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Randomised controlled trial of effect of whole soy replacement diet on features of metabolic syndrome in postmenopausal women: study protocol

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is a public health problem in postmenopausal women. Whole soy foods are rich in unsaturated fats, high quality plant protein and various bioactive phytochemicals that may have a beneficial role in the management of MetS. The aim of the study is to examine the effect of whole soy replacement diet on the features of MetS among postmenopausal women.

Methods and analysis: This will be a 12-month, randomised, single-blind, parallel controlled trial among 208 postmenopausal women at risk of MetS or with early MetS. After 4 weeks' run-in, subjects will be randomly allocated to one of two intervention groups, whole soy replacement group or control group, each for 12 months. Subjects in the whole soy group will be required to include four servings of whole soy foods (containing 25 g soy protein) into their daily diet iso-calorically, replacing red or processed meat and high fat dairy products. Subjects in the control group will remain on a usual diet. The outcome measures will include metabolic parameters as well as a 10-year risk for ischaemic cardiovascular disease. We hypothesise that the whole soy substitution diet will notably improve features of MetS in postmenopausal women at risk of MetS or with early MetS. The study will have both theoretical and practical significance. If proven effective, the application of the whole soy replacement diet model will be a safe, practical and economical strategy for MetS prevention and treatment.

Ethics and dissemination: Ethics approval has been obtained from the Ethics Committee of the Chinese University of Hong Kong. The results will be disseminated via conference presentations and papers in academic peer reviewed journals. Data files will be deposited in an accessible repository.

Trial registration number: NCT02610322.

Strengths and limitations of this study

- The first randomised controlled trial to investigate the effect of whole soy replacement diet on metabolic syndrome among Chinese postmenopausal women.
- Pragmatic design to facilitate implementation in daily life.
- Single-centre and non-blinded design.

INTRODUCTION

Epidemiology of metabolic syndromes and their prevention

Metabolic syndrome (MetS) is a constellation of interrelated metabolic risk factors, including abdominal obesity, raised fasting glucose, dyslipidaemia and hypertension, which predispose an individual to an increased risk of cardiovascular morbidity and mortality.[1] The cardiovascular risk conferred by MetS was found to be threefold higher in women than in men.[2] Menopause is a predictor of MetS independent of age.[3] The Guangdong (South China) Health Survey 2010[4] reported the age-standardised prevalence of MetS had increased fourfold that of the prevalence rate in 2002. Urban midlife women had the highest prevalence of MetS (33.7% in women aged 40–59 years and 42.9% in women aged ≥60) according to the International Diabetes Federation (IDF) criteria.[4] More than 60% of the adults had at least one component of MetS.[5] Thus, there is an urgent need to develop a population level strategy for the prevention of MetS, especially among postmenopausal women.

Major efforts are being made to develop non-pharmacologic approaches to reduce

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the prevalence of MetS.[6] Studies have shown a diet that includes less saturated fats[7] but more unsaturated fats,[8] dietary fibre[9] and low-fat dairy products[10] will benefit patients with MetS.[11] Red meat and full-fat dairy products are among the main sources of saturated fat in diets. Most epidemiological studies have reported that the consumption of low-fat instead of high-fat dairy products are favourable in improving glycaemic control[12 13] and decreasing the risk of MetS[11 13 14] and diabetes.[15–17] Soy is a traditional part of the Asian diet and a valuable source of nutrients and phytochemicals. Soybeans contain a high-quality plant protein, a healthy unsaturated fatty acid profile, and a good source of insoluble polysaccharides, appreciable amounts of B vitamins and minerals. Soybeans are also rich in various types of bioactive phytochemicals such as isoflavones, saponin and sterols which are beneficial to human health.[18]

