Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women¹⁻³

Gong Yang, Xiao-Ou Shu, Fan Jin, Xianglan Zhang, Hong-Lan Li, Qi Li, Yu-Tang Gao, and Wei Zheng

ABSTRACT
Background: Several small-scale clinical trials have suggested a potential beneficial effect of short-term soy consumption on blood pressure (BP). Data are scanty on long-term effects of the usual intake of soy foods on BP in general populations.
Objective: Our aim was to examine the association between usual intake of soy foods and BP.
Design: The usual intake of soy foods was assessed at baseline, and BP was measured 2–3 y after the baseline survey among 45,694 participants of the Shanghai Women’s Health Study aged 40–70 y who had no history of hypertension, diabetes, or cardiovascular disease at recruitment. Multiple regression models were used to estimate mean differences in BP associated with various intakes of soy foods.
Results: Soy protein intake was inversely associated with both systolic BP (P for trend = 0.01) and diastolic BP (P for trend = 0.009) after adjustment for age, body mass index, and lifestyle and other dietary factors. The adjusted mean systolic BP was 1.9 mm Hg lower (95% CI: −3.0, −0.8 mm Hg) and the diastolic BP was 0.9 mm Hg lower (−1.6, −0.2 mm Hg) in women who consumed ≥25 g soy protein/d than in women consuming <2.5 g/d. The inverse associations became stronger with increasing age (P for interaction <0.05 for both BPs). Among women >60 y old, the corresponding differences were −4.9 mm Hg (95% CI: −8.0, −1.9 mm Hg) for systolic BP and −2.2 mm Hg (95% CI: −3.8, −0.6 mm Hg) for diastolic BP.
Conclusion: Usual intake of soy foods was inversely associated with both systolic and diastolic BPs, particularly among elderly women. Am J Clin Nutr 2005;81:1012–7.

SUBJECTS AND METHODS
Study population
The Shanghai Women’s Health Study, initiated in March 1997, is a population-based prospective cohort study of Chinese women aged 40–70 y who are residing in 7 urban communities of Shanghai. Of the 81,170 eligible women identified from the Shanghai Resident Registry, 2,407 (3.0%) refused to participate in the study, 2,073 (2.6%) were not available during the study recruitment period, and 1,469 (1.8%) were not enrolled for miscellaneous other reasons such as mental disorder. The remaining 75,221 women were recruited, and they completed the baseline health assessment. Subjects who had a history of hypertension, diabetes, or cardiovascular disease at recruitment were excluded. The remaining 75,221 women were recruited, and they completed the baseline health assessment.

INTRODUCTION
Because of substantial evidence that soy protein intake improves serum lipid profiles (1), the US Food and Drug Administration and the American Heart Association issued a recommendation of daily consumption of ≥25 g soy protein as a preventive measure to reduce the risk of heart disease (2, 3). Recently, the nonlipid-related effects of soy, especially its influence on vascular function, have become a focus of research (4). Soy isoflavones, an important class of phytoestrogens, have been shown to decrease in vivo oxidation (5), stimulate nitric oxide production (6, 7), improve systemic arterial compliance (8–11), and favorably affect salt and water balance (12–14), all of which suggests a protective role with respect to the development of hypertension. Soy intake has also been suggested to reduce C-reactive protein concentrations (15, 16), a marker of systemic inflammation that has been associated with incident hypertension (17). Several small-scale clinical trials have further provided evidence that soy intake may be effective in lowering blood pressure (BP), although the results are not entirely consistent (18–25). No hypotensive effect of soy supplement was found in some of the previous studies (24, 25). Most of those trials, however, investigated the effects of specific soy components supplemented at a relatively high dose for a short period of time. Data are scanty on usual dietary intake of soy foods in relation to BP in general populations. Two cross-sectional studies conducted in the United States, where soy foods are rarely consumed, examined dietary intake of soy phytoestrogen and found an inverse but statistically nonsignificant association with BP (26, 27).

