatment minus baseline).

^dComposite cognitive score is the sum of the *z* scores of all 13 neuropsychological tests.

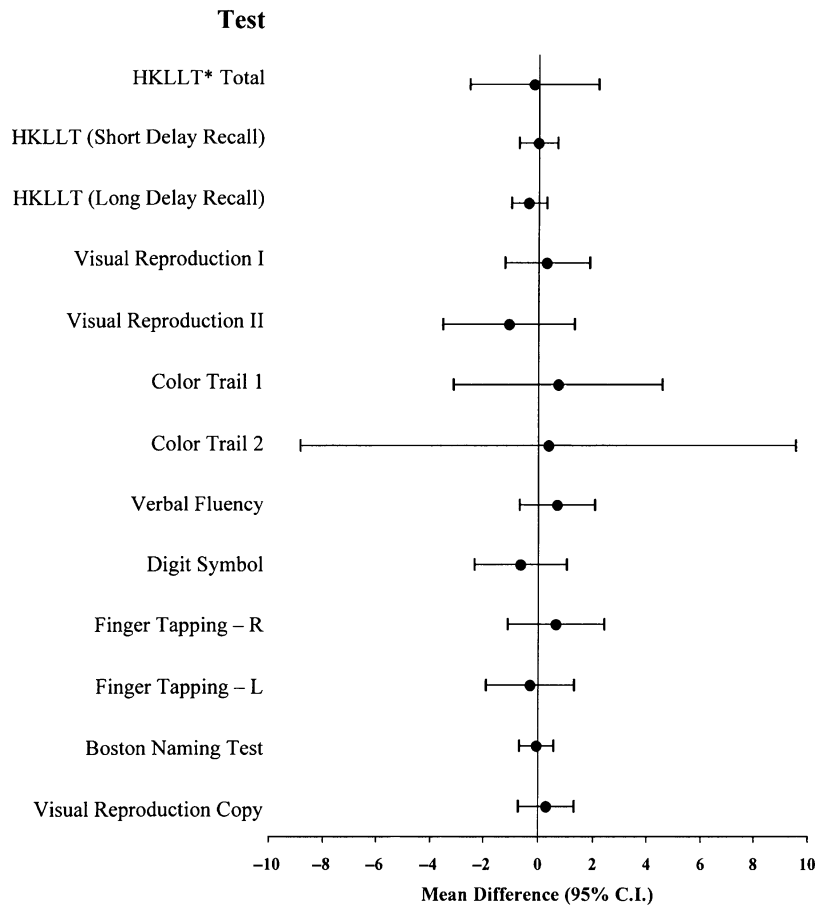


FIG. 2. Mean differences and 95% CIs for changes of test results from baseline to posttreatment between isoflavone and placebo groups. Data are based on the intent-to-treat analysis with 85 women in the intervention group and 91 women in the placebo group. *HKLLT, Hong Kong List Learning Test.

on cognitive functioning have included induction of synaptogenesis in the brain,⁴² regulation of neuronal structure,⁴³ and estrogen receptor activity in glia cells.⁴⁴ A meta-analysis of 10 observational studies in humans showed a 29% reduction in the risk of development of dementia among postmenopausal estrogen users.⁴⁵ A later meta-analysis based on nine randomized trials and eight cohort studies gave provisional conclusions that estrogen improved cognitive performance, especially in tests of verbal memory, vigilance, reasoning, and motor speed in asymptomatic postmenopausal women.⁴ Another meta-analysis, based on 15 double-blind, randomized, controlled trials, failed to provide conclusive evidence of an overall positive effect of HT on cognitive function in postmenopausal women.⁴⁶ Recent data from the Women’s Health Initiative Memory Study revealed an adverse effect on cognitive function among women receiving HT.⁹

Phytoestrogens, especially soy-derived isoflavonoid phytoestrogens, have been shown to have an estrogenic effect and show preferential binding affinity to the β -estrogen receptors present in brain cells.¹¹ It is hypothesized that isoflavone supplements will be beneficial in the promotion and preservation of cognitive function and the overall quality of life, but without the adverse effects of HT.¹⁰