Several large-scale observational studies suggest higher habitual soy intake is associated with lower lipid profiles,[19] blood pressure (BP)[20] and risk of type 2 diabetes.[21] In vitro and animal experiments also suggest that soy intake has selective effects on up-regulation of genes involved in glucose and lipid metabolism, enhances insulin sensitivity, and promotes a selective loss of visceral adipose tissue.[7] However, in clinical trials, soy products are often provided as dietary supplements, and the benefits have typically been small and inconsistent.[22 23] Soy protein isolate and isoflavones are the mostly studied soy components in human trials. The discrepancies between the inconsistent results of clinical trials that use individual soy components and the generally positive results of using habitual soy foods in observational studies suggest that nutrients in supplements may not reduce risk to the same extent as the nutrients in foods. Most of the traditional Asian soy foods such as tofu, soy flour, soy milk, soy nuts and dried bean curd, etc are minimally processed and belong to whole soy foods/diet. The more noted health effect of whole soy than a selected soy component(s) could be due to the alteration of amino acid or phytochemical compositions as a result of complex methods for extraction of soy components which thus influence the nutritional value.[22] Application of single nutrients rather than the whole food may ignore interactions between dietary components. Recent research studies on diet and chronic disease risks have also focused on whole foods or complete diets rather than on individual dietary components.[22]

Evidence gap of research on whole soy replacement diet

Whole soy diets are not only a healthy food choice, but can also act indirectly on health through the displacement of foods of lower nutritional density and quality.[24] The displacement values are unique to soy since other foods or food components are added to the diet rather than exchanging for suboptimal foods, which makes soy a particularly valuable tool in the dietary armamentarium to reduce cardiovascular risks.[22] A recent systematic review,[24] using a predictive model in NHANES III survey data, suggested that soy consumption (13–58 g/day) resulted in an additional 3.6–6.6% low density lipoprotein cholesterol (LDL-C) reduction due to displacement of saturated fat and cholesterol from animal foods. Thus, the combined intrinsic (4.3%) and extrinsic effects of soy foods on LDL-C ranged from 7.9% to 10.3%. The American Heart Association (AHA) review also suggested that although soy protein with isoflavones has minor effects on LDL-C (3–5%), the whole soy foods may be beneficial to cardiovascular and overall health if used to replace fatty foods.[25] Our recent 6 month randomised controlled trial (RCT) involving 270 pre-hypertensive equol-producing postmenopausal women also indicated that whole soy, but not purified daidzein, had a beneficial effect on the reduction of LDL-C and inflammatory markers.[26] However, the replacement effect of soy has not been specifically examined.[24] In the literature, several trials[27–30] used one kind of whole soy food (tofu, soy milk or soy nuts) as a substitute for one animal food (cheese, cow milk or red meat) as treatment and all reported beneficial effects of soy on lipids. However, all the studies had relatively small sample sizes (10–50) and short durations (3–8 weeks). In addition, most of the findings are from laboratory studies, not in free-living conditions. Positive findings from laboratory conditions provide only a theoretical maximum effect that may or may not be achievable under free-living status. Thus, clinical trials exploring the potential displacement value of whole soy diet and the longer-term effect are warranted.[24]

Consumption of soy foods, red or processed meat and dairy products in Hong Kong

Historically, soy was deemed 'the meat without bones' and 'the meat of the field' among the less affluent people of Asia. As Hong Kong (South China) increases its rate of modernisation and westernisation, more people are likely to consume energy-dense western-style diets (inadequate plant food and increase in red meat and high fat dairy products, etc) while the consumption of traditional soy foods is notably reduced. A health behaviour survey commissioned by the Hong Kong Health Department in 2007 indicated that >94% of Hong Kong women consume <1 serving of soy foods (tofu or soy milk, etc) per day and that 34.8% had no intake of any soy foods in the week before the interview.[31] The average daily intake of soy protein is 30 g in Japan, 20 g in Korea, but only 7 g in Hong Kong.[32] Soy consumption is even less in elderly women.[33] Our previous population-based study indicated women aged ≥50 years had significant lower soy intake (29.2 g/week soy protein) than men (36.5 g/week) in the same age group or women <50 years (46.4 g/week).[33] A survey in 2009[34] reported that the average amount of red meat intake in Hong Kong was 130 g/day, 57.8% consumed processed meat at least once per week, and 65% chose full-fat milk rather than low fat or skim milk. The figures

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fall short of the recommendation of the Chinese Dietary Guideline,[35] suggesting room for improvement.

