Available online at www.sciencedirect.com
SCIENCE DIRECT®
Maturitas 52 (2005) 102–110
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Soy isoflavones, body composition, and physical performance

Linda Kok [a], Sanne Kreijkamp-Kaspers [a], Diederick E. Grobbee [a], Johanna W. Lampe [b], Yvonne T. van der Schouw [a, *]

[a] *The Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O. Box 85500, Room Stratenum 6.131, 3508 GA Utrecht, The Netherlands*
[b] *Fred Hutchinson Cancer Research Center, Seattle, USA*

Received 30 June 2004; received in revised form 8 December 2004; accepted 11 January 2005

Abstract

Objectives: Physiologic changes, occurring during the process of aging, can have serious health consequences, such as increased risk of chronic disease and disability. Decline in estradiol levels after menopause is hypothesized to contribute to this risk. Thus, hormone therapy (HT) might prevent or delay those changes. However, HT has serious side effects and alternative approaches are needed.
Methods: We performed a 12-month double-blind randomized trial comparing soy protein containing 99 mg isoflavones (aglycone weights) with milk protein (placebo) daily in 202 postmenopausal women aged 60–75 years. Endpoints were body composition, and physical performance. Randomization resulted in reasonable well-balanced groups, 153 (76%) women completed the trial. Compliance was good (plasma genistein levels 55 ± 101 and 1259 ± 1610 nmol/L for placebo and soy group, respectively). The changes in the endpoints during the intervention period among the two intervention groups were analyzed.
Results: Body mass index (BMI) and waist-to-hip ratio did not change during intervention. Handgrip strength at the final visit was slightly worse in the soy group compared to the placebo group (-0.45 kg (95% C.I.: -2.5, 1.6 kg; $p = 0.7$), but this difference was not statistically significant. Self-reported functional status, mobility and physical performance, all slightly improved during intervention but there were no differences between the groups.
Conclusions: The results of the present trial do not support the view that soy isoflavones have favorable effects on body composition and physical performance in postmenopausal women.

Keywords: Soy isoflavones; BMI; Physical functioning; Randomized trial; Postmenopausal women

1. Introduction

The process of aging is accompanied by several physiological changes. One of these is a change in body composition, characterized by an increase in weight and fat mass and a decrease in lean mass. Changes in

* Corresponding author. Tel.: +31 30 250 9360; fax: +31 30 250 5485.
E-mail address: y.t.vanderschouw@umcutrecht.nl (Y.T. van der Schouw).
URL: http://www.juliuscenter.nl (Y.T. van der Schouw).

0378-5122/$ – see front matter
doi:10.1016/j.maturitas.2005.01.003

body composition and concomitant metabolic effects have been suggested to increase the risk of serious diseases with subsequent loss of functional capacity and loss of independence. An increase in fat mass for instance contributes to a higher risk of cardiovascular diseases, [1] diabetes [2] and certain types of cancer [3]; a decrease in bone mass is associated with an increased risk of hip fractures [4,5], and a decline in muscle mass might be an important factor in the development of disability [6,7].

Several factors, among which dietary factors, lifestyle factors, metabolic factors, and hormonal factors influence body composition around the time of menopause [8]. One of these factors, namely the sudden decline in estrogen levels at the time of menopause seems to play an important role [9–12]. Results of studies on the effect of hormone therapy (HT) on body composition suggest that postmenopausal estrogen use might be beneficial. It was shown that women who had used estrogen for more than 5 years had significantly higher fat-free mass than non-users [13]. Another study showed that combined estrogen–progestogen therapy prevented the increase in abdominal fat usually seen after menopause [14]. Moreover, several studies showed beneficial effects of HT on the preservation of muscle strength [7,15,16]. However, HT is associated with some serious side effects and its risk–benefit ratio is subject to debate; indeed, the WHI showed that overall risks exceeded the benefits [17,18]. For this reason, we set out to assess whether phytoestrogens are able to show beneficial effects without the risks associated with use of HT. Phytoestrogens are a group of compounds derived from plants with a non-steroidal structure that is quite similar to that of estradiol. The three main classes are isoflavones, lignans and coumestans. Soy products are an important source of isoflavones. Various studies have demonstrated positive effects of isoflavones on hot flushes, [19] bone mineral density, [20,21] and cardiovascular disease risk factors [22] without indications for an increased risk of endometrial cancer [23] or breast cancer [24]. Moreover, results from a recently published cross-sectional study in postmenopausal women suggest an inverse association of usual dietary isoflavone intake with total body fat and waist girth [25].

