**Title page**

**Title:** Dietary intake of beans and risk of disabling dementia: The Circulatory Risk in Communities Study (CIRCS)

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**Running title:** Dietary intake of soy beans and other pulses and disabling dementia

**Abstract (250 words)**

**Objective:** To examine whether bean intake (including soybeans) among Japanese adults is associated with risk of disabling dementia severe enough to require care under the national insurance system.

**Methods:** This cohort study involved 3,739 individuals aged 40 to 64 years. The participants were categorized into five groups based on their dietary bean intake estimated by a 24–hour dietary recall. Hazard ratios and 95% confidence intervals of disabling dementia were estimated using Cox proportional hazard models adjusted for potential confounding factors (smoking, drinking, and intakes of energy and fish).

**Results:** During the 59,681 person-year follow-up, 670 cases of disabling dementia were observed. A weak inverse association between bean intake and risk of disabling dementia was found; the multivariable hazard ratios (95%CIs) were 0.79(0.62–1.00), 0.80(0.63–1.01), 0.84(0.67–1.06), and 0.78(0.62–0.99) for the four groups with higher bean intake, respectively, compared with the lowest group (*P* for trend = 0.21). A significant inverse association was observed for dementia without a history of stroke; for the four groups with higher bean intake the multivariable hazard ratios were 0.81(0.61–1.08), 0.70(0.52–

0.95), 0.71(0.52–0.95), and 0.69(0.51–0.92), respectively, ($P$ for trend = 0.03). No such association was observed for dementia with history of stroke. The group with increased natto intake were inversely associated with risk of disabling dementia ($P$ for trend = 0.003), but tofu intake was not ($P$ for trend = 0.19).

**Conclusions:** Bean intake was inversely associated with risk of disabling dementia in those without a history of stroke.

**Introduction:**

With the aging of the global population, the number of individuals with dementia is expected to increase worldwide to 78 million by 2030(1). In Japan, one of the most rapidly ageing populations in the world, it is estimated that there will be more than 7 million people with dementia by 2025(2). The costs of dementia are a social burden with significant social and economic implications including medical, social care, and informal care costs, which are estimated to surpass $2.8 trillion by 2030(1). Considering this situation, primary prevention should be promoted as one of the important public health strategies that could be leveraged to reduce the social burden of dementia-related morbidity.

Beans (including soybeans) have been a traditional feature of the Asian diet for millennia. The low dementia prevalence in East Asia (4.2%), compared with that of Western countries (6.5% in the U.S and 6.9% in Europe), could be related to the unique Asian dietary patterns, which is partly characterized by the regular consumption of beans(3). On average, Japanese consumed 60 g of beans a day in 2019(4). In Japan, most of the beans consumed are soybeans, which contain isoflavones, a natural phytoestrogen.

Isoflavone has been proposed to have beneficial effects on dementia through its anti-inflammatory and anti-oxidant properties and improvement of β amyloid-induced cellular apoptosis(5,6). In addition, soybeans include folate, which acts as coenzyme for metabolizing homocysteine, a potential risk factor for dementia(7). Several animal and *in vitro* studies have reported that isoflavones may be useful in preventing dementia(6). However, previous case-control and cohort studies have shown null(8), protective(9,10), and even adverse(11,12) associations between soybean-derived foods and cognitive function. In the current study, we took advantage of the large sample size and extended follow-up experience of participants in the Circulatory Risk in Communities Study (CIRCS) to examine the association between bean consumption and risk of disabling dementia.

**Subjects and Methods:**

**Subjects and surveys**

CIRCS is an ongoing, dynamic, community-based, prospective study involving five communities in Japan whose details have been described elsewhere(13). In the present study, we included three CIRCS communities: Ikawa, Minami-Takayasu, and Kyowa, where disabling dementia surveillance, annual health checkups, and annual dietary surveys have been conducted. A total of 9,992 people aged 40–69 years living in these three communities participated in the annual health checkups between 1985 and 1999, and the recruitment for the dietary surveys was made every 4 to 5 years during this period. Of the participants of the dietary survey, approximately 38% were chosen as a systematic sample in the annual cardiovascular risk survey. For those participants who completed the dietary survey twice or more, data of the first survey were used for analysis in the current study. Surveillance for disabling dementia was conducted from 1999 to 2019 in Ikawa, 1999 to 2020 (except for from Apr 2005 to Apr 2008, where the data were unavailable) in Kyowa, and from 2006 to 2019 in Minami-Takayasu (Figure 1). The mean time lag between dietary survey and the start of dementia surveillance was 9.2 years.