Study aim

Thus, we propose a 12-month RCT among postmenopausal women in Hong Kong at risk of MetS or with early MetS to examine the effect of whole soy foods in place of red or processed meat and high fat dairy products on metabolic risk factors (central obesity, serum lipids profile, glucose, BP, etc). We hypothesise that a whole soy replacement diet will significantly improve the features of MetS in this group of postmenopausal women.

METHODS AND ANALYSIS

Participants

Women aged 45–70 years will be recruited by advertisements in newspaper, health talks or referrals. They will be initially screened via telephone or in person using a prescreening questionnaire, in which details of their medical history and medication will be reviewed and the risk of MetS will be evaluated based on established risk factors of the condition (obesity, elevated BP, fasting glucose and lipids, family history of hypertension, diabetes or hyperlipidaemia, as well as physical inactivity, etc). Subjects who meet the initial criteria will be invited for a clinic visit to determine their eligibility by assessment of central obesity, BP, glucose and lipids, etc.

Inclusion and exclusion criteria

Participants will be recruited if they are aged 45–70 years within 15 years after menopause; women at risk of MetS or early MetS will be identified based on modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria,[36] which have considered the ethnic difference in the definition of central obesity and the modified American Diabetes Association criteria for impaired fasting glucose. Participants who meet ≥2 of the following items will be enrolled: (1) waist circumference ≥80 cm; (2) triglyceride concentration ≥1.7 mmol/L; (3) high density lipoprotein cholesterol (HDL-C) <50 mg/dL (1.29 mmol/L); (4) systolic blood pressure/diastolic blood pressure (SDP/DBP) ≥130/85 mm Hg; (5) fasting glucose ≥5.6 mmol/L.

Women will be excluded if they have been receiving medications known to affect bodyweight, lipids and glucose within the previous 3 months, such as hypoglycaemic, hypocholesterolaemic or weigh reduction agents or hormone therapy; if they have a medical history of, or currently have, severe systemic or endocrine diseases such as thyroid disease, stroke, cardiac infarction, severe liver and renal dysfunction, or gout; if they present with, or have a history of, breast, endometrial or ovarian cancer, or abnormal uterine bleeding after menopause; or if they are on a prescribed or vegetarian diet and have a known soy allergy.

Study design

This will be a 12-month, randomised, single-blind, controlled, parallel trial (see figure 1 for study flow chart). Before randomisation, a 4-week run-in exercise will be performed to familiarise the subjects with the study requirements. Subjects will undertake training on the estimation of food amounts and fulfilment of a 7-day dietary record, as well as 24 hour urine collections for the study adherence assessment. Subjects who qualify in dietary record keeping and urine collection and are willing to continue after the run-in will be randomly assigned to one of two intervention groups, whole soy replacement diet group (whole soy group) and usual diet group (control group), each for 12 months.

Measurements will be obtained at baseline, 6 and 12 months. Participants will be free-living during the study and will prepare their own meals. The participants will be asked to maintain their habitual physical activity and record their dietary intake for 3 consecutive days in each month during the study. The completed dietary records will be mailed back to the research centre in pre-paid envelopes. All the participants will be in contact with the nutritionist or research staff every month via telephone. The preceding dietary record will be assessed by the nutritionist and discussed with the participant during the interview. Participants who complete the study according to the protocol will be given a 1 year membership to a health centre as an incentive.

Intervention

Participants who are assigned to the usual diet group will receive a 5–10 min conventional lifestyle education on MetS by a member of the research staff in which the general recommendation for macronutrient composition of the control diet will be 50–60% of energy as carbohydrate, 15–20% of energy as protein, and <30% of energy as total fat.