Laboratory studies have shown the attenuation of neurodegeneration and relevant modifications of brain proteins by dietary soy intake.¹² However, only a few randomized, placebo-controlled trials have been conducted to evaluate the effects of soy isoflavones on cognitive function performance, and the results have been equivocal. A 10-week study of a high soy diet containing 100 mg isoflavones conducted in young men and women in their 20s showed significant improvements in short-term and long-term memory and in mental flexibility.¹⁴ Significant improvements in a letter fluency test and in a test of planning were noted in the women only. A 12-week study using the same test batteries, conducted by Duffy et al,¹⁵ in postmenopausal women with a mean age of 56.8 (placebo group) to 58.8 years (supplement group), receiving either lactose or 60 mg soy isoflavones, showed significantly greater improvement in delayed recall of pictures, in immediate story recall tests, and in the Paced Auditory Serial Addition Test results in the soy isoflavone group, but no differences were observed for any other cognitive function tests. The numbers of participants in both studies were relatively small, with less than 20 participants in each of the study arms. A 6-month randomized, controlled trial by Kritz-Silverstein et al¹⁶ using 110 mg soy isoflavone extract and placebo in 175 postmenopausal

TABLE 4. SF-36 scores by treatment groups at baseline and posttreatment

SF-36 ^a	Intent-to-treat analysis				Mean difference (95% CI) ^b	P ^c
	Baseline		Posttreatment			
	Intervention (n = 85)	Placebo (n = 91)	Intervention (n = 85)	Placebo (n = 91)		
Physical functioning	87.2 ± 13.2	84.3 ± 15.0	83.1 ± 15.5	81.0 ± 18.5	-1.10 (-5.40-3.21)	0.61
Role-physical	86.2 ± 32.2	83.2 ± 30.5	78.9 ± 33.0	78.9 ± 35.7	0.14 (-9.24-9.52)	0.98
Bodily pain	76.1 ± 23.8	74.3 ± 25.7	72.7 ± 25.3	73.0 ± 29.0	-2.22 (-10.75-6.32)	0.61
Vitality	75.2 ± 17.5	76.1 ± 17.4	63.7 ± 21.8	68.0 ± 22.4	-3.47 (-10.15-3.21)	0.31
Social functioning	92.1 ± 15.5	90.9 ± 14.8	89.4 ± 18.3	88.6 ± 17.8	-0.19 (-6.18-5.80)	0.95
Role-emotional	95.7 ± 16.9	93.0 ± 20.8	86.5 ± 30.7	84.6 ± 31.9	-2.02 (-11.92-7.88)	0.69
Mental health	84.7 ± 13.6	86.7 ± 12.8	82.0 ± 15.4	83.7 ± 15.5	0.18 (-4.45-4.80)	0.94
General health	67.8 ± 18.3	64.6 ± 19.2	68.0 ± 18.5	67.6 ± 21.7	-1.75 (-6.38-2.87)	0.46

Data are mean ± SD unless noted otherwise. SF-36, Short-Form 36.

^aRange of scores: 0-100.

^bMean difference is the difference in change values from baseline to follow-up between the intervention and placebo groups.

^cP value from *t* tests.

women aged approximately 60 years showed improvements in category fluency in the soy isoflavone group, but no other significant between-group differences were observed for any other cognitive function tests. A more recent 1-year randomized, controlled trial by Kreijkamp-Kaspers et al¹⁷ comparing isolated soy protein containing 100 mg isoflavones with milk protein and involving 175 postmenopausal women (aged approximately 66.5 y) revealed no significant differences between the groups for any of the cognitive function tests. Because the dosages, types of supplements used in intervention and control groups, and test instruments used differed in these three studies in postmenopausal women, methodological issues could contribute to the conflicting results.

In this 6-month double-blind, placebo-controlled, parallel group trial of isoflavone supplementation at 80 mg orally daily, results from 13 different standardized neuropsychological tests covering memory, attention, executive function, naming and verbal fluency, visual reproduction, and motor function were evaluated. None of the differences among the changes of scores from baseline to 6 months were statistically significant. The numbers of test results favoring or disfavoring isoflavone supplementation were equivocal, and all of the 95% CIs overlapped zero. A test of global cognitive function also showed no difference between the treatment and placebo groups.