We performed a double-blind randomized placebo-controlled trial in 202 postmenopausal women, in which we assessed the effects of soy protein containing 99 mg naturally occurring isoflavones for 1 year on body composition and physical performance.

2. Methods

The present study is a double-blind, randomized, placebo-controlled trial to assess the effects of soy protein containing naturally occurring isoflavones on several endpoints, as discussed in detail previously [26]. Endometrium thickness and mammographic breast pattern were monitored as safety measures.

2.1. Subjects

We recruited 202 postmenopausal women, aged 60–75 years, through the national screening program for breast cancer. Inclusion and exclusion criteria are listed in Table 1.

Of 303 women willing to participate, we had to exclude 101 for several reasons; main reasons for exclusion being current use of HT (26), history of carcinoma (15) and history of thrombosis (14). Finally, 202 women were enrolled in the trial and randomized to one of two intervention arms. The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the study protocol and all subjects gave written informed consent.

Table 1
Inclusion and exclusion criteria

Inclusion criteria
Age 60–75 years
Normal mammography in the year prior to enrolment
Exclusion criteria
Conditions for which estrogen use is contraindicated:
Active liver disease
Renal disease with decreased renal function
History of thrombosis
Severe diseases or conditions interfering with the study:
Current or former malignant disease (except for non-melanoma skin cancer)
Current use of hormone replacement therapy or use in the 6 months prior to enrolment
Known allergy for soy protein or casein
Lactose intolerance
Endometrium thickness over 4 mm

2.2. Intervention

The intervention consisted of 25.6 g soy protein containing 52 mg genistein, 41 mg daidzein and 6 mg glycetein (aglycone weights) as a powder (Solae^{TM} brand soy protein; The Solae Company, St. Louis, MO, USA). All three isoflavones are naturally occurring in soy protein. The total serving size of the product was 36.5 g. The powder could be mixed with foods or beverages and was taken daily. The placebo was an identically looking and tasting powder and consisted of milk protein (The Solae Company, St. Louis, MO, USA). Extra vitamins and minerals were added to the supplement for both groups (Vitamin B_2, B_6, B_{12}, folic acid, Vitamin D and calcium). The duration of the intervention was 12 months. Baseline measurements included a validated semi-quantitative food frequency questionnaire on habitual diet in the year prior to enrolment [27], which was slightly modified to capture isoflavone and lignan intake. During the intervention period, participants were asked to keep a diary to record whether or not they took the supplement and how they processed it. Moreover, at each visit to our clinic subjects had to fill in a food frequency questionnaire again covering the months between the last and the current visit. Compliance was checked by assessing plasma genistein levels in the final visit blood sample.

During the intervention period, 49 subjects (24%) dropped out for several reasons, notably gastrointestinal complaints and distastefulness of the supplement. There was no difference in dropout rate between the two intervention groups: 24 subjects in the placebo group and 25 subjects in the soy group. Mean duration of participation of the dropouts was 96 days (range: 4–285 days). We performed a close out visit when a subject participated for at least 1 month. Thirty-five of the subjects who dropped out fulfilled this criterion and 22 of them were willing and able to undergo a close out visit (nine from the placebo group and 13 from the soy group).

2.3. Measurements

2.3.1. Physical measurements

We measured height, without shoes, to the nearest 0.5 cm and weight to the nearest 0.5 kg. Body mass index (BMI) was calculated by dividing weight by height squared (kg m^{-2}).