To focus on the dietary habits of middle-aged people, the surveyed population included 3,750 residents aged 40 to 64 years at the time of the dietary surveys (between 1985 and 1999) who lived in the surveyed communities at the start of dementia surveillance. The participants were apparently healthy at the time of the dietary surveys, and there was no information about medical history of dementia from the time period of the dietary surveys. To minimize the possibility of reverse causation, we set the dietary survey period at an average 9.2 years before the start of dementia surveillance, and incident disabling dementia cases who had completed the dietary survey within a five-year period (n=2) were excluded. A further nine persons with invalid dietary data were excluded. Finally, 3,739 participants were included in the present study.

From the perspective of preventing dementia that requires care, we set the outcome of this study as disabling dementia. Disabling dementia was diagnosed by attending physicians under the National Long-Term Care Insurance (LTCI) system (which is a compulsory insurance for all individuals aged 40 years or over in Japan); the criteria of disabling dementia were the same as those of our previous study(14). Based on the certification information under the National LTCI system, the onset of disabling dementia was defined as the first time the following two conditions were met: (1) LTCI care needs level 1 or greater (requiring assistance with some or all of their daily activities for 6 months or more owing to physical or mental disabilities) and (2) dementia level of grade IIa or greater (grade IIa is equivalent to an individual who has dementia-related symptoms with some behavioral disturbance or difficulty in communication that limit daily living, but independence under someone's attention in the domestic sphere) according to the Health and Welfare Bureau for the Elderly of Japan's standardized assessment manual (Supplemental Table 1)(15). The validation of the above criteria for disabling dementia has been previously confirmed with high specificity (96%) and moderate sensitivity (73%)(16). We did not have information on the dementia types (i.e., Alzheimer or vascular type), instead, we further classified the dementia cases into those with or without a history of stroke based systematic stroke registration described elsewhere(17), as well as self-reports at the dietary surveys. For the subtype analyses, the follow-up terminated at the end of 2015 for Kyowa, and the end of 2018 for Ikawa and Minami-Takayasu, where stroke registry data were available.

Individual consent was not required for the analysis of this study, because it was conducted as a secondary analysis of data obtained for public health practice in the local communities at that time. Participants were retrospectively given the opportunity to withdraw their data from the analysis. The study was approved by the institutional review boards of the Osaka Center for Cancer and Cardiovascular Disease Prevention and the University of Tsukuba.

**Assessment of bean intake**

The 24-hour dietary recall method was adopted for collecting dietary data(18). Participants were interviewed by trained dietitians or nutritionists for approximately 30 minutes regarding their food intake over the 24-hour period before the examination. To ensure consistency throughout the surveys, these interviewers consulted the dietary-recall manual and held regular meetings to review and update the manual before each survey. Efforts were made to retain all dietitians throughout all surveys to avoid variability in interviewing technique but, when hiring new dietitians was unavoidable, the new hires were directly trained by the experienced dietitians. Actual-sized food models, pictures of food materials and dishes, and/or real foods and dishes were used during the interview to stimulate recall of dietary intake, and the foods consumed. Based on the Standard Tables of Food Composition in Japan 2015 (7th revised edition)(19), nutrient intakes were calculated by multiplying the amount of each food consumed by its nutrient content and totaling the nutrient intakes for all foods. Energy adjustment for nutrients was conducted using the residual method(20). The definition of "beans" included soybeans, soybean products (e.g. *natto, tofu*), kidney beans, peas, Adzuki beans, cowpeas, etc.(19)

Participants were divided into five groups based on their daily bean intake (0 intake and 4 incremental quartile groups): group 1 =0 g/day, group 2 =0.5–29.6 g/day, group 3 =29.7–59.9 g/day, group 4 =60.0–111.2 g/day, and group 5 =111.3 g/day or more.

As a supplemental analysis, the association between *natto* and *tofu*, which are the most commonly consumed soybean products by Japanese populations(4), and risk of disabling dementia was assessed. Participants were divided into five groups based on their daily *natto* and *tofu* intake (0 intake and 4 incremental quartile groups); for *natto*: group 1 =0 g/day; group 2 =0.5–39.8 g/day, group 3 =39.9–58.7 g/day, group 4 =58.8–78.7 g/day, and group 5 =78.8 g/day or more; and for *tofu*: group 1 =0 g/day, group 2 =0.1–78.5, group 3 =78.6–130.1, group 4 =130.2–231.2, and group 5 =231.3 g/day or more.

**Other baseline examinations**

Potential risk factors for disabling dementia were measured at the same time as the dietary surveys were conducted. Systolic and diastolic blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-minute rest. Hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg and/or as taking antihypertensive medication. Body mass index (BMI) was calculated as weight (kg) divided by the square of height ($m^2$). Face-to-face interviews were conducted to determine alcohol consumption and smoking status, and treatment of antihypertension and hypercholesterolemia. Serum total cholesterol was measured without a fasting requirement while diabetes mellitus was defined as serum glucose level $\geq$126 mg/dL in the fasting state or $\geq$200 mg/dL in the non-fasting state or use of medication for diabetes mellitus(21). History of stroke was obtained from face-to-face interviews during the annual cardiovascular surveys and/or systematic community surveillance of the cardiovascular disease registration system (including reviews of medical charts and brain imaging studies) from 1981 to 2015 for Kyowa, and 1981 to 2018 for Ikawa and Minami-Takayasu(22).