Participants who are allocated to the whole soy group will receive a 30–40 min counselling session by an experienced nutritionist on: (1) conventional lifestyle education on MetS; (2) the benefits of whole soy diet; (3) practical techniques to incorporate four servings of whole soy foods (equivalent to 25 g soy protein) into their daily diet and reduce/replace high saturated fat and cholesterol-rich animal foods (including red/processed meat and full-fat dairy products) based on their prior 7-day dietary record during the run-in. Participants will also receive a pamphlet and a 30 min DVD which will provide practical cooking recipes with both illustrations and demonstrations on how to prepare whole soy foods/diets in an easy and fun way to replace fatty animal meat and dairy products; a food composition table with major nutrients in common soy and animal foods/products; updated information on soy intake and women's health; tips on how to estimate food amounts and utensil sizes, and how to record their dietary intake; and a detailed and practical soy food exchange/replacement list which can be applied in daily meal schedules.

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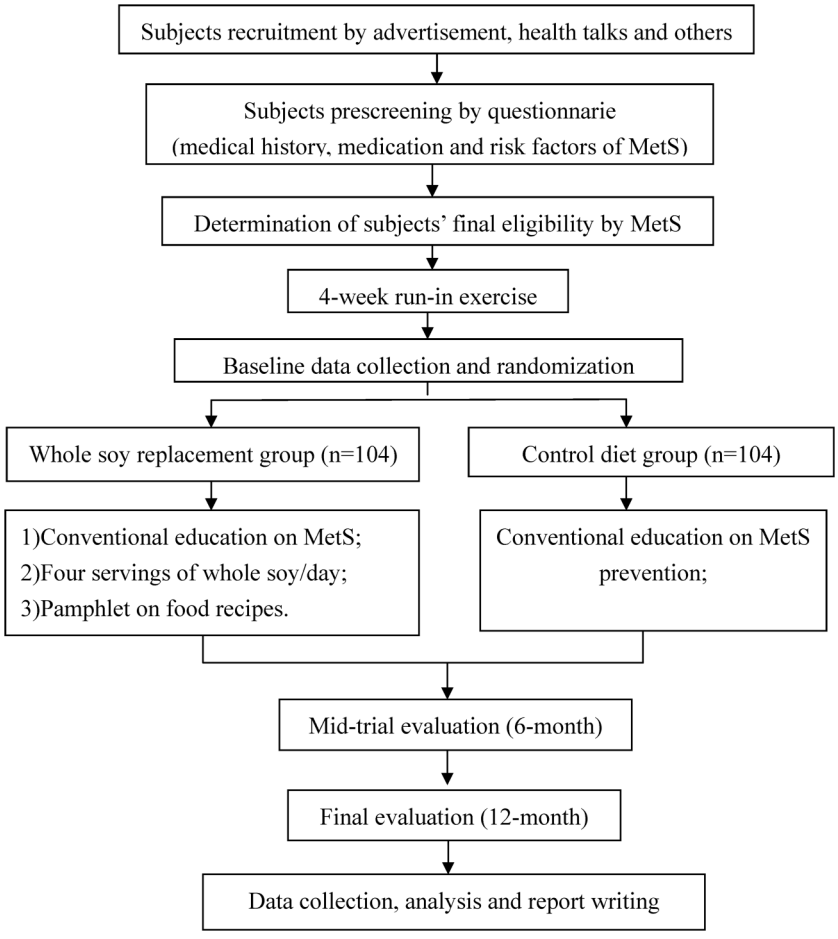

Figure 1 Study flow of chart based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines. MetS, metabolic syndrome.