Previous studies of the effects of HT on cognitive function seemed to indicate a potential positive effect in younger postmenopausal women and in symptomatic women. The human trials of soy isoflavones reporting favorable effects were conducted among young, premenopausal women¹⁴ or younger postmenopausal women (mean age of approximately 57-60 y),^{15,16} whereas participants in the study reporting no difference were older (mean age 66.5 y).¹⁷ The mean age of our study population was approximately 63.8 years, ranging from 55 to 76 years, and women were approximately 14 years postmenopause. Subgroup analyses were conducted for two age groups, 65 years and younger and older than 65 years, but no differences in any outcomes were seen. The prevalence of vasomotor symptoms is generally low in Hong Kong Chinese postmenopausal women.³³ Only 12% of the participants in this study reported vasomotor symptoms at baseline. Even controlling for vasomotor symptoms did not change the statistical test results of no difference between the treatment groups. The ceiling effects of the neuropsychological test results are also not apparent, as a wide range of scores was observed. Only the results of the MMSE were close to the ceiling in this group of generally healthy women, who had been screened for mental function before entry into the study.

Duncan et al⁴⁷ reported a modest hormonal effect of soy isoflavones in premenopausal women. Although soy isoflavone supplementation resulted in a slight increase in the estradiol concentration in the supplementation group, whereas a mean reduction was noted in the placebo group,

TABLE 5. Adverse events reported by study participants

System	Treatment	Placebo	Difference (treatment – placebo)	P for difference
Gastrointestinal				
Constipation/diarrhea	8	10		
Stomach pain, nausea, bloating	14	6		
Feelings of hunger	3	2		
Hemorrhoids	1	1		
Subgroup n	26	19	7	0.458
Musculoskeletal				
Joint/bone pain, degeneration	17	8		
Knee/feet weakness, tiredness	7	2		
Others (spasm, numbness, swollen)	3	4		
Subgroup n	27	14	13	0.322
Neurological/sensory				
Headache/dizziness	8	4		
Memory	1	—		
Hearing	1	1		
Swollen eye	2	—		
Subgroup n	12	5	7	0.626
Gynecological/urinary				
Vaginal discharge/bleeding	4	2		
Breast tenderness/nipple discharge	3	2		
Breast cancer	—	1		
Others	3	3		
Subgroup n	10	8	2	0.649
Nonspecific				
Sleepiness/lack of energy	2	3		
Weight loss/gain	6	3		
Itchiness	2	2		
Hair loss	1	—		
Sweating	5	3		
Dry mouth/heatiness	3	3		
Subgroup n	19	14	5	0.781
Others				
Heart/palpitation/blood pressure	4	2		
Sore throat/respiratory symptoms/ allergic rhinitis	2	2		
Thyroid/glucose/potassium	2	3		
Others	1	1		
Subgroup n	9	8	1	0.589
Total no. of complaints	103	68		
Total individuals with complaints	58	43		

$P = 0.842$ from a χ^2 test for differences in distribution of events in subgroups of complaints between the treatment groups.

the difference in our study did not achieve statistical significance.

HT is effective in relieving menopausal symptoms and improving quality of life.⁴⁸ Few studies have measured the effect of soy isoflavone supplementation on quality of life.⁴⁹ The 3-month study by Woo et al,¹⁸ using *P lobata*-containing isoflavones, demonstrated no effect in any of the SF-36 domains,¹⁸ but the same study indicated improvement in flexible thinking, as shown by the Figure Trail test. Kok et al⁵⁰ also used the SF-36 as an outcome measure in a 1-year randomized, controlled trial comparing soy protein containing 100 mg isoflavones with milk protein in healthy, older, postmenopausal women and reported no difference between the treatment groups in any of the domains. As in the study of Kok et al, our study was conducted in relatively healthy women, who were free from depression and cognitive impairment. The SF-36 study questionnaires were validated in the Chinese population.³¹ The baseline scores were high with mean values generally above 70 or even as high as 95 out of a maximal score of 100. Except for the

general health domain with a mean baseline score below 70, which showed a slight improvement at the 6-month assessment, all domains showed a slight reduction of scores at follow-up. Therefore, the results of this study concur with those of the previous studies^{49,50} in showing that isoflavones may not further improve quality of life in generally healthy asymptomatic postmenopausal women.