**Statistical Analysis**

Age- and sex-adjusted means and proportions of selected disabling dementia risk factors and dietary factors were calculated across the five groups using linear or logistic regression analyses. Follow-up started from the start of dementia surveillance and ended at the date of developing dementia, death, moving out of the studied area, or at the end of the study period in 2019 or 2020. Hazard ratios and 95% confidence intervals (95% CIs) for the incidence of disabling dementia according to bean intake levels were calculated using Cox proportional hazard models. Model 1 was stratified jointly by area of residence and adjusted for age (continuous) and sex. Model 2 further included the following potential confounding factors: current smoking status (never, former, current 1–20, and >20 cigarettes/day), current drinking status (never, former, current <46, and ≥46g ethanol/day), and intakes of energy and fish (quintiles). Dummy variables were set for any missing values and included in the models. Vegetables and fruits were not adjusted in our analysis, because these intakes were not found to be associated with the risk of disabling dementia in our cohort(14). Trend tests were performed using the median value of beans intake for each group. We did not have information on dementia types (e.g., Alzheimer's disease or vascular type) but instead classified disabling dementia into cases with or without a history of stroke. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). All probability values for the statistical tests were 2-tailed and probability values below 0.05 were considered significant.

**Results:**

Bean intake was positively associated with age, dietary intakes of energy, fat, protein, vegetable, and sodium, while it was inversely associated with dietary intakes of carbohydrate and meat. The other baseline characteristics did not differ materially between them (Table 1).

During 16.0 years follow-up totaling 59,681 person-years, we documented 670 incident cases of disabling dementia. We found a weak inverse association between bean intake and risk of incident disabling dementia (Table 2). The respectively multivariable hazard ratios (95% CIs) for the groups with higher bean intake (groups 2, 3, 4, and 5) were: 0.79(0.62–1.00), 0.80(0.63–1.01), 0.84(0.67–1.06), and 0.78(0.62–0.99), as compared with the group with the lowest bean intake (group 1) (*P* for trend =0.21). The associations were confined to dementia without a history of stroke; the respective hazard ratios were: 0.81(0.61–1.08), 0.70(0.52–0.95), 0.71(0.52–0.95), and 0.69(0.51–0.92) (*P* for trend =0.03). No such association was observed for dementia with a history of stroke; the respective hazard ratios were: 0.95(0.53–1.70), 0.92(0.52–1.62), 1.03(0.59–1.80) and 0.84(0.47–1.50) (*P* for trend =0.63).

As supplemental analyses, we examined the association of *natto* and *tofu* with the risk of disabling dementia. For the groups with higher *natto* intake (groups 2, 3, 4, and 5) the respectively multivariable hazard ratios (95% CIs) were: 0.91(0.68–1.21), 0.75(0.55-1.01), 0.77(0.56–1.07), and 0.68(0.49–0.96), compared with the lowest group (*P* for trend =0.003). For *tofu* intake, no such association was observed; the respective hazard ratios (95% CIs) were: 0.88(0.69–1.13), 0.90(0.70–1.15), 0.97(0.77–1.23), and 0.83(0.65–1.07) (*P* for trend =0.19) (Table3).

**Discussion:**

An inverse association between bean intake and risk of incident disabling dementia, especially of that without a history of stroke, was found in the Japanese adult population. To our knowledge, this is the first prospective study to find the inverse association in a general population in Japan.

Most of the studies focusing on dietary pattern including high consumption of legumes and specific nutritional components of beans such as soy isoflavones in relation to cognitive impairment have not examined clinical events (i.e. dementia) as endpoints.

The National Institute for Longevity Sciences-Longitudinal Study of Aging (773 Japanese men and women aged 60–81 years with 8-years follow-up) found an inverse association between higher intake of beans or soy foods and risk of cognitive impairment(8). Similarly, 6–year follow-up of 4,749 Chinese men and women aged ≥80 years in the Chinese Longitudinal Healthy Longevity Survey found an association between intake of soybean-derived products and lower risk of cognitive impairment(12).