Rationale of whole soy dosage

Soy intake recommendation is based on three considerations: Asian soy intake, clinical and epidemiologic studies assessing the health consequences of soy consumption, and general principles of dietary practice.[37] Existing epidemiologic studies and clinical trials on soy and health indicate the optimal adult soy intake is two to four servings per day.[38] The proposed 25 g soy protein intake exceeds the intake of at least 90% of the Japanese and Shanghai (China) populations, but it is still within the dietary range.[20 39] Higher dosage may not be practical and may affect the participants' compliance. Participants are required to consume four servings of whole soy foods (tofu, soy milk, soy flour, bean curb or soy nuts, etc) per day. One serving of soy foods contains 6.25 g soy protein. Twenty-five grams of soy protein is equivalent to 300 g tofu, 600 mL soy milk, 120 g dried bean curd or 65 g dried soy nuts, and will iso-calorically substitute for high saturated fat/cholesterol animal sources foods such as red meat (pork, beef and mutton), processed meat (bacon, sausage, roast, etc), and full-fat dairy products (cow's milk, cheese and ice-cream, etc). Each 30 g soy nut will be exchanged as one serving of red meat.[40] Dietary records will then be coded according to the prescribed protocol and analysed for content of energy and the other nutrients based on Chinese Food Composition Table 2007.

Sample size planning

Based on our previous RCTs on soy, we assume a whole soy replacement diet will result in a 5 mm Hg (SD of change, 10 mm Hg) reduction in SBP,[41] 5 mg/dL (SD of 12 mg/dL) reduction in fasting glucose,[23] 2% (SD of 4%) reduction in bodyweight,[42] and 5% (SD of 12%) reduction in LDL-C.[43] Based on the change and SD of change of fasting glucose or bodyweight (the largest ratio of SD/change among above outcomes), 90 subjects per group will yield at least 80% power at the 5% level of significance (two-sided) to detect a difference in the above four metabolic components. Our previous RCTs on soy reported dropout rates of 7.8% (RGC-CUHK 4450/06M)[41] and 6.3% (RGC-GRF 465810)[44] and >90% good compliance (>80% required amount) with soy supplementation in Chinese postmenopausal women. Thus, assuming 15% non-compliance including dropouts, 104 subjects per group for a total 208 participants will be appropriate for the project.

Randomisation and blindness

A block randomisation procedure will be used for subject allocation in a block size of eight using the SPSS (V.21.0, SPSS Inc, Chicago, USA) procedure. In brief, 208 continuous serial numbers (1–208) will be divided into 26 sub-blocks. Two treatments will be randomly allocated to the two groups. A total 208 numbers will be

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assigned to eligible participants according to the sequence of their visits after run-in. The allocation code will be placed in numbered envelopes to be opened by the nutritionist or research staff in the presence of the participants. The statistician, investigators, and laboratory staff who analyse the samples or conduct data collection and analyses will be unaware of participant allocation.

Adherence assessment

Adherence assessment will be mainly based on the monthly 3-day dietary records and 24 hour urinary isoflavones concentration at basal and final term visits. Good compliance of whole soy diet is defined as a daily average soy protein intake >20 g (80% of target amount of 25 g) and urinary total isoflavones levels notably exceeding the baseline level in the whole soy group.

Code breaking and conditions for withdrawal

The principal investigator will be responsible for breaking the randomisation code after the completion of data analyses or in emergency situations (if subjects experience adverse reactions/side effects to the treatments). Conditions for withdrawal include any situation where, in the opinion of the investigator, continuation of the study would not be in the best interest of the subject, including but not limited to: reaction or discomfort from the treatments; subjects developed conditions or received medications as specified under the exclusion criteria; or the subjects requested withdrawal from the study.

Data collection/outcome measures

The primary outcome of the study is to examine the effect of whole soy replacement diet on the metabolic components of MetS. Data collection will be performed at baseline, 6 and 12 months after treatment. Twenty-four hour urine and overnight fasting (10–12 hours) blood samples will be collected at baseline and at 12 months after intervention. Plasma/serum will be isolated within 2 hours after collection. Specimens will be stored at −80°C until analysis. All samples from each subject will be run in the same batch to avoid inter-assay variability. A structured questionnaire interview and anthropometric measurements will be performed at baseline, 6 and 12 months.