We determined waist circumference just above the crista iliaca and hip circumference at the level of the greater trochanter (in centimeters). From these the waist-to-hip ratio was calculated. This ratio gives a measure for upper body adiposity.

2.3.2. Physical performance and impairment

We assessed physical performance by means of the Stanford Health Assessment Questionnaire (HAQ), the questionnaire on mobility in elderly, a physical performance test (PPT), and handgrip strength. We asked subjects to fill in the questionnaires at home on the day before their visit to our clinic. Research nurses checked the questionnaires for missing answers or inconsistencies. The questionnaires and the PPT were carried out at baseline and at final visit. However, handgrip strength was only measured at final visit in a random part of the cohort.

2.3.3. The Stanford Health Assessment Questionnaire (HAQ)

The Stanford Health Assessment Questionnaire (HAQ) is a self-administered questionnaire to measure physical ability. We used a Dutch version of the HAQ [28], which consists of 24 questions about ordinary activities in eight categories. The categories are dressing, arising, eating, walking, hygiene, reach, grip and common activities. All questions have four alternatives to choose from, ranging from “without difficulty” (assigned a score of zero) to “unable to perform” (assigned a score of three). Moreover subjects can indicate whether they need aid or need an assistive device.

The total score on the HAQ is calculated by taking the highest item score within each category and subsequently, calculating the mean of the eight category scores. When a subject indicates the need for aid or a device on a certain question, the corresponding category score is increased to two when that score was zero or one.

2.3.4. The questionnaire on mobility in elderly

To get an impression of physical activity, we asked subjects to fill in the questionnaire on mobility in elderly developed and validated by L.E. Voorrips et al. [29]. Again the research nurses went over this questionnaire when subjects visited the outpatient clinic.

The questionnaire on mobility in elderly consists of three parts. The first part concerns 10 questions about

household activities with four or five possible ratings. The second and third part about sports and leisure time activities ask for type of activity, hours per week and months per year spend on it. Each activity mentioned in the second and third part is classified by an intensity code based on net energetic costs of activities. The three parts together yield a total physical activity score. Higher scores indicate a higher level of physical activity.

In a group of 31 subjects (men and women, aged 63–80 years), in which the relative validity of the questionnaire was determined, the mean activity score was 13.6 (S.D. 6.8; range 1.2–31.4) [29].

2.3.5. The physical performance test

The physical performance test (PPT) comprises three parts: a test for standing balance including tandem, semi-tandem and side-by-side stands, a test for walking speed and a test for ability to rise from a chair [30]. The standing balance tests start with a semi-tandem stand (the heel of one foot next to the toes of the other foot), which has to be maintained for 10 s. When a subject succeeds, the test continues with the tandem stand (one foot in front of the other foot) for 10 s, but when a subject does not succeed, the side-by-side stand (feet together) has to be tried. The three tests of standing balance are considered hierarchical in level of difficulty and a single score of 0–4 is assigned as a result. In the test for walking speed, an 8-feet walk has to be performed two times at the subjects' usual speed. The fastest time of the two is denoted. Finally, in the chair stand subjects have to stand up and sit down as fast as possible from a straight-backed chair for five times with their arms folded across their chest. For the last two tests, quartiles of performance times of all subjects are determined and subjects get a score of 1–4 for both tests dependent on the quartile their performance time fits in. The total score for the PPT can range from 2 to 12.

2.3.6. Handgrip strength

The handgrip strength test was only performed after 1 year of intervention and in a random sample of the participants in the trial. Eighty-eight subjects performed the test; 48 in the placebo group and 40 in the soy group. To measure handgrip strength, we used a Jamar hand dynamometer on the non-dominant hand. We asked subjects to perform the test twice, with a minimum of 30 s between the consecutive efforts. Both results were noted. For our analysis, we used the highest result of the two attempts.

Subjects were sitting on a straight-backed chair and were instructed to keep their shoulders in neutral position and the elbow in 90° flexion. The arm was not supported. If necessary, the handle was adjusted to the grip span. The force was recorded to the nearest 0.1 kg. Handgrip strength measurements were performed in late spring and during summer.