On the other hand, the Honolulu-Asia Aging Study of 3,232 Japanese-American men and 502 women aged 71–93 years found that higher *tofu* intake was associated with poor cognitive test performance after adjustment for confounding factors such as education, occupation, and fish consumption(9). The Singapore Chinese Health Study of 16,948 Chinese men and women aged 45–74 years with 20.2 years follow-up found no association between intakes of *tofu* and isoflavones with cognitive impairment (8). Furthermore, the Study of Women's Health Across the Nation of 195 Japanese-American and 185 Chinese-American women aged 42–52 years with 4 years of follow-up, found no association between genistein intake and cognitive performance (10). The reasons for the discrepancy between these studies are unknown, but the difference in ethnicity (the metabolic capacity of equol, a metabolite of a soy isoflavone associated with improved cognitive function(24), was about 50% in Japanese and Korean(25,26) compared to 14% in Americans(26)), endpoint determination (cognitive impairment in the previous study, compared to disabling dementia in the current study), and different types of beans and food items across the studies might explain the inconsistent results. In Japan, soybeans make up the majority of beans consumed(4). *Natto* is a traditional Japanese food made by fermenting soybeans whereas *tofu* uses unfermented soybeans. Compared with *tofu, Natto* contains a 3.5-fold higher amount of isoflavones and isoflavone aglycones(27), which are absorbed faster and in greater amounts than isoflavone glucosides in humans(28). In the present study, *natto* intake was significantly and inversely associated with risk of disabling dementia, while *tofu* intake was not.

As secondary analysis, the association with bean intake was stronger for dementia without a history of stroke, which is likely to correspond with Alzheimer disease. A potential mechanism underlying the protective effect of bean consumption on Alzheimer disease, has been proposed as an anti-apoptotic effect of soybeans, especially isoflavone(29). In Japan, 98% of bean intake is derived from soy and soy products(4) and several recent studies have suggested that soy isoflavones, an estrogen-like substance, may have a neuroprotective effect of brain via estrogenic receptor pathways, and may reduce reactive oxygen species (oxidants) and ameliorate β amyloid-induced cellular apoptosis(29,30). In a meta-analysis, estrogen replacement therapy has been associated with reduced risk of Alzheimer disease: the summary odds ratios were 0.66(0.53–0.20)(31). Additionally, in a meta-analysis of 16 randomized controlled trials involving 1,386 participants, a higher soy isoflavone intake was inversely associated with cognitive function(34).

Furthermore, beans are a good source of folate. Folate has an essential roles in one-carbon metabolic pathway and plays down-regulation of homocysteine, a potential risk factor for dementia(35,36). Several prospective cohort studies reported that folate intake was associated with reduced risks of cognitive impairment(37), cognitive decline(38), Alzheimer disease(39,40), and dementia(41). In a randomized double-blind placebo-controlled trial, 3 years supplementation of 800μg daily oral folic acid decreased plasma total homocysteine and improved cognitive function compared with the placebo supplementation(42).

The strengths of our study included its longitudinal, population-based design with a large sample size, a long follow-up, and populations with a high bean intake. Several limitations of this study should be noted. First, we used the data from a single 24-hour recall for nutrition and no consideration was given to any subsequent change in diet. We found moderate reproducibility of major foods estimated from two recalls conducted one year apart among samples of CIRCS participants (n =262), the correlation coefficients were 0.48 in men and 0.56 in women for bean intake(43). Second, we did not have the information regarding medical history of dementia at the time of the dietary survey. Instead, the baseline survey was set at an average of 9.2 years before the beginning of the dementia follow-up. In addition, we further excluded incident cases of disabling dementia who had dietary survey within five years. These procedures should have minimized the possibility of reverse causation. Third, we did not have the information on dementia type (e.g., Alzheimer dementia, vascular-type dementia). Instead, we used information on dementia with or without a history of stroke and postulated that dementia without a history of stroke was more likely to be Alzheimer disease. The inverse associations with bean intake were primarily observed for dementia without a history of stroke. Fourth, we did not have the data from dementia surveillance in one community between 2005 and 2008. However, when we analyzed all participants from 2009, the results did not change materially, so the impact of the unavailability of data for this period may have had little impact on the results. Finally, socioeconomic status could have confounded our findings; however, a previous study that analyzed data from the National Health and Nutrition Survey in 2010, reported no association between household income and soy intake in men and women aged over 20 years(44).

In conclusion, bean intake was inversely associated with risk of disabling dementia without a history of stroke in a community-based setting, which suggests that a higher bean intake may carry a beneficial effect on prevention of dementia among general populations.

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**Conflict of Interest**

The authors have no conflict of interest to declare.

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**Figure legends:**

The total number of participants was 3,739: 1,319 in Ikawa, 725 in Minami-Takayasu, 1,695 in Kyowa. Dietary surveys were carried out from 1985 to 1999. The participants were followed up to identify disabling dementia from 1999 to 2019 in Ikawa, from 2006 to 2019 in Minami-Takayasu, and from 1999 to 2020 (except for from Apr 2005 to Apr 2008, where the data were unavailable) in Kyowa. Participants who developed incident disabling dementia within 5 years of the dietary survey were excluded.