The study is limited by the short treatment period of only 6 months, and only one single dose of 80 mg isoflavones was given. It is possible that different doses, different soy isoflavone components, or longer periods of exposure than those used in this study are necessary to detect changes. This study initially included 191 participants, with 85 and 91 women in the intervention and placebo groups, respectively, completing the 6-month trial. Although the sample size was comparable to that of a few previous studies^{16,17} and larger than that of others,¹⁵ it may still not be adequate to detect any changes over a 6-month observation of intervention. The mean differences in changes of test scores noted between the two treatment arms were small, and thus a substantially

larger sample size would have been required to detect a significant difference in the small changes, if present. Moreover, the study was conducted in a middle-aged and a "young-older" group, among whom the changes might be small over a 6-month period, and a longer observation time would probably be required to detect a significant change.

It has been proposed that the equol status of individuals may alter their responses to isoflavone intake. Equol, a metabolic product of the intestinal bacteria of the biotransformation precursor daidzein, has the strongest affinity to estrogen receptors of the components of isoflavones and has a slower plasma clearance.⁵¹ It can therefore prolong an individual's exposure to the bioactive component of isoflavones. Previous studies have revealed that only 30% to 50% of populations under investigation were equol producers, and such individual variation may affect individuals' responses to soy isoflavone interventions.^{52,53} However, one study by Kreijkamp-Kaspers et al¹⁷ failed to show different soy effects on cognitive function between equol producers and nonproducers. Because equol status was not measured in the women in this study, we were unable to delineate the treatment effects among equol producers and nonproducers. Further studies of the effects of equol status in the Asian population are warranted.

This study is unique because it is the first such trial conducted in a population for which soy is a staple food throughout life. The mean soy protein intake in the study population was approximately 7.6 g/day. With the soy protein content of soy isoflavones ranging from 2 to 3 mg/g, the mean usual dietary isoflavone intake in this study population was approximately 20 mg/day. The addition of 80 mg isoflavones would increase the intake of soy in the intervention group to approximately 100 mg/day. However, a lifetime habitual intake of soy foods could have had some overall protective effect on cognitive function, even among the placebo group, and thus could have lessened the between-group differences of the trial results.

The advantages of this study include a stratified randomization strategy that controlled for the important prognostic factor for cognitive functioning, education, and the use of a wide range of neuropsychological evaluations as outcome measures. The study had an acceptable dropout rate of 12%. Extensive information on potential confounders was collected, and adjustments were made for these covariates, such as age, sleep difficulty, vasomotor symptoms, and habitual dietary isoflavone intake, in assessing the differences in outcome measures between the treatment groups.

Few studies on the health effects of soy have reported adverse events, but generally mild effects have been noted. Careful monitoring of adverse events was carried out throughout this study. The types of complaints, mostly gastrointestinal and musculoskeletal, were similar among the treatment and placebo groups, although more were noted in the treatment group. However, these complaints are also common among postmenopausal and older women in general. Similar observations have also been noted in the

few trials with reports on adverse effects in postmenopausal women.⁵⁴ The adverse events were generally tolerable, and 88% of the participants completed the 6-month trial. Withdrawals from the study attributable to adverse effects were few and similar among the two treatment groups.

CONCLUSIONS

In the present study we were unable to show improvement in cognitive function and overall quality of life in generally healthy and asymptomatic Chinese postmenopausal women taking soy isoflavone supplementation. However, the relatively small sample size and short duration of follow-up are strong limitations, and thus the null results can be treated only as preliminary and should be interpreted with caution.

Acknowledgments: Acatris Holding B.V. (Giessen, The Netherlands) supplied the soy isoflavones extract, and Mekim Limited (Kowloon, Hong Kong) supplied the calcium supplements. We are grateful to Daisy Fung and Aggie Ip for preparation of the manuscript.