2.4. Laboratory measurements

Plasma genistein levels were measured in the final visit blood sample using Labmaster TR-FIA kits (Turku, Finland). Fluorescence was measured on the Wallac Victor 2 model 1420 spectrofluorimeter (Turku, Finland). Data were analyzed using GraphPad Prism software (GraphPad Software Inc., San Diego, CA, USA). Intra-assay and inter-assay CVs were 2.2 and 14.8%, respectively. Equol has been proposed to be the bio-active metabolite of daidzein. However, only one-third of the population is capable of producing equol. Equol producer status was defined as equol > 83 nmol/L in plasma [31]. The proportion of equol producers was 29.9%. Equol producer status could only be assessed within the soy group because an exposure to isoflavones is required prior to the analysis.

2.5. Power calculation

The a priori power calculation was based on conventional assumptions of alpha (α) = 0.05 and beta (β) = 0.20, and withdrawal from intervention of 25%. With a planned number of subjects of 200 in total and further assuming that soy isoflavones are as effective as conventional hormone replacement therapy, we would have been able to demonstrate an improvement of 5% on the PPT and 19% on the HAQ.

2.6. Data analysis

First we checked distribution of outcome variables, which were normal. Linear regression analysis was used with handgrip strength as dependent factor and group allocation as independent factor. Results of waist-to-hip ratio, BMI and activity scores were analyzed using the change during the intervention year as

dependent factor and group allocation as independent factor. Results are given as the difference in baseline-to-final visit change between isoflavone and placebo treatment including a 95% confidence interval.

All analyses were carried out using the SPSS 9.0 for Windows statistical package (SPSS Inc., Chicago, USA).

3. Results

Baseline characteristics of participants are shown in Table 2. Except for two women (one black and one Asian), all were Caucasian. Randomization appeared to be successful, with no material differences between both intervention groups at baseline except for a somewhat higher frequency of current smoking in the soy group. Adjustment for smoking in our analysis did not materially change the results.

The laboratory measurement of genistein levels indicated that compliance was good. The levels were markedly different between the intervention group and the placebo group (1259 ± 1610 and 55 ± 101 nmol/L, respectively, p for difference <0.001). Six percent of the soy group had a genistein level that was under the median of the placebo group, and 0% of the placebo group had a genistein level above the median of the intervention group. In addition, we checked compliance using the diary reports. It appeared that about 90% of the subjects took the supplement for at least 80% of the total intervention period, which also indicates good compliance.

Table 2
Baseline characteristics of participants

	Soy protein ($n = 100$)	Placebo ($n = 102$)
Mean age (years)	66.6 (4.8)	66.8 (4.7)
Height (cm)	164.3 (6.4)	163.8 (6.3)
Weight (kg)	71.3 (11.7)	69.7 (10.2)
Waist circumference (cm)	85.4 (11.4)	84.1 (8.6)
Hip circumference (cm)	103.0 (8.1)	102.5 (8.3)
BMI ($kg\,m^{-2}$)	26.4 (4.1)	26.0 (3.4)
Systolic blood pressure (mmHg)	138.5 (18.5)	142.0 (20.5)
Diastolic blood pressure (mmHg)	74.5 (11.5)	76.0 (13.5)
Age at menopause (years)	48 (6)	49 (4)
Years postmenopausal (years)	18.5 (7.5)	18.0 (6.0)
Fertile years (years)	34.5 (6.5)	35.5 (4.5)
Ever use of estrogens	22 (22.2)[a]	23 (22.5)[a]
Current smoking	19 (19.0)	13 (12.7)
Former smoking	33 (33.0)	34 (33.3)
HAQ	0.14 (0.29)	0.12 (0.28)
Questionnaire on mobility in elderly	14.9 (8.9)	13.9 (7.6)
Physical performance test	9.32 (1.76)	9.09 (1.68)

Values are means or numbers with S.D. or percentage in parentheses.
[a] Not known for all subjects.

