

# Association of soy and fermented soy product intake with total and cause specific mortality: prospective cohort study

Ryoko Katagiri,<sup>1</sup> Norie Sawada,<sup>1</sup> Atsushi Goto,<sup>1</sup> Taiki Yamaji,<sup>1</sup> Motoki Iwasaki,<sup>1</sup> Mitsuhiro Noda,<sup>2</sup> Hiroyasu Iso,<sup>3</sup> Shoichiro Tsugane<sup>1</sup>, for the Japan Public Health Center-based Prospective Study Group

Cite this as: *BMJ* 2020;368:m34  
<http://dx.doi.org/10.1136/bmj.m34>  
 Accepted: 16 December 2019

## ABSTRACT OBJECTIVE

To investigate the association between several types of soy products and all cause and cause specific mortality.

## DESIGN

Population based cohort study.

## SETTING

Japan Public Health Centre-based Prospective Study, which includes 11 public health centre areas in Japan.

## PARTICIPANTS

92 915 participants (42 750 men and 50 165 women) aged 45 to 74 years.

## EXPOSURES

Intake of total soy products, fermented soy products (natto and miso), non-fermented soy products, and tofu from a five year survey questionnaire.

## MAIN OUTCOME MEASURES

All cause and cause specific mortality (cancer, total cardiovascular disease, heart disease, cerebrovascular disease, respiratory disease, and injury) obtained from residential registries and death certificates.

## RESULTS

During 14.8 years of follow-up, 13 303 deaths were identified. In the multivariable adjusted models, intake of total soy products was not significantly associated with total mortality. Compared with the lowest fifth of total soy product intake, the hazard ratios in the highest fifth were 0.98 (95% confidence interval 0.91 to 1.06,  $P_{trend}=0.43$ ) in men and 0.98 (0.89 to 1.08,  $P_{trend}=0.46$ ) in women. Intake of fermented soy products was inversely associated with all cause mortality in both sexes (highest versus lowest fifth: 0.90 (0.83 to 0.97),  $P_{trend}=0.05$  in men, and 0.89 (0.80 to 0.98),  $P_{trend}=0.01$  in women). Natto showed significant and inverse associations with total cardiovascular disease related mortality in both sexes.

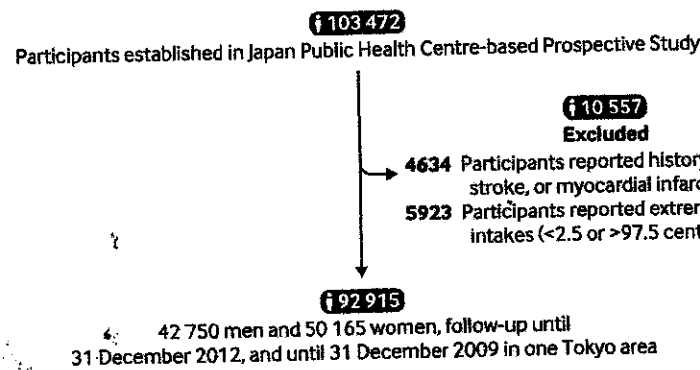
## CONCLUSIONS

In this study a higher intake of fermented soy was associated with a lower risk of mortality. A significant association between intake of total soy products and all cause mortality was not, however, observed. The findings should be interpreted with caution because the significant association of fermented soy products might be attenuated by unadjusted residual confounding.

**Table 1 | Baseline characteristics of study participants according to fifth of total soy product intake. Values are numbers (percentages) unless stated otherwise**