REFERENCES

1. Ho SC, Chan SG, Yi Q, Wong E. Soy intake and the maintenance of peak bone mass in Hong Kong Chinese Women. *J Bone Miner Res* 2001;16:1363-1369.
2. Woods NF, Mitchell ES, Adams C. Memory functioning among midlife women: observations from the Seattle Midlife Women's Health Study. *Menopause* 2000;4:257-265.
3. Halbreich U. Possible acceleration of age effects on cognition following menopause. *J Psychiatr Res* 1995;29:153-163.
4. Yaffe K. Estrogens, selective estrogen receptor modulators, and dementia: what is the evidence? *Ann N Y Acad Sci* 2001;949:215-222.
5. Maki PM, Resnick SM. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. *Neuroimage* 2001;14:789-801.
6. Shaywitz SE, Shaywitz BA, Pugh KR, et al. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *JAMA* 1999;281:1197-1202.
7. Steffens DC, Norton MC, Plassman BL, et al. Enhanced cognitive performance with estrogen use in nondemented community-dwelling older women. *J Am Geriatr Soc* 1999;47:1171-1175.
8. de Moraes SA, Szklo M, Knopman D, Park E. Prospective assessment of estrogen replacement therapy and cognitive functioning: atherosclerosis risk in communities study. *Am J Epidemiol* 2001;154:733-739.
9. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative memory study. *JAMA* 2004;291:2959-2968.
10. Writing Group for the Women's Health Initiative Investigators. Risk and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321-333.
11. Setchell KDR, Cassidy A. Dietary isoflavones: biological effects and relevance to human health. *J Nutr* 1999;129:758S-767S.
12. Kim H, Li Xia H, Gewin L. Attenuation of neurodegeneration-relevant modification of brain proteins by dietary soy. *Biofactors* 2000;12:243-250.
13. Pan Y, Anthony M, Clarkson TB. Evidence for up-regulation of brain-derived neurotrophic factor mRNA by soy phytoestrogens in the frontal cortex of retired breeder female rats. *Neurosci Lett* 1999;261:17-20.
14. File SE, Jarrett N, Fluck E, Duffy R, Casey K, Wiseman H. Eating soya improves human memory. *Psychopharmacology (Berl)* 2001;157:430-436.
15. Duffy R, Wiseman H, File SE. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. *Pharmacol Biochem Behav* 2003;75:721-729.
16. Krititz-Silverstein D, Von Mühlen D, Barrett-Connor E, Bressel MAB. Isoflavones and cognitive function in older women: the SOY and