3.1. Physical measurements (Table 3)

Mean BMI at baseline was comparable between the placebo and the soy group and normal for women in this age range. In both intervention groups BMI remained virtually stable during the intervention year; the difference in change of BMI was $0.09\,kg\,m^{-2}$; 95% C.I.: −0.20, 0.39; $p = 0.53$ (Table 3).

Subgroup analyses by fertile years of postmenopausal or for groups of physically active and less active women did not show differences in effect of the intervention.

Mean waist-to-hip ratio at baseline was 0.82 (S.D. 0.07) for the placebo group and 0.83 (S.D. 0.08) for the soy group. In both groups, waist-to-hip ratio decreased (1.4×10^{-2} in the placebo group and 0.5×10^{-2} in the soy group), indicating that there was a slight improvement in upper body adiposity, although not statistically significantly different between the intervention groups (difference 0.9×10^{-2}; 95% C.I.: -0.7×10^{-2}, 2.5×10^{-2}; $p = 0.26$).

3.2. Physical performance and impairment (Table 4)

For the HAQ, the mean scores at baseline were 0.12 (S.D. 0.28) for the placebo group and 0.14 (S.D. 0.29) for the soy intervention group. At the end of intervention, mean scores were 0.12 (S.D. 0.25) for the placebo group and 0.12 (S.D. 0.26) for the soy group. For the HAQ, a lower score indicates a better self-reported functional status. The difference in change between groups was not statistically significant (Table 4).

The questionnaire on mobility in elderly showed an improvement (increasing score) during the intervention year. Difference in baseline-to-final visit change in scores was 1.4 (95% C.I.: −1.1, 3.9; $p = 0.27$). Table 5

Table 3
Difference in baseline-to-final visit change in measures of body composition

	Change in the soy group	Change in the placebo group	Difference in change	95% C.I.	*p*-value
Body mass index (kg m^{-2})	−0.038	−0.133	0.09	−0.20; 0.39	0.53
Waist-to-hip ratio	−0.005	−0.014	0.009	−0.007; 0.025	0.26

Table 4
Difference in baseline-to-final visit change in scores on the physical performance measures

	Change in the soy group	Change in the placebo group	Difference in change	95% C.I.	*p*-value
HAQ	−0.02	0.00	−0.02	−0.08; 0.03	0.42
Mobility questionnaire	3.1	1.7	1.4	−1.1; 3.9	0.27
PPT	0.07	0.18	−0.11	−0.60; 0.38	0.66

shows the results for the domains separately, from which it is obvious that differences in change on separate domains are also small.

Scores on the physical performance test showed a slight increase in both intervention groups; in the placebo group the score changed from 9.1 (S.D. 1.7) at baseline to 9.3 (S.D. 1.8) at final visit, and in the soy group from 9.3 (S.D. 1.8) at baseline to 9.4 (S.D. 1.7) at final visit. The difference in change between the groups was not statistically significant (difference 0.1; 95% C.I.: −0.6, 0.4; $p = 0.66$).

3.3. Handgrip strength

Handgrip strength at the final visit was slightly better in the placebo group compared to the soy group, but this difference was not statistically significant. Mean handgrip strength was 26.75 kg in the placebo group, in the soy group this was 0.45 kg less (95% C.I.: −2.5, 1.6 kg; $p = 0.7$). Because we had no baseline grip strength measurements, we adjusted for baseline age, BMI, past use of HT, postmenopausal years, fertile years and height. There were slight changes, but none of these factors affected the results materially.

4. Discussion

The present study did not demonstrate statistically significant effects of an increased intake of soy isoflavones on physical measures of body composition, physical performance and handgrip strength in postmenopausal women.

To interpret these findings, some strengths and limitations of the study need to be addressed. There are several strengths. The study was randomized and double blind, and was conducted in a large cohort. The drop-out remained within reasonable limits and adherence appeared to be good. Furthermore, we used well-established measurements that were carried out according to well-defined standards.