In the current study, we examined the association between usual intake of soy foods and BP among the participants in the Shanghai Women’s Health Study, a large cohort study that was conducted in a population that had a wide range of soy food intake and that thus was uniquely suited for an evaluation of the health effects of soy.

KEY WORDS
Blood pressure, soy foods, women, longitudinal observation
survey between 1997 and 2000, for a participation rate of 92.7%. After the exclusion of women who were found to be outside of the study’s age range at the time of interview, the final cohort of the Shanghai Women’s Health Study consisted of 74 943 women. Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Board of Vanderbilt University and all other participating institutions.

Trained retired nurses conducted the baseline survey at participants’ homes by using a structured questionnaire designed to collect information on demographic characteristics, diet and lifestyle habits, medical history, and use of medications, including antihypertensives and hormones. The prevalence of hypertension was based on self-reporting because BP was not measured at baseline. Anthropometric measurements were taken with the use of a standardized protocol. All interviews were tape-recorded and selectively checked by quality-control staff to monitor the quality of the interview data. All study participants were followed through biennial in-person interviews.

Assessment of soy food consumption

At the baseline survey, the interviewers collected information on usual dietary intake over the previous 12 mo for all the cohort members through a face-to-face interview by using a validated food-frequency questionnaire (28). The questionnaire included 11 soy food items (i.e., tofu, soy milk, fried bean curd, bean curd cake, and other kinds of soy products), covering virtually all soy foods consumed in urban Shanghai. Fresh and dried soybeans were also included. For each food item, study participants were first asked to report how frequently (daily, weekly, monthly, yearly, or never) they consumed the food; this question was followed by a question on the amount of intake in the Chinese measure, lians (1 lian = 50 g). For seasonal foods (e.g., fresh legumes), in-season consumption patterns were determined, and the average daily consumption over a 12-mo period was calculated by adjustment for the estimated months during which the foods were consumed. We estimated total soy food intake by tallying the soy protein content for each specific soy food on the basis of the Chinese Food Composition Table (29). We also estimated isoflavone intake by using the published data on the isoflavone content of soy foods (30).

We have published elsewhere the validation study of the food-frequency questionnaire (28). Briefly, in a random sample of 200 participants in the Shanghai Women’s Health Study, we compared the estimates of dietary intake derived from the food-frequency questionnaire with those derived from 24-h dietary recalls conducted twice a month for 12 mo. The Pearson correlation coefficient for soy food intake was 0.49. The coefficients for nutrient intakes ranged from 0.41 to 0.64.

Blood pressure measurement

The first follow-up survey was conducted 2–3 y after the baseline survey, with a response rate of 99.7%. BP was measured for 91% of the participants (n = 68 427) as part of the first follow-up survey. After the participants sat quietly for ≥5 min, trained interviewers (retired nurses) measured BP with the use of a conventional mercury sphygmomanometer according to a standard protocol (31).

Statistical analysis

For the current study, we excluded women who reported a history of hypertension (n = 16 455), diabetes (n = 3004), coronary heart disease (n = 5068), or stroke (n = 776) or who took antihypertensive medications (n = 11 086). These exclusions were made because of concerns that dietary practice and BP could be substantially influenced by disease diagnosis and use of medications. We also excluded from this analysis users of postmenopausal hormones (n = 1409) and women who underwent hysterectomy (n = 3701), out of concern that potential hormone-related mechanisms may under-cut the effects of soy or soy isoflavones. In addition, we excluded women with missing BP data (n = 46) or with an extreme total energy intake (<500 or >3500 kcal/d; n = 97). After these exclusions (not mutually exclusive), 45 694 women remained for the analysis.