- Postmenopausal Health In Aging (SOPHIA) Study. *Menopause* 2003; 10:196-202.
17. Krejckamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 2004;292:65-74.
 18. Woo J, Lau E, Ho SC, et al. Comparison of *Pueraria lobata* with hormone replacement therapy in treating the adverse health consequences of menopause. *Menopause* 2003;10:352-361.
 19. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;3:385-401.
 20. Chan AS, Kwok I. *Hong Kong List-Learning Test: Manual and Preliminary Norm*. Hong Kong: Department of Psychology and Clinical Psychology Centre, The Chinese University of Hong Kong, 1999.
 21. Osterrieth PA. Le test de copie d'une figure complexe: Contribution à l'étude de la perception et de la mémoire. *Arch Psychol* 1944;30: 286-356.
 22. D'Elia L, Satz P. *Color Trails 1 and 2*. Odessa, FL: Psychological Assessment Resources, 1989.
 23. Chan AS, Poon MW. Performance of 7- to 95-year-old individuals in a Chinese version of the category fluency test. *J Int Neuropsychol Soc* 1999;5:525-533.
 24. Wechsler D. *Wechsler Adult Intelligence Scale-Revised*. Chicago, IL: Psychological Corporation, Harcourt Brace Jovanovich, 1981.
 25. Wechsler D. *Wechsler Memory Scale-Revised*. New York, NY: Psychological Corporation, 1987.
 26. Lewis RF, Rennick PM. *Manual for the Repeatable Cognitive-Perceptual-Motor Battery*. Grosse Pointe Park, MI: Axon Publishing, 1979.
 27. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Interpretation*. Tucson, AZ: Neuropsychology Press, 1985.
 28. Kaplan EF, Goodglass H, Weintraub S. *The Boston Naming Test: Experimental Editor*. Philadelphia, PA: Lea & Febiger, 1978.
 29. Tang EL, Chui HC. The Modified Mini-Mental State (3MS) Examination. *J Clin Psychiatry* 1987;48:314-318.
 30. Chiu HFK, Lee HC, Chung WS, Kwong PK. Reliability and validity of the Cantonese version of Mini-Mental State Examination: a preliminary study. *J Hong Kong Coll Psychiatr* 1994;4(Suppl 2):25-28.
 31. Lam CLK, Gandek B, Ren XS, Chan MS. Tests of scaling assumptions and construct validity of the Chinese (HK) version of the SF-36 health survey. *J Clin Epidemiol* 1998;51:1139-1147.
 32. Ho SC, Woo J, Chen YM, Sham A, Lau J. Soy protein consumption and bone mineral density in early postmenopausal Chinese women. *Osteoporos Int* 2003;14:835-842.
 33. Ho SC, Chan SG, Yip YB, Cheng A, Yi Q, Chan SY. Menopausal symptoms and symptom clustering in Chinese women. *Maturitas* 1999; 33:219-227.
 34. Li RHY, Wing YK, Ho SC, Fong SY. Gender differences in insomnia—a study in the Hong Kong Chinese population. *J Psychosom Res* 2002;53:601-609.
 35. Manly JJ, Merchant CA, Jacobs DM, et al. Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. *Neurology* 2000;54:833-837.
 36. Rogers W, Fisk AD. Age-related differences in the maintenance and modification of automatic processes: arithmetic Stroop interference. *Hum Fact* 1991;33:45-56.
 37. Cerella J. Aging and information processing rate. In: Birren J, Schaie KW, eds. *Handbook of the Psychology of Aging*, 3rd ed. San Diego, CA: Academic Press, 1990:201-221.
 38. Kampen DL, Sherwin BB. Estrogen use and verbal memory in healthy postmenopausal women. *Obstet Gynecol* 1994;83:979-983.
 39. Kimura D. Estrogen replacement therapy may protect against intellectual decline in postmenopausal women. *Horm Behav* 1995; 29:312-321.
 40. Sherwin BB, Tulandi T. Estrogen reverses cognitive deficits induced by a gonadotropin-releasing-hormone agonist in women with leiomyomata uteri. *J Clin Endocrinol Metab* 1996;81:2545-2549.
 41. Smith YR, Giordani B, Lajiness-O'Neill R, Zubieta JK. Long-term estrogen replacement is associated with improved nonverbal memory and attentional measures in postmenopausal women. *Fertil Steril* 2001;76:1101-1107.
 42. McEwen BS, Alves SE. Estrogen actions in the central nervous system. *Endocr Rev* 1999;20:279-307.
 43. McEwen BS, Wooley CS. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adult as well as developing brain. *Exp Gerontol* 1994;29:431-436.
 44. Magistretti PJ, Morrison JH, Shoemaker WJ, Bloom FE. Effect of 6-hydroxydopamine lesions on norepinephrine-induced [³H]glycogen hydrolysis in mouse cortical slices. *Brain Res* 1983;261:159-162.
 45. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women. *JAMA* 1998;279:688-695.
 46. Hogervorst E, Yaffe K, Richards M, Huppert F. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev* 2002:CD003799.
 47. Duncan AM, Underhill KEW, Xu X, LaValleur J, Phipps WR, Kurzer MS. Soy isoflavones exert modest hormonal effects in premenopausal women. *J Clin Endocrinol Metab* 1999;84:192-197.
 48. Rebar RW, Trabala J, Mortola J. Low-dose esterified estrogens (0.3 mg/day): long-term and short-term effects on menopausal symptoms and quality of life in postmenopausal women. *Climacteric* 2000;33: 176-182.
 49. Amato P, Young R, Cramer M, et al. The effect of soy isoflavone supplementation on menopausal quality of life: a multicenter, randomized, controlled trial [abstract]. *Menopause* 2005;12:788.
 50. Kok L, Krejckamp-Kaspers S, Grobbee DE, Lampe JW, Schouw YT. A randomized, placebo-controlled trial on the effects of soy protein containing isoflavones on quality of life in postmenopausal women. *Menopause* 2005;12:56-62.
 51. Setchell KDR, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol—a clue to the effectiveness of soy and its isoflavones. *J Nutr* 2002;132:3577-3584.
 52. Lampe JW, Karr SC, Hutchins AM, Slavin JL. Urinary equol excretion with a soy challenge: influence of habitual diet. *Proc Soc Exp Biol Med* 1998;217:335-339.
 53. Lampe JW, Skor HE, Li S, Wahala K, Howald WN, Chen C. Wheat bran and soy protein feeding do not alter urinary excretion of the isoflavone equol in premenopausal women. *J Nutr* 2001;131: 740-744.
 54. Tufts—New England Medical Center Evidence-Based Practice Centre. *Effects of Soy on Health Outcomes*. Rockville, MD: Agency for Healthcare Research and Quality, US Department of Health and Human Services. Evidence Report Number 126, 2005.