The limitations of the study relate to the HAQ questionnaire, which we considered to be a suitable measure given the age at inclusion. However, participants in our study turned out to be very healthy and active women; thus, the HAQ did not have good discriminatory value.

A disadvantage of the assessment of effects on handgrip strength is that we do not have a measurement at baseline for the 88 subjects concerned. This means we do not know whether subjects in the placebo group

Table 5
Difference in baseline-to-final visit change in scores on the domains of the questionnaire on mobility in elderly

Modules	Change in the soy group	Change in the placebo group	Difference in change	95% C.I.	*p*-value
Household activities	0.054	0.004	0.05	−0.04; 0.14	0.26
Sports	−1.15	−1.00	−0.15	−1.31; 1.00	0.79
Leisure time activities	3.80	2.62	1.18	−1.05; 3.41	0.30

also performed better at baseline. However, participants were randomized to the two interventions and can therefore assumed to be comparable at baseline. Furthermore, for the handgrip strength we cannot rule out the possibility that the study was underpowered to show an effect of soy isoflavone treatment on muscle strength. Estimating statistical power for this outcome is difficult because of the small number of studies on muscle strength. The number of subjects in our study on handgrip strength was similar to other studies [32–34].

Overall, power is an important issue in designing clinical trials. Although some might argue that we lacked power to find significant results for all endpoints, we designed the study in a way that we had power to detect clinically relevant improvements in PPT and HAQ, so if the sample was too small to find an effect, the effects must be very small and their clinical relevance is debatable.

To our knowledge, our study is the first to assess the effect of soy protein containing isoflavones on handgrip strength and is one of a handful evaluating the effect on measures of body composition. Data from a cross-sectional study showed an inverse association of usual dietary isoflavone intake with total body fat and waist circumference and also a significant association of genistein intake with BMI. There was no significant association with waist to hip ratio, which is in accordance with our findings [25]. A possible explanation for the discrepancy between their results and our results might be the cross-sectional design. Phytoestrogen intake in the cross-sectional study is likely to reflect a much longer period and may also be associated with other health behaviors [35]. In contrast, participants in our study typically had a very low isoflavone intake before they entered the trial. The present study also may have been too short to show significant effects on body composition. In studies on HT and body composition the duration of HT use was often several years. In the FELS Study, it was shown that women who had used estrogens for more than 5 years had significantly higher fat-free mass than non-users, while women with an estrogen use of less than 5 years had no difference in fat-free mass compared to non-users [13].

Most studies assessing effects of HT on body composition also have used cross-sectional designs. It is well recognized that results from cross-sectional studies have limitations when drawing longitudinal conclusions. One well-known problem in cross-sectional studies is the “healthy user” bias, which implicates that women on HT have a certain lifestyle that might include other beneficial factors.

There have been several intervention studies to investigate the role of HT in the preservation or improvement of handgrip strength, or more in general, in muscle strength and in the prevention of perimenopausal changes in body composition [32,33,36–41]. Results from these studies are not consistent. This is probably due to differences in study design, characteristics of study participants, muscle groups tested, methods of measuring body composition and type of intervention.

An important difference between studies on effects of HT and the present study is the age of the subjects. The mean age of participants in our trial was considerably higher than the age of participants in the HT studies. In a recent review on the effects of HT on the preservation of postmenopausal muscle strength, it was suggested that in older women a certain amount of muscle tissue is already converted into fibrous tissue, and therefore, HT can no longer exert an effect on muscle strength. Rather, an effect of HT can only be seen when started shortly after the onset of menopause [42]. The same might hold for phytoestrogens.

Another factor that may influence response to the intervention is differences in intestinal metabolism of soy isoflavones. Daidzein, one of the major soy isoflavones, is metabolized to equol by gut flora. It has been proposed that equol, rather than daidzein and genistein, is the active component [43]. Only approximately, 30% of humans are able to produce equol [43–45]. Consequently, only about 30% of subjects in the intervention might be expected to benefit from soy isoflavone supplementation. We assessed equol producer status in our study subjects; there was no difference in effects of the intervention between equol producers and non-producers.