We applied a multiple regression model to evaluate the association between usual dietary soy protein intake and BP. We categorized the study subjects into 5 groups according to daily soy protein intake, with cutoffs being 2.5 (x̅ –SD), 8.8 (x̅), 15.1 (x̅ + SD), and 25 g/d (the minimum amount recommended by the US Food and Drug Administration). Subjects with soy protein intake <2.5 g/d were chosen as the reference group. Mean BP differences associated with each category of soy protein intake compared with the reference group (the lowest category) and their 95% CIs were estimated by using the multiple regression models that adjusted for potential confounding variables. The variables adjusted for included age (continuous), body mass index (BMI; in kg/m²; continuous), education (5 categories), household income (4 categories), alcohol consumption (yes or no), cigarette smoking (yes or no), regular physical activity during the past 5 y (yes or no), and dietary factors (continuous), such as intakes of total energy, nonsoy protein, fruit, vegetables, and sodium from both salt and food. A linear trend test was performed by treating each ordinal score variable as a continuous variable in the model. Because many dietary factors highly correlate with each other, we used the variable inflation factor to measure the effect of multicollinearity for each variable. All dietary factors included in the models had a variable inflation factor <10. To minimize a potential influence of recent dietary change on the results, we conducted separate analyses among women who reported no significant changes in vegetable consumption during the past 5 y. We also conducted analyses stratified by age and menopausal status (menopause was defined as an absence of the menstrual period for ≥12 mo, excluding lapses related to either pregnancy or breastfeeding). Tests for interaction were performed by introducing a multiplicative interaction term into the main effect models. All tests of statistical significance were based on two-sided probability. Statistical analyses were performed with the use of SAS software (version 8.2; SAS Institute Inc, Cary, NC).

RESULTS

The mean age of the study population was 49.9 ± 8.5 y, and 38.0% were postmenopausal (Table 1). Approximately 13% of the study participants had attended college or had other higher education. Few women had ever smoked cigarettes (2.5%) or consumed alcohol regularly (2.4%). More than 30% of women reported exercising ≥1 time/wk during the past 5 y. The mean intake of soy protein was 8.8 ± 6.3 g/d. A higher intake of soy
protein was more common among older and postmenopausal women. Women with higher soy protein intake were more likely to have a higher BMI and higher educational level and were also more likely to have ever been a regular alcohol drinker or exercised regularly but less likely to be a cigarette smoker than were women with lower soy protein intake. Soy intake was also associated with intakes of total energy, fruit, vegetables, sodium, and nonsoy protein.

The mean values of systolic and diastolic BPs were 117.6 ± 16.4 and 75.6 ± 9.5 mm Hg, respectively, in this study population. Age, BMI, and sodium intake were found to be positively associated with both systolic and diastolic BPs, whereas higher education and household income, regular exercise, and higher intakes of vegetables, fruit, and nonsoy protein were associated with lower systolic and diastolic BPs.

After adjustment for age and BMI, soy protein intake was inversely associated with both systolic \( (P \text{ for trend } = 0.002) \) and diastolic \( (P \text{ for trend } = 0.007) \) BPs (Table 2). Further adjustment for lifestyle and other dietary factors, including intakes of sodium, total vegetables, fruit, and nonsoy protein, did not appreciably change the inverse association. The adjusted mean systolic BP was 1.9 mm Hg lower (95% CI: -3.0, -0.8 mm Hg) and the diastolic BP was 0.9 mm Hg lower (-1.6, -0.2 mm Hg) in women who consumed ≥25 g soy protein/d than in women who consumed <2.5 g/d. The effects were found to be slightly greater (≈10% increase) when analyses were confined to subjects who reported no obvious changes in their consumption of vegetables during the previous 5 y. Similar inverse associations with BP were also found for dietary intake of soy isoflavones.