Characteristics	Men (n=42 750)*					Women (n=50 165)*				
	First (lowest intake)	Second	Third	Fourth	Fifth (highest intake)	First (lowest intake)	Second	Third	Fourth	Fifth (highest intake)
No of participants	8550	8550	8550	8550	8550	10033	10033	10033	10033	10033
Mean (SD) age (years)	55.1 (8.0)	55.9 (7.8)	56.2 (7.6)	56.7 (7.5)	57.6 (7.5)	55.8 (8.4)	56.4 (8.0)	56.5 (7.8)	57.0 (7.5)	58.0 (7.4)
Mean (SD) body mass index (kg/m <sup>2</sup> )	23.5 (2.9)	23.5 (2.8)	23.6 (2.8)	23.6 (2.8)	23.8 (2.9)	23.2 (3.2)	23.3 (3.1)	23.4 (3.1)	23.5 (3.1)	23.9 (3.2)
Current smoker	4220 (52.0)	4005 (49.2)	3804 (46.6)	3687 (45.3)	3380 (41.8)	835 (9.0)	565 (6.0)	482 (5.1)	439 (4.6)	424 (4.5)
Alcohol intake (≥1 day/week)	5833 (69.0)	6064 (71.5)	6002 (70.9)	5733 (67.6)	5320 (63.3)	1732 (17.9)	1509 (15.5)	1375 (14.1)	1116 (11.4)	917 (9.4)
Diabetes mellitus	504 (5.9)	564 (6.6)	573 (6.7)	599 (7.0)	755 (8.8)	330 (3.3)	322 (3.2)	312 (3.1)	363 (3.6)	471 (4.7)
Antihypertensive drugs	1320 (15.4)	1487 (17.4)	1543 (18.1)	1635 (19.1)	1811 (21.2)	1659 (16.5)	1871 (18.7)	1926 (19.2)	1966 (19.6)	2329 (23.2)
Health check-up	6708 (78.5)	7061 (82.6)	7132 (83.4)	7178 (84.0)	7081 (82.8)	8063 (80.4)	8459 (84.3)	8570 (85.4)	8677 (86.5)	8573 (85.5)
Sports or physical exercise (almost every day)	395 (4.8)	424 (5.1)	423 (5.1)	492 (6.0)	528 (6.5)	426 (4.5)	503 (5.2)	507 (5.3)	533 (5.5)	631 (6.7)
Postmenopausal	-	-	-	-	-	6503 (69.3)	7080 (74.3)	7189 (75.7)	7500 (78.9)	7677 (82.6)
Use of exogenous female hormones	-	-	-	-	-	254 (2.7)	239 (2.5)	246 (2.6)	263 (2.8)	270 (2.9)
Coffee intake (>once/day)	3567 (44.3)	3076 (37.7)	2650 (32.5)	2409 (29.5)	2079 (26.0)	4719 (50.0)	3918 (40.7)	3511 (36.5)	2989 (31.2)	2611 (27.8)
Green tea intake (>once/day)	4010 (49.6)	4845 (58.7)	5058 (61.2)	5028 (60.7)	4796 (58.0)	5467 (57.8)	6210 (64.0)	6361 (65.7)	6155 (63.2)	5512 (57.2)
Median (interquartile range) dietary intake†:										
Energy (kcal/day)	2035 (1643-2494)	2140 (1744-2607)	2129 (1747-2575)	2091 (1711-2557)	1993 (1615-2487)	1742 (1403-2164)	1819 (1485-2244)	1815 (1498-2209)	1778 (1461-2168)	1716 (1384-2128)
Fruit (g/day)	115 (51-201)	130 (66-219)	143 (77-231)	149 (79-237)	146 (78-239)	184 (104-294)	203 (127-310)	207 (129-309)	204 (129-304)	193 (118-291)
Vegetables (g/day)	129 (81-193)	57 (107-224)	172 (119-245)	177 (120-252)	194 (128-281)	163 (110-233)	190 (136-265)	206 (148-283)	212 (152-289)	220 (151-309)
Fish (g/day)	71 (47-105)	78 (53-112)	81 (56-114)	82 (56-116)	79 (53-115)	70 (46-100)	78 (53-107)	80 (56-109)	80 (56-109)	75 (5-107)
Meat (g/day)	59 (37-89)	57 (36-84)	55 (35-80)	52 (33-78)	49 (29-75)	53 (33-80)	51 (33-77)	49 (31-71)	47 (29-69)	43 (25-66)
Total soy products (g/day)‡	37 (27-46)	67 (60-73)	92 (85-98)	121 (112-130)	178 (157-221)	37 (27-45)	64 (58-70)	87 (81-93)	115 (107-124)	174 (151-221)
Natto (g/day)	2.5 (1.1-6.9)	5.9 (1.5-13.3)	10.0 (2.5-19.8)	13.6 (3.9-28.0)	16.2 (2.8-36.3)	3.4 (1.3-7.9)	7.3 (2.0-15.0)	11.8 (4.0-22.2)	15.5 (5.3-28.8)	17.4 (4.1-36.8)
Miso (g/day)	6.7 (3.1-11.1)	14.8 (9.6-21.7)	22.1 (13.5-28.9)	26.3 (17.6-34.7)	28.8 (19.0-39.3)	6.0 (2.7-9.9)	12.2 (7.7-17.9)	17.6 (10.7-24.5)	22.3 (13.4-29.2)	24.4 (14.7-33.5)
Tofu (g/day)	17 (10-17)	26 (17-38)	32 (21-47)	44 (28-64)	80 (48-121)	18 (11-25)	28 (19-39)	35 (24-49)	48 (32-65)	83 (52-124)

\*Numbers of missing men and women were, respectively, 942 and 1347 for body mass index, 2112 and 3134 for smoking, 455 and 1396 for alcohol consumption, 1569 and 2280 for physical exercise, 2232 and 2482 for coffee intake, and 1583 and 1947 for green tea intake. 2745 women were missing for use of exogenous female hormones and 2954 for menopausal status.  
 †Food intakes were adjusted for energy intake using the residual method.  
 ‡Sum of seven soy foods in the questionnaire. Along with total soy products, the table shows the amount of main soy products. The amount of miso was calculated from the amount of miso soup. Total tofu intake was calculated as the sum of the amount of tofu, tofu in miso soup, and other tofu products.