In our study, both intervention groups showed an increase in scores on the questionnaire on mobility and the physical performance test. There are some possible explanations for this finding. Subjects might have become more aware of the importance of physical activity when filling in the questionnaire on mobility at baseline, and thus improved their levels of activity during the intervention year. Alternatively, subjects might have been better prepared to the questions at the final

visit and thus reported more activities. Also, the results of the physical performance test showed an equal increase in both groups.

In conclusion, supplementation of 99 mg isoflavones for 1 year does not appear to have a beneficial effect on body composition, handgrip strength, or physical performance in older women.

Acknowledgements

The study was financially supported by The Netherlands Organization for Scientific Research (NWO) no. 014-91-024, The Netherlands Organization for Health Research and Development (ZON) no. 2200.0048, and The Solae Company, St. Louis, MO, USA. The Solae Company neither controlled nor influenced the contents of the research or of this paper, nor played any part in the decision to submit this manuscript for publication.

References

[1] Kannel WB, Cupples LA, Ramaswami R, Stokes III J, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. J Clin Epidemiol 1991;44:183–90.
[2] Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjostrom L. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg. Sweden Int J Obes 1989;13:413–23.
[3] Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002;3:565–74.
[4] Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254–9.
[5] Schott AM, Cormier C, Hans D, et al. How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporos Int 1998;8:247–54.
[6] Rantanen T, Avlund K, Suominen H, Schroll M, Frandin K, Pertti E. Muscle strength as a predictor of onset of ADL dependence in people aged 75 years. Aging Clin Exp Res 2002;14:10–5.
[7] Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci (London) 1993;84:95–8.
[8] Panotopoulos G, Raison J, Ruiz JC, Guy-Grand B, Basdevant A. Weight gain at the time of menopause. Hum Reprod 1997;12(Suppl. 1):126–33.
[9] Poehlman ET, Toth MJ, Gardner AW. Changes in energy balance and body composition at menopause: a controlled longitudinal study. Ann Intern Med 1995;123:673–5.
[10] Douchi T, Yamamoto S, Nakamura S, et al. The effect of menopause on regional and total body lean mass. Maturitas 1998;29:247–52.
[11] Aloia JF, McGowan DM, Vaswani AN, Ross P, Cohn SH. Relationship of menopause to skeletal and muscle mass. Am J Clin Nutr 1991;53:1378–83.
[12] Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metabolism 1995;44:369–73.
[13] Guo SS, Zeller C, Chumlea WC, Siervogel RM. Aging, body composition, and lifestyle: the Fels Longitudinal Study. Am J Clin Nutr 1999;70:405–11.
[14] Haarbo J, Marslew U, Gotfredsen A, Christiansen C. Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. Metabolism 1991;40:1323–6.
[15] Gardner-Thorpe D, O'Hagen C, Young I, Lewis SJ. Dietary supplements of soya flour lower serum testosterone concentrations and improve markers of oxidative stress in men. Eur J Clin Nutr 2003;57:100–6.
[16] Skelton DA, Phillips SK, Bruce SA, Naylor CH, Woledge RC. Hormone replacement therapy increases isometric muscle strength of adductor pollicis in post-menopausal women. Clin Sci (London) 1999;96:357–64.
[17] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
[18] Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.
[19] Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. Obstet Gynecol 1998;91:6–11.
[20] Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman Jr JW. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. Am J Clin Nutr 1998;68:1375S–9S.
[21] Lydeking-Olsen E, Beck Jensen J, Setchell KD, Damhus M, Holm Jensen T. Isoflavone-rich soymilk prevents bone loss in the lumbar spine of postmenopausal women: a two-year study. J Nutr 2002;132:581S.
[22] Hermansen K, Sondergaard M, Hoie L, Carstensen M, Brock B. Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. Diabetes Care 2001;24:228–33.
[23] Goodman MT, Wilkens LR, Hankin JH, Lyu LC, Wu AH, Kolonel LN. Association of soy and fiber consumption with the risk of endometrial cancer. Am J Epidemiol 1997;146:294–306.
[24] Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer [see comments]. Lancet 1997;350:990–4.
[25] Goodman-Gruen D, Kritz-Silverstein D. Usual dietary isoflavone intake and body composition in postmenopausal women. Menopause 2003;10:427–32.
[26] Kok L, Kreijkamp-Kaspers S, Grobbee DE, van der Schouw YT. Design and baseline characteristics of a trial on health ef-