1. Anthropometric measures: Bodyweight, height, waist and hip circumferences will be measured according to standard procedures. Body mass index (BMI) and waist-to-hip ratio (WHR) will be calculated. Body fat percentage (BF%), fat mass (FM) and free fat mass (FFM) will be measured by a bioelectrical impedance analyser (TBF-410-GS Tanita Body Composition Analyzer, Japan).
2. Blood pressure: BP will be measured twice on a standardised procedure after the participants sit for 15 min using cycling Dinamaps (GE Medical System Information Technologies, Milwaukee, Wisconsin, USA) at the baseline, 6 and 12 months. Two readings will be obtained at least 1 min apart. If there is >5 mm Hg difference in SBP between the two readings, a third reading will be obtained.
3. Serum lipids and glucose values: A fasting blood sample (10–12 hours) will be collected into plain tubes and centrifuged at 4°C and 3000 *g* for 10 min to separate the serum. Fasting serum glucose, total cholesterol and triglycerides will be measured by standardised enzymatic colorimetric methods. Serum HDL-C and LDL-C will be measured by enzymatic clearance assay. All analyses will be performed on automated analyser at a certified clinical laboratory.
4. Number of MetS characteristics: The number of metabolic characteristics (a maximum of five: waist circumference, BP, glucose, triglyceride and HDL-C) will be counted at baseline and the end of the trial.
5. Estimation of 10-year risk for ischaemic cardiovascular disease: The 10-year ischaemic cardiovascular disease risk score will be estimated based on an established equation model recalibrated for the Chinese population.[45]

Covariates and biomarkers for compliance and safety

1. Sociodemographic data: collected by face-to-face interview based on structured and previously validated questionnaire.
2. Habitual physical activities: collected by a modified Baecke questionnaire validated in the Hong Kong population.
3. Urinary isoflavones: will be determined by high performance liquid chromatography (HPLC).
4. Serum thyroid stimulating hormone (TSH): Given that soy may increase iodine requirements, serum TSH will be measured at baseline and the end of the trial. Serum TSH will be measured by a standardised immunoassay.

Statistical analysis

The primary analysis will be an intention-to-treat analysis that includes all subjects who are randomised. A secondary per protocol analysis will be performed including subjects with good compliance (defined as subjects who consumed 80% of required amounts and completed all assessments and sample collections). The non-compliant subjects will be described and compared to the compliant subjects. Skewed variables or variables with significant heterogeneity will be log-transformed first. Relevant parametric and non-parametric tests will be used for test of differences in the baseline characteristics of the two study groups. Comparisons of means of outcome measures (MetS components) at 6 and 12 months between groups will be made using both repeated-measures analysis of variance and analysis of covariance (ANCOVA) with baseline data as covariate. All results will be considered significant if the two-tailed p value is <0.05. Statistical analysis will be performed using SPSS V.21.0 software.

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DISCUSSION

This study is specifically designed to address postmenopausal women at risk of MetS and explores the effect of using whole soy diet in place of high saturated fat and cholesterol-rich animal foods on features of MetS. Application of a whole soy replacement diet model should be a safe, practical, and economical diet strategy to improve metabolic diseases and cardiovascular health. The modality may obtain more effective compliance than other dietary restrictions. If proven effective, this dietary strategy will offer an additional or alternative nutritional approach to the prevention and management of MetS. The study will have important public health implications when the findings are disseminated in communities. With the increasing prevalence of MetS and its complications in postmenopausal women, this study will explore an area with important public health implications both locally and internationally.

Ethics and dissemination

Written informed consent will be obtained from all participants before the intervention. Ethics approval has been obtained from the Ethics Committee of the Chinese University of Hong Kong (CRE2013.121). The results will be disseminated via conference presentations and papers in academic peer reviewed journals. The protocol will be performed in accordance with the Declaration of Helsinki. A report will be submitted to the ethics committee yearly. The scientific committee does not require auditing for this study. Data files will be deposited in an accessible repository.

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Competing interests None declared.

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