In stratified analyses, a tendency for a more pronounced hypotensive effect of soy food intake was found in postmenopausal women, although interaction tests were not significant (Table 3). The hypotensive effect was substantially strengthened in elderly women. Among women aged ≥60 y, daily soy protein intake ≥25 g, as compared with the lowest intake, was associated with a decrease of 4.9 mm Hg (95% CI: -8.0, -1.9 mm Hg) in systolic BP and of 2.2 mm Hg (-3.8, -0.6 mm Hg) in diastolic BP. The test for multiplicative interaction was significant for both systolic (\( P = 0.008 \)) and diastolic (\( P = 0.01 \)) BP.

### DISCUSSION

In this large, population-based longitudinal study, we found that usual intake of soy food assessed at baseline was significantly and inversely associated with both systolic and diastolic BPs measured 2–3 y later in apparently healthy women. This association was independent of important risk factors for hypertension and other dietary factors. Elderly postmenopausal women appear to benefit more from soy consumption than do premenopausal women in terms of reductions in BP. Because there is a continuum of increased cardiovascular risk across levels of BP (32), and because soy products can be readily incorporated into most diets, our findings, if confirmed by further research, would have important public health implications.

The observed inverse association between soy food intake and BP is biologically plausible. Oxidative stress and inflammation have been implicated in the development of hypertension (17, 23). Soy isoflavones have been shown to reduce both in vitro and in vivo redox-sensitive markers of oxidative stress and inflammation, such as nitrotyrosine, 8-hydroxy-2'-deoxyguanosine, and superoxide anion generation (19, 20). These flavonoids may also reduce blood pressure via stimulation of nitric oxide production (21, 22) and inhibition of angiotensin converting enzyme (24).
TABLE 2
The association of dietary intake of soy protein at baseline with blood pressure (BP) measured during the follow-up period in the Shanghai Women’s Health Study, 1997–2002

<table>
<thead>
<tr>
<th>Soy protein intake (g/d)</th>
<th>SBP, age- and BMI-adjusted</th>
<th>SBP, fully adjusted</th>
<th>DBP, age- and BMI-adjusted</th>
<th>DBP, fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (n = 45 694)</td>
<td></td>
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</tr>
<tr>
<td>&lt;2.5 (n = 4007)</td>
<td>0.0 (reference)(^3)</td>
<td>0.0 (reference)</td>
<td>0.0 (reference)</td>
<td>0.0 (reference)</td>
</tr>
<tr>
<td>2.5–8.7 (n = 23 273)</td>
<td>−0.4 (−0.9, 0.1)</td>
<td>−0.2 (−0.7, 0.3)</td>
<td>−0.3 (−0.6, 0.0)</td>
<td>−0.2 (−0.6, 0.1)</td>
</tr>
<tr>
<td>8.8–15.0 (n = 12 859)</td>
<td>−0.7 (−1.3, −0.2)</td>
<td>−0.5 (−1.0, 0.1)</td>
<td>−0.4 (−0.7, −0.1)</td>
<td>−0.4 (−0.7, −0.1)</td>
</tr>
<tr>
<td>15.1–24.9 (n = 4560)</td>
<td>−0.5 (−1.1, 0.1)</td>
<td>−0.3 (−1.0, 0.4)</td>
<td>−0.4 (−0.8, 0.0)</td>
<td>−0.4 (−0.8, 0.0)</td>
</tr>
<tr>
<td>≥25 (n = 995)</td>
<td>−1.8 (−2.8, −0.7)</td>
<td>−1.9 (−3.0, −0.8)</td>
<td>−0.8 (−1.4, −0.1)</td>
<td>−0.9 (−1.6, −0.2)</td>
</tr>
</tbody>
</table>

\(^1\) P for trend

Subjects with no recent change in diet (n = 39 895)\(^4\)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–50</td>
<td>0.0 (reference)(^2)</td>
<td>0.0 (reference)(^2)</td>
</tr>
<tr>
<td>51–60</td>
<td>−0.4 (−1.7, 1.0)</td>
<td>−0.8 (−1.1, 0.3)</td>
</tr>
<tr>
<td>61–70</td>
<td>−0.7 (−2.1, 0.7)</td>
<td>−1.2 (−2.7, 0.4)</td>
</tr>
</tbody>
</table>