fects of soy protein with isoflavones in postmenopausal women. Maturitas 2004;47:21–9.
[27] Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, et al. Dietary assessment in the elderly: validation of a semi-quantitative food frequency questionnaire. Eur J Clin Nutr 1998;52:588–96.
[28] Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3:305–9 [JID – 8211469].
[29] Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. Med Sci Sports Exerc 1991;23:974–9.
[30] Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94 [JID – 0374762].
[31] Setchell KD, 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.
[32] Meeuwsen IB, Samson MM, Duursma SA, Verhaar HJ. Muscle strength and tibolone: a randomised, double-blind, placebo-controlled trial. BJOG 2002;109:77–84.
[33] Preisinger E, Alacamlioglu Y, Saradeth T, Resch KL, Holzer G, Metka M. Forearm bone density and grip strength in women after menopause, with and without estrogen replacement therapy. Maturitas 1995;21:57–63.
[34] Bemben DA, Langdon DB. Relationship between estrogen use and musculoskeletal function in postmenopausal women. Maturitas 2002;42:119–27.
[35] Frankenfeld CL, Patterson RE, Horner NK, et al. Validation of a soy food-frequency questionnaire and evaluation of correlates of plasma isoflavone concentrations in postmenopausal women. Am J Clin Nutr 2003;77:674–80.
[36] Dobs AS, Nguyen T, Pace C, Roberts CP. Differential effects of oral estrogen versus oral estrogen–androgen replacement therapy on body composition in postmenopausal women. J Clin Endocrinol Metab 2002;87:1509–16.
[37] Ribom E, Piehl-Aulin K, Ljunghall S, Ljunggren O, Naessen T. Six months of hormone replacement therapy does not influence muscle strength in postmenopausal women. Maturitas 2002;42:225.
[38] Hanggi W, Lippuner K, Jaeger P, Birkhauser MH, Horber FF. Differential impact of conventional oral or transdermal hormone replacement therapy or tibolone on body composition in postmenopausal women. Clin Endocrinol (Oxf) 1998;48:691–9.
[39] Dittmar M. Comparison of soft tissue body composition in postmenopausal women with or without hormone replacement therapy considering the influence of reproductive history and lifestyle. Ann Hum Biol 2001;28:207–21.
[40] Heikkinen J, Kyllonen E, Kurttila-Matero E, et al. HRT and exercise: effects on bone density, muscle strength and lipid metabolism. A placebo controlled 2-year prospective trial on two estrogen–progestin regimens in healthy postmenopausal women. Maturitas 1997;26:139–49.
[41] Taaffe DR, Luz VM, Delay R, Marcus R. Maximal muscle strength of elderly women is not influenced by oestrogen status. Age Ageing 1995;24:329–33.
[42] Meeuwsen IB, Samson MM, Verhaar HJ. Evaluation of the applicability of HRT as a preservative of muscle strength in women. Maturitas 2000;36:49–61.
[43] Setchell KD, Borriello SP, Hulme P, Kirk DN, Axelson M. Nonsteroidal estrogens of dietary origin: possible roles in hormone-dependent disease. Am J Clin Nutr 1984;40:569–78.
[44] 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;217:335–9.
[45] Rowland IR, Wiseman H, Sanders TA, Adlercreutz H, Bowey EA. Interindividual variation in metabolism of soy isoflavones and lignans: influence of habitual diet on equol production by the gut microflora. Nutr Cancer 2000;36:27–32.