**Fig 1 | Flow of participants through study**

**Table 2 | Risk of all cause mortality according to fifths of total soy, fermented soy, and non-fermented soy product intake in Japanese men and women. Values are hazard ratios (95% confidence intervals) unless stated otherwise**

Variables	Men (n=42 750)					$P_{trend}$	Women (n=50 165)					$P_{trend}$
	First	Second	Third	Fourth	Fifth		First	Second	Third	Fourth	Fifth	
<b>Total soy products*:</b>												
Intake (g/day)	<53.2	53.2-79.2	79.2-104.6	104.6-141.3	>141.3		<51.6	51.6-75.3	75.3-99.7	99.7-135.9	>135.9	
No of deaths	1531	1593	1626	1676	1944		942	958	917	977	1139	
Cumulative mortality rate (%)†	7.30	6.76	6.53	6.29	6.82		2.78	2.65	2.44	2.47	2.61	
Model 1‡	1.00	0.92 (0.86 to 0.99)	0.89 (0.83 to 0.96)	0.86 (0.80 to 0.92)	0.93 (0.87 to 1.00)	0.03	1.00	0.96 (0.87 to 1.05)	0.88 (0.80 to 0.96)	0.89 (0.81 to 0.98)	0.94 (0.86 to 1.03)	0.09
Model 2§	1.00	0.96 (0.89 to 1.03)	0.94 (0.87 to 1.01)	0.91 (0.84 to 0.98)	0.98 (0.91 to 1.06)	0.43	1.00	1.01 (0.92 to 1.11)	0.95 (0.86 to 1.04)	0.96 (0.87 to 1.06)	0.98 (0.89 to 1.08)	0.46
<b>Fermented soy products¶:</b>												
Intake (g/day)	<13.4	13.4-24.1	24.1-35.2	35.3-50.2	>50.2		<12.5	12.5-22.2	22.2-32.9	32.9-46.6	>46.6	
No of deaths	1657	1530	1600	1763	1820		1033	955	925	963	1057	
Cumulative mortality rate (%)†	7.32	6.63	6.56	6.86	6.40		2.88	2.67	2.50	2.46	2.49	
Model 1‡	1.00	0.90 (0.84 to 0.97)	0.89 (0.83 to 0.96)	0.93 (0.87 to 1.01)	0.87 (0.81 to 0.94)	0.009	1.00	0.92 (0.85 to 1.01)	0.87 (0.79 to 0.95)	0.85 (0.77 to 0.94)	0.86 (0.78 to 0.95)	0.002
Model 2§	1.00	0.92 (0.85 to 0.98)	0.91 (0.85 to 0.98)	0.95 (0.88 to 1.03)	0.90 (0.83 to 0.97)	0.05	1.00	0.95 (0.87 to 1.04)	0.91 (0.83 to 1.00)	0.90 (0.81 to 0.99)	0.89 (0.80 to 0.98)	0.01
<b>Non-fermented soy products**:</b>												
Intake (g/day)	<17.3	17.3-28.3	28.3-45.5	43.5-72.9	>72.9		<19.2	19.2-30.7	30.7-45.9	45.9-74.7	>74.7	
No of deaths	1654	1515	1641	1723	1837		1054	909	860	963	1147	
Cumulative mortality rate (%)†	7.17	6.38	6.65	6.56	6.71		2.87	2.51	2.27	2.51	2.73	
Model 1‡	1.00	0.89 (0.83 to 0.95)	0.92 (0.86 to 0.99)	0.91 (0.85 to 0.98)	0.93 (0.87 to 1.00)	0.17	1.00	0.87 (0.80 to 0.95)	0.79 (0.72 to 0.95)	0.87 (0.80 to 0.95)	0.95 (0.87 to 1.04)	0.31
Model 2§	1.00	0.94 (0.87 to 1.01)	1.00 (0.93 to 1.07)	0.99 (0.92 to 1.06)	1.01 (0.94 to 1.09)	0.32	1.00	0.93 (0.85 to 1.02)	0.84 (0.77 to 0.93)	0.95 (0.86 to 1.04)	1.00 (0.92 to 1.10)	0.80

\*Sum of natto, miso, three kinds of tofu (tofu, yushidofu, and koyadofu), fried tofu (abura-age), and soy.  
 †Age and geographical area adjusted mortality risk at 10 years.  
 ‡Adjusted for age and geographical area.  
 §Adjusted for age, geographical area, smoking, frequency of alcohol intake, body mass index, sports or physical exercise, history of diabetes or taking drugs for diabetes, taking antihypertensives, health check-up, total energy intake, and intake of green tea, coffee, fish, meat, fruit, and vegetables.  
 ¶Sum of natto and miso.  
 \*\*Tofu, abura-age, and soy milk.

Handwritten notes in Chinese and Japanese:

- 死因: 消化 (Cause of death: Digestive)
- 交際用+9補正不足 (Adjustment for social use +9 insufficient)
- BC式 (BC formula)
- 14.8% change
- 1.5% (1.5%)

Handwritten notes: DM, BP, 糖圧等 (DM, BP, blood sugar etc.)