Menopausal status

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>−0.1 (−0.7, 0.5)</td>
<td>−0.4 (−1.0, 0.3)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>−0.3 (−1.2, 0.6)</td>
<td>−0.7 (−1.7, 0.3)</td>
</tr>
</tbody>
</table>

Diastolic BP

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<tr>
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<tbody>
<tr>
<td>Premenopausal</td>
<td>−0.2 (−0.6, 0.2)</td>
<td>−0.3 (−0.7, 0.1)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>−0.4 (−0.9, 0.1)</td>
<td>−0.7 (−1.2, −0.1)</td>
</tr>
</tbody>
</table>

\(^{1}\) Adjusted for age, BMI, education, household income, alcohol consumption, cigarette smoking, regular physical activity during the previous 5 y, and intakes of total calories, nonsoy protein, sodium, fruit, and total vegetables.

\(^{2}\) \(P\) for trend

\(^{3}\) Adjusted for age, BMI, education, household income, alcohol consumption, cigarette smoking, regular physical activity during the previous 5 y, and intakes of total calories, nonsoy protein, sodium, fruit, and total vegetables.

\(^{4}\) \(P\) for interaction

\(^{5}\) \(P\) for trend

\(^{6}\) Subjects who reported no major changes in vegetable consumption during the previous 5 y.

in vivo oxidation (5, 34). It has also been reported that genistein (an important isoflavone) stimulates the production of nitric oxide (6, 7), a factor that is known to have potent vasodilatory and antiinflammatory effects (35). In a recent clinical trial (16), a dietary portfolio of cholesterol-lowering foods, including soy foods, significantly lowered serum lipid and C-reactive protein (a marker of systemic inflammation) concentrations, and the effect size was comparable to that achieved with the initial therapeutic dose of a first-generation statin. BP is known to rise with increasing arterial stiffness (36), which relates to aging and menopause (4), and intakes of phytoestrogens from both food and supplement sources have been inversely associated with arterial stiffness among postmenopausal women (4, 8, 18, 37). It is not surprising that we observed a more pronounced inverse

### TABLE 3
Dietary intake of soy protein at baseline and blood pressure (BP) measured during the follow-up period, stratified by age and menopausal status, in the Shanghai Women’s Health Study, 1997–2002

<table>
<thead>
<tr>
<th>Adjusted difference in BP by soy protein intake (g/d)(^7)</th>
<th>P for trend</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5</td>
<td>2.5–8.7</td>
<td>8.8–15.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic BP</th>
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</tbody>
</table>

\(^{7}\) Adjusted for age, BMI, education, household income, alcohol consumption, cigarette smoking, regular physical activity during the previous 5 y, and intakes of total calories, nonsoy protein, sodium, fruit, and total vegetables.

\(^{8}\) \(P\) for trend

\(^{9}\) \(P\) for interaction

\(^{10}\) \(P\) for trend

\(^{11}\) Subjects who reported no major changes in vegetable consumption during the previous 5 y.
association of soy intake with BP among older postmenopausal women, because the adverse structural changes in the vessel wall are more prominent among that group. Soy intake may also lower BP through a natriuretic effect similar to furosemide (13, 14).

Data linking soy intake with BP have been limited and inconsistent. Soy consumption is extremely low in most Western populations, and this hinders epidemiologic studies of its health effects (38). In the Framingham Offspring Study of 939 postmenopausal US women, a relatively high intake of isoflavone was found to be associated with a reduction of 2.0 mm Hg in systolic BP and a reduction of 0.7 mm Hg in diastolic BP, although the associations were not significant (27). One small cross-sectional study in Japan observed a significant inverse association of BP with soy food intake in men but, unexpectedly, not in women (39). Several randomized controlled clinical trials showed that short-term soy supplementation significantly reduced both systolic and diastolic BPs (18–23, 40), and the reductions were substantially more pronounced in subjects with mild-to-moderate hypertension than in normotensive subjects (22). In an additional analysis of 11 086 subjects taking antihypertensive medication, we also found a slightly stronger inverse association between soy intake and BP (data not shown)—a mean difference of −2.8 mm Hg (95% CI: −5.2, −0.5 mm Hg) in systolic BP and of −1.7 mm Hg (−3.0, −0.5 mm Hg) in diastolic BP—when we compared the highest with the lowest intake of soy protein. In contrast, no effects of soy on BP were reported in other trials (24, 25). Differences in characteristics of the study participants, soy components being used, and the doses and durations may partly explain the inconsistency.

To our knowledge, this is the first population-based longitudinal study on usual soy food intake and BP. The large sample size and the wide range of soy consumption in our study subjects allowed us to evaluate the effect of usual soy food intake on BP in the general population, with a study power of ≥80% (α = 0.05) to detect a difference of 0.17 mm Hg in systolic BP and a difference of 0.10 mm Hg in diastolic BP associated with each 5 g/d increase in soy protein intake. The population-based prospective study design and the extremely high response rates in both the baseline and follow-up surveys eliminated potential recall bias and minimized selection bias, 2 principal concerns in most case-control studies. The dietary questionnaire used in this study has been shown to be of good validity in measuring usual intake of important nutrients and food groups (28). Moreover, dietary data were collected before BP measurement (2–3 y before). Thus, potential errors in assessment of usual dietary intake may not be a big concern in this study. The comprehensive information collected at baseline allowed us to account for potential confounding from other dietary and nondietary factors. Furthermore, very few women in our study smoked cigarettes, drank alcoholic beverages, and used hormone replacement therapy, which substantially limited the potential confounding effects of those variables on the association of soy food intake and BP.

However, this observational study cannot definitively prove a causal effect of soy consumption on BP. Women in the different categories of soy consumption also differed in several other respects, such as other dietary factors. Although careful adjustment for these potential confounding factors did not appreciably change the results (which suggests an independent effect), we could not completely exclude the possibility of residual confounding because of unmeasured or inaccurately measured covariates. For example, information on family history of hypertension was not collected in the study. People with a family history of hypertension are likely to pursue a healthy lifestyle and dietary practice. Nevertheless, we have adjusted for a broad range of potential confounding variables, and the adjustment did not materially alter the results, which suggests that the potential residual confounding is unlikely to explain away the observed robust association between intake of soy foods and BP.

Some women may have changed their usual diets around the time of the baseline survey. We found a slightly greater decrease in BP associated with soy food intake in the analyses confined to subjects with no significant changes in vegetable intake during the past 5 y, which suggests that our results could not be explained by recent dietary changes in some cohort members. The use of BP values measured on a single occasion is another limitation. Nevertheless, a single BP reading has been shown to be a strong predictor for future cardiovascular disease events (41).

In summary, we found in this large longitudinal study that usual intake of soy foods was significantly and inversely associated with both systolic and diastolic BPs, particularly among late postmenopausal women. Although the magnitude of reduction in BP associated with daily consumption of ≥25 g soy protein in the whole cohort of healthy women may not have significant clinical relevance, the public health implications may be important, given that a small reduction in populationwide BP can lead to a substantial decrease in cardiovascular risk in the society (42, 43). These data lend further support to the recommendation to increase consumption of soy foods to promote cardiovascular health.

We thank the participants and research staff of the Shanghai Women’s Health Study for their contribution to the study. We also thank Bethanie Hull for her assistance in preparing the manuscript.

GY, X-Os, XZ, and WZ designed the study; GY, X-Os, FJ, H-LL, QL, Y-TG, and WZ collected the data; GY, X-Os, XZ, and WZ analyzed the data; and all authors contributed to manuscript preparation. None of the authors had a personal or financial conflict of interest.

REFERENCES


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